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Lipid metabolism and lipophagy in cancer

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Abstract

The tumor microenvironment can be hypoxic, acidic, and deficient in nutrients. This can cause the metabolism of tumor cells as well as the neighboring stromal cells to be remodelled to facilitate tumor survival, proliferation, and metastasis. Abnormal tumor lipid metabolism is a fairly new field, which has received attention in the past few years. Cross-talk between tumor cells and tumor associated stromal cells modulates the high metabolic needs of the tumor. Fatty acid turnover is high in tumor cells to meet the energy as well as synthetic requirements of the growing tumor. Lipolysis of lipids stored in lipid droplets was earlier considered to be solely carried out by cytosolic lipases. However recent studies demonstrate that lipophagy (autophagic degradation of lipids by acidic lipases) serves as an alternate pathway for the degradation of lipid droplets. Involvement of lipophagy in lipid turnover makes it a crucial player in tumorigenesis and metastasis. In this review we discuss the metabolic reprogramming of tumor cells with special focus on lipid metabolism. We also address the lipid turnover machinery in the tumor cell, especially the lipophagic pathway. Finally, we integrate the current understanding of lipophagy with tumor lipid metabolism.

Keywords

Tumor; tumor microenvironment; lipid metabolism; lipid droplets; lipophagy

Introduction

It is now well established that metabolic adaptations are important for cancer cell survival and proliferation [1]. The tumor microenvironment (TME) and oncogenic events (oncogene activation and loss of tumor suppressors) are critical for metabolic adaptation of cancer cells. The TME is composed of blood vessels, fibroblasts, immune cells, and proteins that compose the extracellular matrix. The TME is characterized by heterogeneous regions of

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poor oxygen supply (hypoxia) and nutrient deprivation surrounding the tumor cells. In proliferating tumor cells, oxygen demand is far greater than oxygen supply. This can creates regions of hypoxia which is one characteristic of solid tumors [2]. Insufficient diffusion of oxygen in these regions caused by increased distance between the tumor cells and vasculature can markedly influence cancer growth. Hypoxia triggers molecular changes resulting in metabolic adaptations essential for survival of cancer cells. The first adaptive metabolic reprogramming in tumor metabolism was identified to be alterations in glucose metabolism [3; 4]. Tumor cells exhibit the Warburg effect characterized by increased glucose uptake and increased rate of glycolysis leading to lactate production [5]. Malignant cancer cells tend to increase the rate of glycolysis followed by metabolism to pyruvate, which is converted to lactate by lactate dehydrogenase even in the presence of oxygen [5; 6; 7]. This is one of the reasons underlying the acidosis which is another distinctive attribute of the TME. Metabolic reprogramming is also triggered in stromal cells, so that they are able to synthesize glutamine from unconventional sources in the nutrient scarce TME [8]. Glutamine is significant in cancer because of its ability to donate its carbon and amino-nitrogen to metabolites involved in amino-acid and nucleotide metabolism and other growth-promoting pathways [9]. Though altered glycolysis and glutamine metabolism are hallmarks of cancer, lipid metabolic abnormalities in tumor cells have become increasingly recognized in the past few years [10; 11; 12].

Lipids, including sterols, di-/tri-acylglycerols and phospholipids are integral part of biological membranes and are also used for energy storage, production, and cellular signalling. Fatty acids (FA) are indispensable for lipid biosynthesis. They are a diverse class of molecules consisting of hydrocarbon chains of varying lengths and different degrees of unsaturation which comprise the hydrophobic tails of phospholipids and glycolipids. Phospholipids (phosphatidylcholine and phosphatidylethanolamine) and glycolipids along with cholesterol are major components of biological membranes and markedly influence membrane fluidity. FAs also comprise of the hydrophobic tails of diacylglycerol (DAG) and phosphatidylinositol-3,4,5-trisphosphate (PIP3), which are important signalling molecules. During sufficient nutrient availability, FAs are stored in the adipose tissue as triglycerides (TG), and when energy is depleted, TGs are degraded to release FAs. FAs can then undergo oxidation to release energy in the form of high energy phosphate; at a much greater equivalent as compared to that produced by carbohydrates.

Lipids are stored in lipid droplets (LDs) by cells when energy supplies are high (e.g., after eating). Degradation of lipids stored in LDs occurs in response to starvation to meet the energy needs of the cell or when there is an abundance of dietary lipids. Neutral lipolysis and autophagy are two pathways the cell uses to metabolize fat stored in LDs [13]. Autophagic degradation of lipids or lipophagy is a fairly recent discovery, first reported in 2009 [14]. Since then, it has been reported in a wide variety of cells [15; 16; 17; 18; 19], and in different species [20; 21; 22]. The ubiquitous nature of lipophagy across species suggests a conserved role of autophagy in cellular lipid metabolism. In this review, we describe the remodulation of the lipid metabolic profile that occurs in cancer cells. We note the role of TME in this process, and how this modulation of lipid metabolism is one of the underlying factors for tumor metastasis. Finally, we present the role of autophagy in mobilization of stored lipids in the form of LDs and its effect on cancer progression.

Lipid metabolism in the tumor microenvironment

Alteration in lipid metabolism, especially FA synthesis (FAS) and fatty acid oxidation (FAO), has increasingly become recognized as an important metabolic rewiring phenomenon in tumor cells [23] (Figure 1). Cytosolic acetyl CoA serves as a substrate for FA (FA) synthesis. Acetyl-CoA is generated when ATP citrate lyase (ACLY) catalyzes the conversion of citrate to oxaloacetate in the cytoplasm. High ACLY expression has been observed in gastric adenocarcinoma patients [24]. Moreover, genetic suppression of ACLY can reduce cell proliferation and invasion in prostate, lung, osteosarcoma and cervical cancers cells [25]. Acetyl CoA can be carboxylated to malonyl CoA and this reaction is catalysed by the enzyme acetyl-CoA carboxylase (ACC). ACC catalyses the rate limiting step of FAS pathway. There are two isoforms of ACC. The cytosolic ACC1 is present in lipogenic tissues, while the mitochondrial outer membrane bound ACC2 is predominantly present in lipid oxidizing tissues. Because of their differential subcellular location, the two isoforms perform different metabolic functions. ACC1 is involved in lipid synthesis and ACC2 in inhibition of lipid degradation. Enhanced expression of ACC1 has been linked to vascular invasion and disease recurrence in hepatocellular carcinoma patients [26]. Several preclinical studies have also shown the effectiveness of anticancer therapies targeting ACC1 [27; 28].

Fatty-acid synthase (FASN) is a multi-enzyme protein complex that catalyzes *de novo* biosynthesis of saturated fatty acids (SFA). The complex utilizes one acetyl-CoA molecule and a sequential addition of seven molecules of malonyl-CoA to form palmitic acid (16:0). Several studies have reported overexpression of FASN in a number of cancers including breast, prostate, ovarian, and colorectal [29; 30; 31]. Further, inhibition of FASN can inhibit proliferation, migration and invasion of hepatocellular carcinoma cells [32].

The end product of the FASN catalysed *de novo* lipogenesis pathway, palmitate, can be elongated by ELOVL6 (elongation of very long chain fatty acids protein 6) or be desaturated by SCDs (stearoyl-CoA desaturases). SCDs catalyze the conversion of SFA to Δ-9 monounsaturated FAs (MUFAs); e.g., conversion of palmitic acid (16:0) to palmitoleic acid (16:1) and conversion of stearic acid (18:0) to oleic acid (18:1). Humans are reported to have two isoforms of SCD, SCD1 and SCD5 [33]. SCD1 has been shown to be highly expressed in lung adenocarcinoma and was found to be important for cell proliferation, migration and invasion. Moreover, the study suggested SCD1 as a potential biomarker of lung adenocarcinoma [34]. A separate study showed delayed tumor growth in colorectal cancer mouse model on SCD1 inhibitor administration [35]. However, it is important to note that clinically, SCD1 inhibitors have not always proven to be effective therapeutics in humans [36].

In addition to enhanced *de novo* lipogenesis, tumor cells can acquire FAs through lipolysis to support growth. LPL is a key enzyme for extracellular lipolysis. The enzyme is responsible for hydrolysis of the TGs in circulating chylomicrons and very-low-density lipoprotein (VLDL). The FAs released by hydrolysis of circulating TGs can be taken up by the cells via CD36, a transmembrane channel protein for exogenous free FA uptake. High LPL activity was reported in non-small cell lung cancer tissue [37]. LPL has also been identified as a biomarker for poor prognosis in chronic lymphocytic leukemia [38]. In a

separate study, LPL was found to be upregulated in triple negative breast cancer cell lines [39]. Further, the study reported overexpression of CD36, in cancer cell lines. These findings suggest that certain cancer cells use LPL and CD36 to acquire diet-derived FA from the bloodstream by lipolysis which can fuel their growth.

FAs obtained through lipolysis are broken down through mitochondrial fatty acid β-oxidation pathway to meet the energy requirement of the rapidly proliferating cells [40]. FAO involves a cyclical series of reactions that result in the oxidation of β-carbon of the fatty acid. Each cycle of FAO leads to shortening of fatty acids by two carbons and generation of NADH, $FADH_2$ and acetyl CoA. NADH and $FADH_2$, generated by FAO, enter the electron transport chain (ETC) to produce ATP. FAO plays an important role in satisfying the energy needs of cancer cells and ensuring their survival and proliferation in acidic and hypoxic tumor environment. Evidence suggests that cancer cells chronically exposed to acidosis show increased FAO [41]. Due to acidosis, cancer cells show dramatic reduction of glucose derived acetyl-CoA. In such conditions, FAO contributes to the generation of acetyl-CoA which drives the tricarboxylic acid (TCA) cycle for energy production [41].

In addition to the role of FAO in driving the TCA cycle, acetyl CoA produced during the process of FAO is also used for FAS in cancer cells. This is supported by the findings that ACC1 (involved in FAS) is frequently found to be upregulated [30; 42] and ACC2 (involved in inhibition of FAO) inhibited in various cancers [43]. FAs are activated to form acyl CoA in the cytoplasm before they undergo FAO. Acyl CoA is transported to the mitochondrial matrix with the help of carnitine palmitoyltransferase 1 (CPT1) where FAO occurs. CPT1 is considered as the rate limiting enzyme for FAO. CPT1C, an isoform of CPT1, is known to be primarily expressed in the brain [44]. Zaugg and colleagues reported that CPT1C has oncogenic potential [45]. The study reported that CPT1C expression in cancer cells promoted FAO and ATP production, tumor growth, and rescued the cells from metabolic stress [45]. More recently, CPT1C was identified as a biomarker and key regulator of cancer cell senescence through mitochondria-associated metabolic reprogramming. The study went on to suggest that inhibition of CPT1C may be used as a therapeutic strategy for cancer treatment through induction of tumor senescence [46]. Unlike CPT1C, CPT1A, another isoform of CPT1, is expressed in many tissues and most abundantly in the liver. CPT1A is reported to promote metastasis in alveolar rhabdomyosarcoma cells by promoting cell motility [47]. Further, inhibition of CPTIA can result in impaired cancer cell proliferation in acute myeloid leukemia [48; 49].

Metabolic reprogramming by cells in tumor microenvironment

The TME is a highly complex combination of tumor and the neighboring cellular and molecular components. Cellular components of TME include stromal cells (blood and lymphatic endothelial cells, cancer associated fibroblasts (CAFs)), tumor-infiltrating lymphocytes (B cells, T cells and NK cells) and myeloid populations (dendritic cells, myeloid-derived suppressor cells and macrophages) [50]. Molecular components of the TME include chemokines, cytokines, extracellular matrix and the soluble immunosuppressive molecules. The cellular and molecular components of TME co-ordinately act to maintain a condition of chronic inflammation and immune suppression

which promotes tumorigenesis, progression, invasion and immune-evasion of tumor [51]. There is a cross-talk between neighboring cells in stromal and cancer cells, and this is essential for cancer cell survival and proliferation.

It has been reported in colon and ovarian cancers that endothelial cells trigger metabolic reprogramming by inducing an over-expression of poly-unsaturated fatty acids (PUFA) and glycerophospholipids in cancer cells [52]. These changes in fatty acid metabolism are essential for tumor progression and aggression [52]. Recently, CAFs have also been shown to enhance lipid synthesis due to over-expression of FASN. Cancer cells over-express fatty acid transporter protein 1, which mediates uptake of FAs from CAFs [53]. Tumor associated dendritic cells are responsible for initiation and maintenance of immune responses. Studies suggest that tumor associated dendritic cells show abnormal lipid accumulation induced by ER stress response factor XBP1. Lipid accumulated dendritic cells were found to be ineffective in presenting tumor-associated antigens thereby promoting kidney, thyroid, ovarian and head and neck cancer [54; 55].

The lipid-activated transcription factors, peroxisome proliferator-activated receptors (PPARs) are a group of nuclear receptors that play a role in regulating lipid homeostasis. The PPAR family comprises of three members: PPARα, PPARβ/δ, and PPARγ. Numerous studies have established the role of PPARα in lipid and lipoprotein metabolism [56; 57]. PPARα has a central role for increasing FAO in hepatocytes [58]. PPARβ/δ promotes FA catabolism in skeletal muscle and may suppress macrophage derived inflammation [59]. In cancers, PPARβ/δ plays an important role in apoptotic cell clearance. In mice, dead cancer cells polarize tumor activated macrophages into an IL-10 expressing, pro-tumor phenotype by inducing FASN and PPARβ/δ activation [60]. However, this has not been demonstrated in a human model to date. This is important to note because the role of PPARβ/δ in cancer remains controversial, with some studies showing that activating this PPAR promotes cancer while others indicate that activating this PPAR isoform inhibits cancer [61; 62; 63]. PPARγ induces differentiation of preadipocytes into adipocytes and stimulates triglyceride storage [64]. Several studies indicate that activation of PPARγ suppresses tumor development and progression by making the TME less hospitable for tumor growth and metastasis [65; 66]. PPARγ and FASN expression have recently been reported to be positively correlated with human prostate cancer [67]. However, similar to PPARβ/δ, the role of PPARγ in some cancers remains controversial. For example, there are ongoing clinical trials examining whether PPARγ agonists may be effective for preventing or treating cancer [63]. Another lipid activated transcription factor, the liver X receptor (LXR), also plays an important role in modulating the TME. Apoptotic tumor cells containing oxysterols activate LXR in macrophages causing suppression of dendritic cell migration and recruitment of neutrophils in tumors resulting in tolerance and immunosuppression [68].

The role of lipid metabolism in metastasis

The metastatic potential of cancer cells positively correlates with the expression of genes involved in fatty acid synthesis, oxidation and intracellular lipid storage. Metabolic alterations are important in metastasis of melanoma, breast and prostate cancers. Enzymes involved in lipid metabolism have been shown to play a role in metastasis. For example,

SCD and long chain fatty acyl synthetase (ACSL) 1 and 4 cooperate to induce epithelial to mesenchymal transition resulting in an increased invasion potential of colon cancer cells [69]. This is further supported by findings that inhibition of these enzymes restores epithelial features and restricts cancer cell growth. More recently, a study reported over-expression of genes involved in fatty acid uptake (CAV1, CD36, PPARα) and *de novo* lipogenesis (MLXIPL) in metastatic tumors [70]. A separate study reported an association between metastatic potential and levels of several phospholipids including phosphatidylcholine (PC), phosphatidylinositol (PI), phosphatidylethanolamine (PE) and phosphatidylserine (PS) in metastatic breast cancer cell line. The study reported that higher metastatic potential strongly correlated with higher levels of PS 18:0/20:4, PI 18:0/20:4, and PC 18:0/20:4. On the other hand, lower metastatic potential correlated with lower levels of PE 18:1/18:1 and PI 18:0/18:1 [71].

Dietary lipid dependence of metastasis-initiating cells has recently been reported in melanoma- and breast cancer. Inhibition of fatty acid translocase CD36 was shown to impair metastasis [72]. Conversely, over-expression of CD36 significantly increased lymph node metastasis of oral squamous cell carcinoma cell lines with low metastatic potential [72]. These findings establish fatty acid receptor CD36 as a marker and functional driver of metastasis in a lipid metabolism-dependent manner. CD36 has been associated with progression and poor prognosis in several other tumor types, such as glioblastoma and hepatocellular carcinoma. Metastatic-initiating cells are also characterized by a distinct lipid metabolic signature related to fatty acid degradation, *de novo* lipogenesis and lipid storage. In invasive ductal carcinoma, acetyl-CoA synthetase 2 (ACSS2), an enzyme that catalyzes the conversion of acetate to acetyl-CoA, was found to be overexpressed under hypoxic and lipid depleted conditions. ACSS2 increases acetate consumption and thereby fatty acid biosynthesis in harsh TME and scarcity of alternate carbon sources for lipogenesis [73].

Lipid rafts are highly dynamic lipid microdomains in the plasma membrane. They are known to be rich in cholesterol and sphingolipids. The highly dynamic nature of lipid rafts are known to be important for cancer metastasis [74; 75; 76; 77; 78]. Edelfosine, a synthetic analog of ether phospholipid, has been shown to accumulate in lipid rafts and induce apoptosis in several hematopoietic cancer cells [79; 80]. Palmitoylation of the CD44 antigen, a cell-surface glycoprotein cell adhesion and migration, facilitates its sequestration in lipid rafts and was shown to influence migration of invasive breast cancer cells [75]. A separate study showed that cholesterol depletion disrupts lipid rafts, and enhances microdomain-dependent CD44 shedding, thereby suppressing tumor cell metastasis in human glioma and pancreatic cancer cells [77].

Lipophagy in cancer

As discussed above, both lipid uptake and *de novo* lipogenesis can be enhanced in cancer cells. Complementary lipid degradation mechanisms are required to serve the purpose of energy generation, biosynthesis of membranes, and synthesis of other biomolecules.

Lipid droplets

The surplus lipids in a cell do not exist in the form of non-esterified free fatty acids (FFAs) because FFAs have a potential for cytotoxicity at high concentration [81]. Therefore, cells store excess fatty acids and cholesterol in the form of neutral, inert biomolecules such as sterol esters and TGs in cellular structure called lipid droplets or LDs [82; 83]. LDs are intracellular deposits of lipids surrounded by a layer of phospholipids and finally separated from the hydrophilic cytosol by structural proteins known as perilipins (PLINs) [84; 85; 86]. Stored lipids in the form of LDs with sizes ranging from 0.1–10 μm are present in all cells, however in the adipose tissue they coalesce to form a single large droplet with sizes up to 100 μm. Apart from size, the content of LDs in adipose tissue also differs from other cells. While lipids are stored in the core of LDs as cholesterol and triglycerides, only triglycerides are predominant in the core of LDs in adipose tissue [87; 88]. Cancer cells are characterized with upregulation of FAS and FA uptake, leading to increased accumulation of LDs. This is supported by studies which show that a phenotype of abundant LDs in cells is a marker for colorectal cancer [89] and is also associated with lung cancer [90]. Recent studies have also linked LD abundance with increased aggressiveness [91], as well as to chemotherapy resistance [92] of tumors.

Lipophagy

The mobilization of lipids from LDs is mediated by lipolysis (Figure 2). The dynamic interactions between cytosolic lipases with inhibitory proteins (also present in cytosol) and perilipins regulates the rate of lipolysis [93]. Cells initiate lipolysis to meet their energy requirement as well as on overabundance of lipids to prevent stores from being compromisingly enlarged. Previously, mobilization of lipids in LDs by lipolysis was perceived to be entirely carried out by LD associated lipases. However, recent findings indicate that autophagy serves as an alternate pathway [14]. Autophagy is a catabolic process which involves self degradation of cellular components [94]. Degradation of cellular organelles and proteins is the most well studied function of autophagy. It has been well established that under nutrient stress, autophagy degrades cellular components to provide the cells with essential building blocks as well as to satisfy its energy needs. Most of these studies were focused on protein degradation by autophagy to release amino acids which could be later used as building blocks or to provide substrates for energy. However, recent studies suggest that autophagy has a role in degradation of lipids to release free fatty acids which are a highly efficient source of energy as compared to amino acids or carbohydrates. Lipophagy was initially demonstrated in hepatocytes [14; 95]. Since this original observation a variety of cell types like adipocytes [19], enterocytes[18], glial cells [17], T cells [16], neurons [15] have also exhibited lipophagy under conditions of lipotoxicity or nutrient stress. Interestingly, lipophagy has also been reported in rice [96], yeast [22], C.elegans [21] as well as some fungi [20]. Therefore, lipophagy seems to be a well-conserved mechanism of lipid degradation.

Singh and colleagues showed that lysosomes do not directly fuse with LDs [14]. LDs as a whole or a part thereof is encapsulated in a double membrane autophagosome which then provides its components to lysosomes for degradation [14]. It has been proposed that LD surface proteins (PLINs) act as gatekeepers of LDs, with their degradation being a pre-

requisite for lipolysis to occur. Degradation of PLINs has been shown to correlate with lipolysis [97; 98] with both being induced under starvation. The former group showed that polyubiquitination of PLINs tags them for proteasomal degradation. Kaushik and Cuervo show that PLINs are targeted for chaperone mediated autophagic (CMA) degradation [97]. HSC70 binds with PLIN2 and PLIN3 by recognising a canonical pentapeptide motif present in both proteins. The HSC70 and PLIN complex binds with lysosome associated membrane protein 2A (LAMP2A), leading to their uptake and simultaneous degradation by lysosome. Kaushik and Cuervo show that blocking of CMA results in decreased association of cytosolic lipases and autophagic machinery with LDs and thereby reduced LD degradation [97]. Thus, cross-talk between proteolytic and lypolytic machinery of cell regulates LD turnover. The mechanism underlying the recognition of LDs by autophagic machinery and involvement of any receptors still remain unanswered. Poly-ubiquitination with specific lysine linkages are a well established tag for lysosomal degradation of proteins. However, the role of poly-ubiquitination in lipophagy remains unclear. Interestingly, an Ube2g2 (E2 ubiquitin conjugase G2) interacting protein, ancient ubiquitous protein (AUP1) has been shown to associate with LDs. This may be involved in tagging LDs for lysosomal degradation [99]. However, as LDs are known to sequester several proteins [100], the specificity of this interaction to LD degradation needs to be further studied. Apart from polyubiquitination as a signal for specific autophagic degradation of LDs, autophagy selective receptors may also be involved in conferring selectivity to lipophagy. One such receptor of interest is Huntingtin, which acts as a scaffold for component recognition by autophagy [101]. Importantly, cells lacking functional Huntingtin exhibit lipid accumulation [102]. Therefore, the possibility of Huntingtin as a lipophagic receptor for LD recognition should be explored. A separate study reports that LC3, an autophagic protein involved in autophagosome biogenesis is capable of binding the phospholipid, cardiolipin [103]. It may therefore be presumed that LC3 may directly recognize LD lipids. Further studies are therefore warranted to establish the molecular mechanisms behind specific recognition of LDs by lipophagic machinery.

The relationship between autophagy and cancer is complex and unclear. Autophagy is reported to show both positive and negative effects on tumor progression [104]. Autophagy catabolizes damaged proteins and organelles like mitochondria and peroxisomes, which are potential sources of ROS. Autophagy thus protects the cell from oxidative stress damage and chronic inflammation [105; 106]. In the presence of intracellular stress, autophagy eliminates the damaged and toxic cellular components to ensure cellular homeostasis. Mathew and colleagues showed that the absence of autophagy led to an accumulation of protein aggregates and ER chaperones which led to an activation of the DNA damage response [107]. In addition to preventing genetic mutations, autophagy may also hinder the growth of mutation bearing cancer cells [88]. Therefore, as a cytoprotective mechanism which plays the role of cell’s garbage disposal system, autophagy may prevent tumor initiation and progression. However, autophagy is responsible for the metabolic plasticity which is characteristic of cancer cells. Therefore, autophagy may play an essential role in survival of cancer cells in oxygen, pH, and nutrient stress [108; 109; 110].

Lipophagy also plays a dual pro- and anti-cancer role. A tumor suppressor function has been ascribed to lysosomal acid lipase (LAL), with their activity associated with tumorigenesis

and metastasis [111]. LAL deficiency results in an abnormal haematopoiesis leading to an abundance of immature myeloid-derived suppressor cells (MSDCs). MSDCs mediate suppression of immune surveillance and thus evasion of host immunity by the tumor [112]. In addition, it is reported that LAL deficiency induced MSDCs can directly stimulate tumorigenesis and metastasis [113]. By contrast, a tumor suppressor role for LAL is suggested by studies showing that expression of LAL improves lipid metabolism, as well as reduces metastasis in lung and liver cancer [114; 115]. Another recent study reported that lipophagy mediates ER stress induced apoptosis [116]. Moreover, lipophagy impairment correlates with poor patient prognosis and survival [117; 118; 119]. Apart from its tumor suppressor role, lipophagy-dependent degradation of lipids, may provide the rapidly proliferating cancer cells with energy substrates and intermediates for synthesis of biomolecules, thus helping them survive [120]. These studies though still preliminary, provide an insight into the significance of hitherto underappreciated role of lipophagy in cancer metabolism. Thus, it is clear that further studies are needed to determine the role of lipophagy in cancer, which could vary depending on tumor type, and the stage of tumorigenesis.

It is now well established that metabolic adaptations are important for cancer cell survival and proliferation. The TME has an essential role in the metabolic adaptation of cancer cells. To meet the nutrient requirements of the rapid cell proliferation of cancer cells, multiple substrates other than glucose are likely needed. It has been suggested that lipids may be a major alternate fuel supporting cancer cell proliferation. Redirecting lipid metabolism in tumor cells and its role in tumor progression and metastasis has received widespread attention in recent years. The role of autophagy in degradation of lipids stored in the form of lipid droplets in now increasingly recognized in the regulation of lipid homeostasis. Despite major advancement in our understanding of lipophagy, many questions still remain unanswered. (i) Whether cross-talk occurs between neutral lipolysis and lipophagy, and if so, under what circumstances? (ii) Is selectivity and specificity involved in degradation of LDs by lipophagy? (iii) Is a subset of lipids preferentially degraded by lipophagy over others? (iv) What are the structural and functional characteristics of the lipophagic machinery? Finally, characterization of the mechanistic details of lipophagy perturbations in tumor progression is required to fully take advantage of its potential as a target for novel cancer chemoprevention and chemotherapy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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ABBREVIATIONS

ACC	Acetyl-CoA carboxylase

ACLY	ATP citrate lyase
ACSS	Acetyl-CoA synthetase
AUP1	Ancient ubiquitous protein
CAF	Cancer associated fibroblast
CMA	Chaperone mediated autophagy
CPT	Carnitine palmitoyltransferase 1
DAG	diacylglycerol
ER	Endoplasmic reticulum
FA	Fatty acid
FAO	Fatty acid oxidation
FAS	Fatty acid synthesis
FASN	Fatty-acid synthase
FAT	Fatty acid translocase
FFA	Free fatty acid
HSC70	Heat shock cognate 71 kDa protein
LAL	Lysosomal acid lipase
LAMP	Lysosomal-associated membrane protein
LD	Lipid droplets
LPL	Lipoprotein lipase
LXR	Liver X receptor
MSDC	Myeloid-derived suppressor cells
MUFA	Monounsaturated fatty acid
PIP3	Phosphatidylinositol-3,4,5-trisphosphate
PLIN	Perilipin
PPAR	Peroxisome proliferator-activated receptors
PUFA	Poly-unsaturated fatty acid
ROS	Reactive oxygen species
SCD	Stearoyl-CoA desaturase
SFA	Saturated FA

SFA	Saturated fatty acid
TG	Triglycerides
TME	Tumor microenvironment
Ube2g2	E2 ubiquitin conjugase G2

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Highlights

- Alterations in lipid metabolism modulate tumor development and progression
- Lipophagy plays a central role in regulating lipid homeostasis in tumors
- The role of lipophagy in cancer remains underappreciated

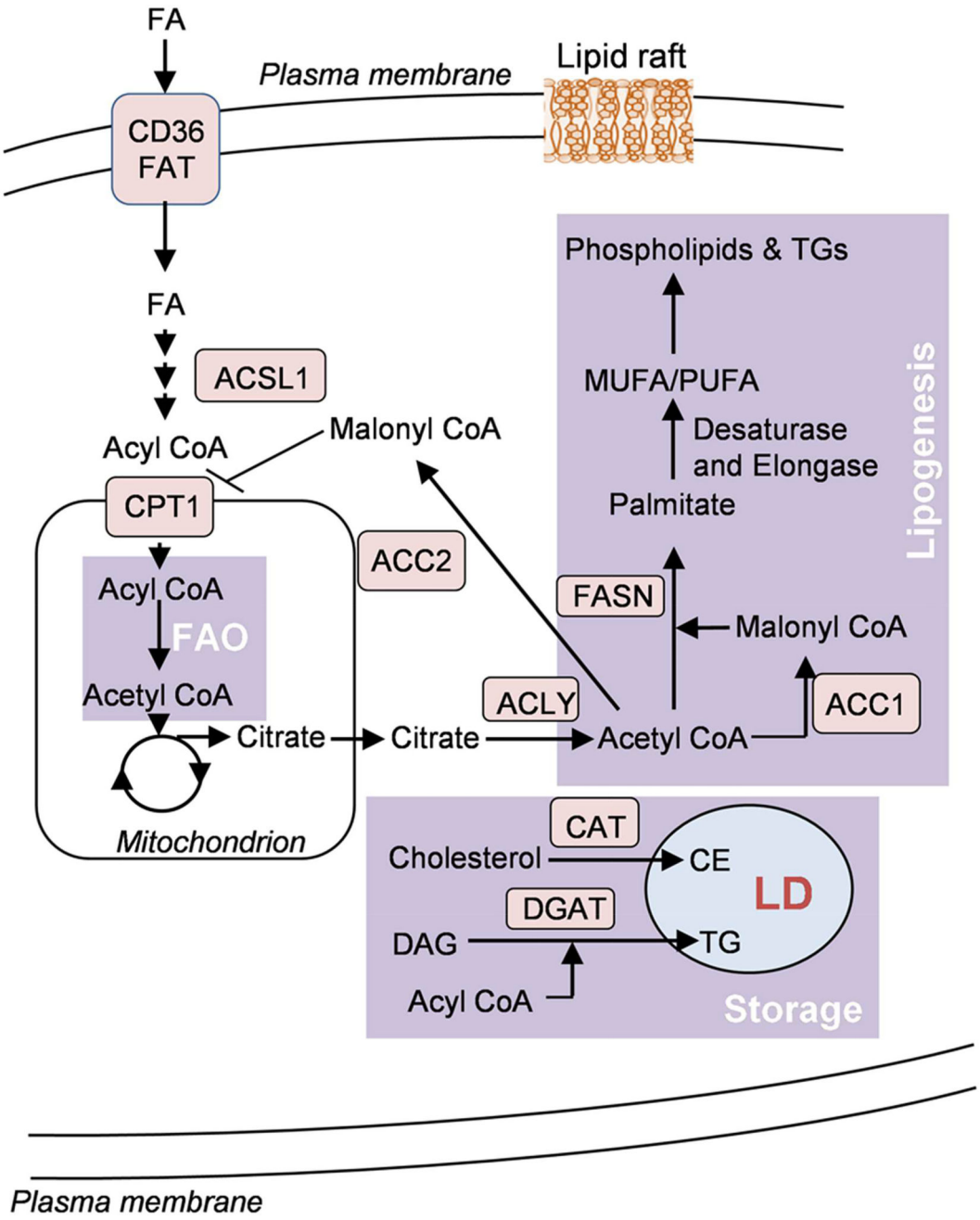

Figure 1.

A simplified schematic representation of lipid metabolism in tumor cells. Tumor cells show altered lipid metabolic networks involving catabolism (fatty acid oxidation (FAO)), biosynthesis pathways (de novo lipogenesis) and storage as lipid droplets (LDs). Cancer cells show increased fatty acid (FA) uptake by fatty acid translocase (FAT), CD36, which then undergo β-oxidation in the mitochondrial matrix. Acetyl CoA, the end product of FAO pathway, can then either enter TCA cycle or may be transported to the cytosol in the form of citrate for fatty acid synthesis. Excess acyl CoA can undergo esterification with cholesterol

or diacylglycerol (DAG) to form cholesterol ester (CE) or triacylglycerol (TG) and is stored in the form of lipid droplets.

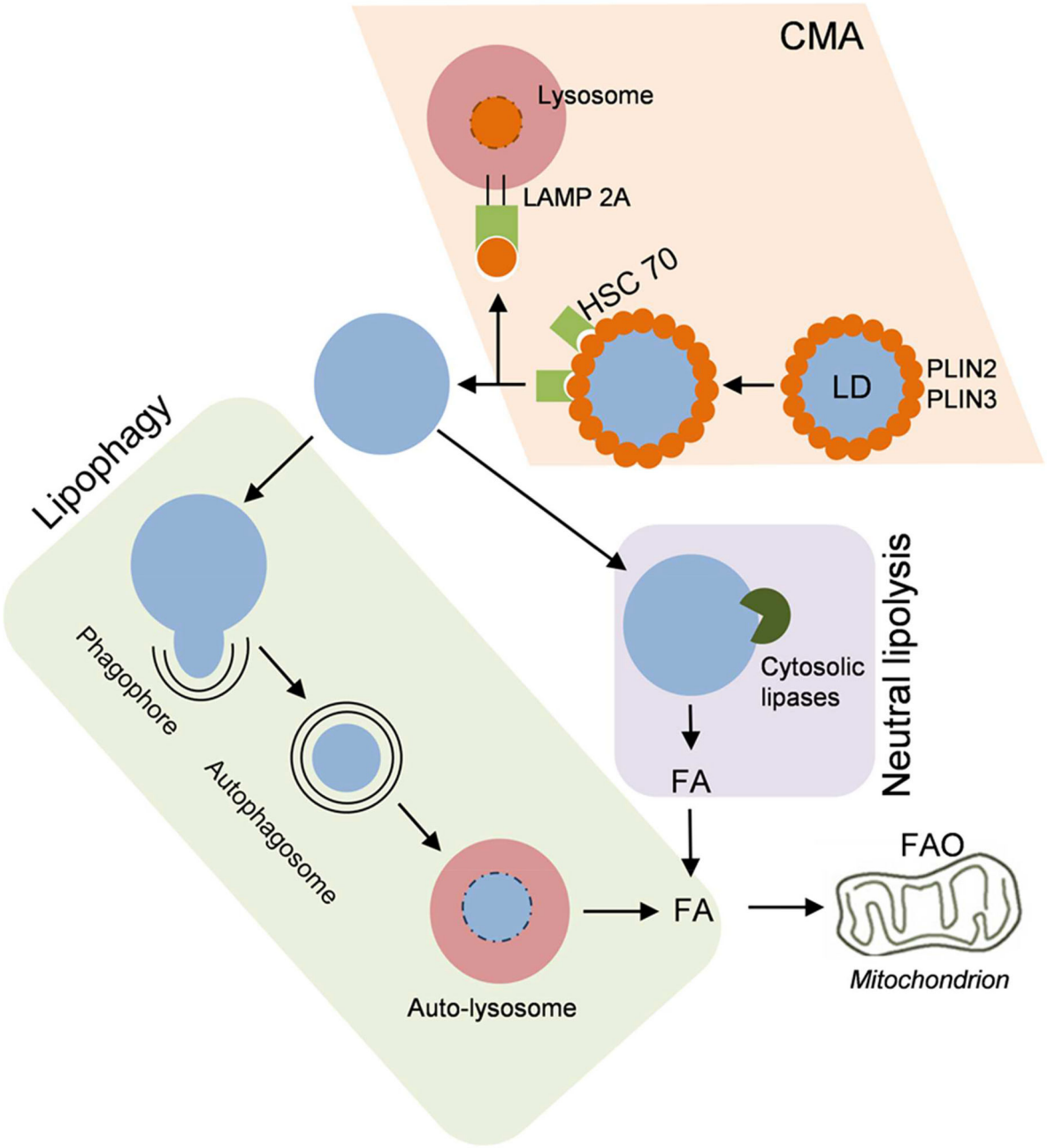

Figure 2.

Schematic representation of Lipolysis: Lipid droplet surface proteins PLIN2 and PLIN3 are degraded via chaperone mediated autophagy (CMA). Consequently the LD surface is exposed for the action of neutral cytosolic lipases and lipophagic machinery. A double membrane engulfs a part of or whole LD, thus forming autophagosome which fuses with lysosome to form autolysosome. Lysosomal acid lipases act on the lipids to form free fatty acids. Cytosolic lipases directly act on LD surface to degrade lipids to fatty acids.

Subsequently, β-oxidation of fatty acids takes place in mitochondria to generate energy and metabolic intermediates.