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REVIEW **Open Access**

Lipid metabolic reprogramming in tumor microenvironment: from mechanisms to therapeutics

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Abstract

Lipid metabolic reprogramming is an emerging hallmark of cancer. In order to sustain uncontrolled proliferation and survive in unfavorable environments that lack oxygen and nutrients, tumor cells undergo metabolic transformations to exploit various ways of acquiring lipid and increasing lipid oxidation. In addition, stromal cells and immune cells in the tumor microenvironment also undergo lipid metabolic reprogramming, which further affects tumor functional phenotypes and immune responses. Given that lipid metabolism plays a critical role in supporting cancer progression and remodeling the tumor microenvironment, targeting the lipid metabolism pathway could provide a novel approach to cancer treatment. This review seeks to: (1) clarify the overall landscape and mechanisms of lipid metabolic reprogramming in cancer, (2) summarize the lipid metabolic landscapes within stromal cells and immune cells in the tumor microenvironment, and clarify their roles in tumor progression, and (3) summarize potential therapeutic targets for lipid metabolism, and highlight the potential for combining such approaches with other anti-tumor therapies to provide new therapeutic opportunities for cancer patients.

Keywords Lipid metabolism, Tumor microenvironment, Cancer progression, Immune response, Targeted therapy

Introduction

Metabolic reprogramming has emerged as a critical feature of cancer. To adapt to the hypoxic and nutrient-poor microenvironment, in addition to increasing glucose uptake and aerobic glycolysis, tumor cells also undergo lipid metabolism reprogramming to enhance their biological behaviors [1]. This is characterized by increased lipid uptake, lipid synthesis, fatty acid oxidation (FAO), and lipid storage. Mounting evidence demonstrated that lipids play a critical role in cancer progression by serving as energy sources, membrane structures, signaling molecules (including bioactive lipids like S1P, PGE2, and LPA), and even causing epigenetic modifications through fatty acylation of key molecules [2, 3]. Mechanically, alterations in lipid metabolic phenotype in tumor cells are directly driven by continuous oncogenic events and extracellular tumor microenvironment (TME) factors such as hypoxia, acidosis, and nutritional alterations [4, 5].

In addition to supporting tumor development, lipid metabolic reprogramming also modifies the TME by influencing the recruitment, activation, and function of immune cells and stromal cells. Tumor cells and cells in TME interact with each other and form a reciprocal

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entity [6]. On one hand, tumor cells can actively modify the TME by secreting signaling molecules and metabolites, which affect the functions of cancer-associated fibroblasts (CAFs) and immune cells in TME [6]. On the other hand, lipid metabolic reprogramming, an adaptive change in cells within the TME, manifests as increased lipid uptake and accumulation, or FAO, driving the TME toward an immunosuppressive phenotype supporting tumor progression [7]. For example, upregulated lipid uptake and FAO increase lipid metabolic levels in regulatory T cells (Tregs), tumor-associated macrophages (TAMs), and myeloid-derived suppressor cells (MDSCs), facilitating their immunosuppressive function [8–10]. Moreover, upregulation of CD36 in $CD8^+$ T cells leads to excessive lipid accumulation, which impairs secretion of anti-tumor factors such as IFN-γ and TNF-α, ultimately suppressing their anti-tumor efficacy [11, 12]. Similarly, upregulation of CD36 in natural killer (NK) cells also impairs their tumor-killing activity through intracellular lipid accumulation. Studies have suggested that blocking lipid uptake via inhibition of CD36 on cytotoxic $CD8^+$ T cells or Tregs enhances anti-tumor immune responses [8, 11].

Given the critical role of lipids in cancer progression, targeting to lipid metabolism-related pathways offers new therapeutic opportunities for cancer. A large body of evidence shows that inhibitors targeting lipid uptake, lipogenesis, and FAO in tumor cells have shown significant therapeutic effects in various cancers [13–15]. Besides, modulating lipid metabolism in stromal cells and immune cells also provides a new choice for anti-tumor therapy. Moreover, it can be combined with chemotherapy and immunotherapy, providing a new comprehensive strategy for optimizing cancer treatment. This review aims to clarify the lipid metabolic landscape in tumor cells and TME cells, and summarize potential targets to offer clues for further research and clinical applications of targeting lipid metabolism in cancer.

Landscape and mechanisms of lipid metabolic reprogramming in cancer

Lipid metabolic reprogramming in cancer

Most lipid molecules in the human diet are triacylglycerols (TAGs) and cholesterol. After absorption, TAGs can be hydrolyzed into glycerol and fatty acids (FAs). Glycerol is then converted into glycerol-3-phosphate (G-3-P), which enters glycolysis. FAs can either be stored as the primary component of membrane synthesis or converted to acyl-CoA for β-oxidation to provide energy. In tumors, several steps of lipid metabolism show universal enhancement to maintain their biological progressions. This includes increased lipid uptake, synthesis, storage, and FAO. To delve deeper into these lipid metabolic alterations, the following section provides an in-depth analysis (Fig. 1).

Lipid uptake in cancer

The increase in intracellular lipid content can be achieved through two pathways: endogenous and exogenous pathways. Endogenous lipids are primarily produced through de novo lipogenesis (DNL), which utilizes acetyl-CoA as a substrate. Exogenous lipids require the involvement of transport molecules, including CD36, fatty acid transport protein family (FATPs/SLC27), and fatty acid-binding proteins (FABPs) [4]. Notably, recent studies have established a link between the overexpression of these transport molecules and the poor prognosis across various cancers. For instance, CD36 overexpression is associated with a poor prognosis in breast, ovarian, gastric, colorectal, and prostate cancer [15]. Moreover, FABPs have been found to contribute to the promotion of cervical cancer metastasis by increasing intracellular Fas [16], while knockdown of FABPs suppressed tumor progression in vivo by inhibiting lipid uptake in glioblastoma [17]. FATP members have been implicated in cancer initiation and progression in melanoma and breast cancer in multiple studies [18, 19].

Lipid synthesis in cancer

Although the exogenous lipid sources increase, cancer cells also activate DNL to respond to their high metabolic demands[2]. This pathway begins with acetyl-CoA, which can be mainly generated from citrate, a substrate in the TCA cycle during nutrient catabolism, via ATP-citrate lyase (ACLY). Besides, acetate conversion via acetyl-CoA synthetase (ACSS) is another pathway to produce acetyl-CoA for DNL. Acetyl-CoA is activated by acetyl-CoA carboxylases (ACCs) to form malonyl-CoA, which is further catalyzed by fatty acid synthase (FASN) to form saturated fatty acids (SFA), palmitate (C16:0). The resulting palmitate can be elongated by elongation of very-long-chain fatty acids gene family (ELOVLs) and desaturated by stearoyl-CoA desaturases (SCDs) or fatty acid desaturases (FADSs) to synthesize monounsaturated fatty acid (MUFA), such as oleic acid (OA) (C18:1) and palmitoleic acid (C16:1). Moreover, desaturation caused by ELOVLs and FADSs converts ingested polyunsaturated fatty acids (PUFAs) like linoleic acid (LA) (C18:2) and alpha-linolenic acid (ALA) (C18:3) into other PUFAs like arachidonic acid (AA) (C20:4) and adrenic acid (AdA) (C22:4) [20, 21]. Interestingly, overexpression or increased activity of ACLY has been correlated with the progression of various cancers [22]. ACSS is transcriptionally upregulated by SREBP, highly expressed in tumor cells, and plays a role in maintaining cancer cell growth under nutrient deficiency by catalyzing acetate [23]. FASN is commonly

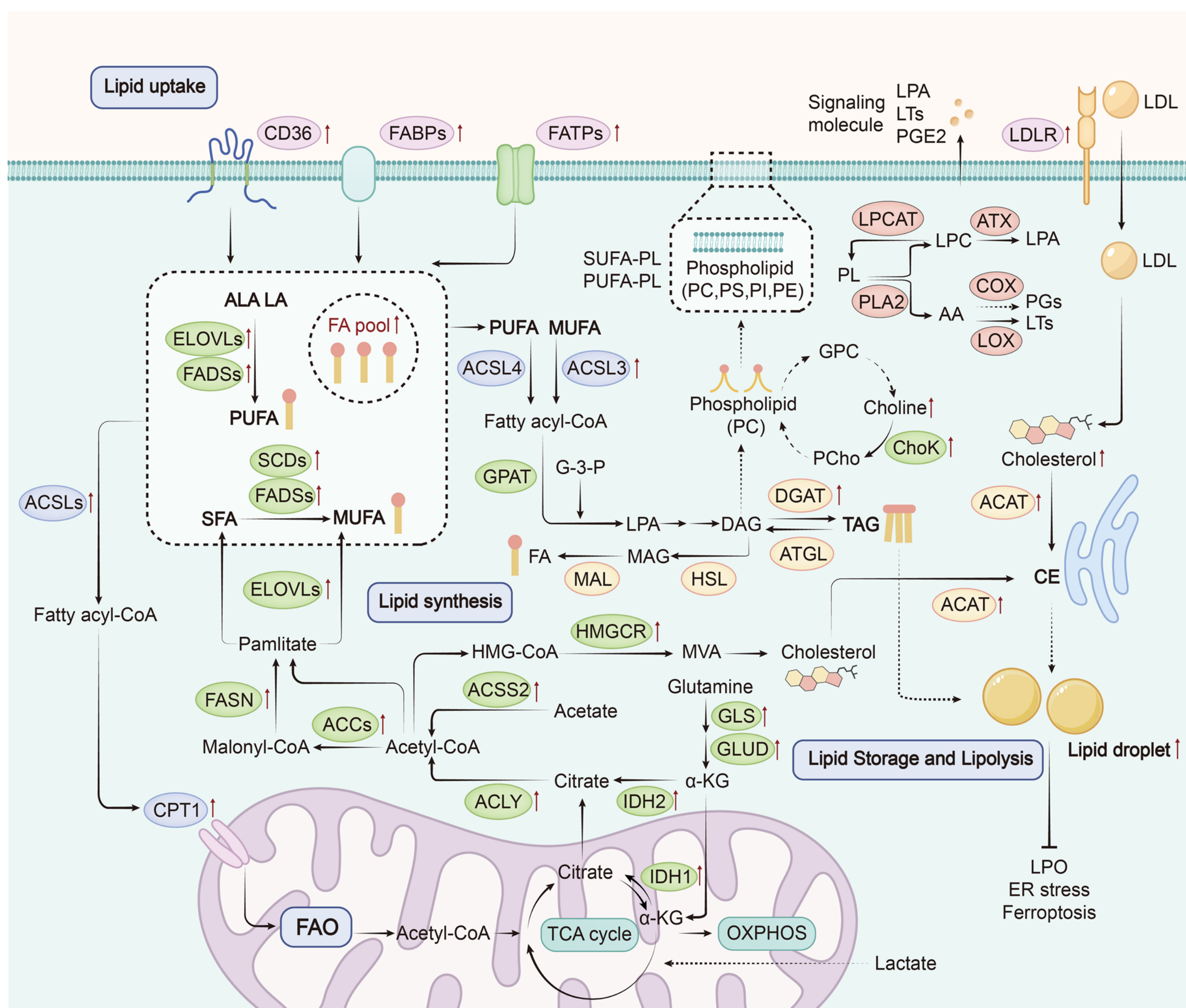

Fig. 1 Lipid metabolic reprogramming in cancer. Tumor cells enhance lipid metabolism by increasing exogenous lipid uptake and lipid synthesis, leading to increased intracellular lipid content. Upregulation of lipid transport proteins such as CD36, FATPs, FABPs, and LDLR increases lipid uptake. These upregulations increase intracellular SUFA, PUFA, and cholesterol levels. Meanwhile, endogenous lipid synthesis originates from citrate in the TCA cycle, as well as intracellular glutamine, lactate and acetate, leading to the synthesis of SFA and cholesterol. The process is catalyzed by key enzymes such as FASN and SCD. FAs in tumor cells are catalyzed by ACSL to form acyl-CoA, which is involved in the subsequent synthesis of intracellular phospholipids with bioactive lipids and FAO. Acyl-CoA facilitates the translocation of enzymes into mitochondria through CPT1, the key enzyme of FAO, participating in the production of acetyl-CoA, providing energy for the biological behavior of tumor cells. Excess lipids in tumor cells are stored in LD as CE and TAG. This storage significantly prevents LPO and attenuates its risk of mediating tumor cell death

overexpressed in many epithelial and precancerous lesions and is associated with a high risk of cancer recurrence and mortality [24]. Inhibition of FASN can suppress breast cancer growth in the brain, highlighting its potential as a therapeutic target for metastasis in breast cancer [25]. SCD1 facilitates the formation of MUFAs, including OA, and its increased expression has been shown to promote the progression of cancers [26, 27].

In oncogenic processes, tumor cells utilize other metabolic substances in the microenvironment, such as glutamine and lactate, as sources of lipid synthesis. Glutamine dependence has been considered a metabolic hallmark of cancer cells. A growing body of evidence has shown that glutamine uptake and synthesis is upregulated in various cancers [28]. Cellular glutamine undergoes a transformation into α-ketoglutarate through the activation of glutaminase (GLS) and glutamate dehydrogenase (GLUD), ensuring the replenishment of vital metabolic intermediates within the TCA cycle. Subsequently, α- ketoglutarate is carboxylated by isocitrate

dehydrogenase (IDH) to generate citrate [29]. In addition to glutamine, lactate is also an important source of TCA cycle intermediates and acetyl-CoA [30]. A recent study identified that lactate in the TME can reprogram lipid metabolism by increasing the expression of the genes involved, promoting tumor progression [31]. Notably, lactate promotes glutamine uptake and catabolism in oxidative cancer cells [32]. Therefore, utilizing glutamine and lactate to produce acetyl-CoA as a source of lipid synthesis is one of the important indirect ways for tumor cells to regulate lipid metabolism.

The synthesis of triacylglycerol (TAG) from long-chain fatty acids (LCFAs) derived from lipid intake and DNL involves a series of enzymatic reactions. Specifically, glycerol-3-phosphate acyltransferase (GPAT) catalyzes the combination of LCFAs with G-3-P to generate lysophosphatidic acid (LPA), which is a crucial intermediate in TAG synthesis. LPA is then converted to diacylglycerol (DAG) and subsequently to TAG via diacylglycerol acyltransferase (DGAT) [33]. Notably, DAG is also involved in compound lipid synthesis, such as cholesterol and phospholipids, which play critical roles in supporting key oncogenic functions and cancer hallmarks, and in regulating intercellular communication and immune responses [34].

Cholesterol, like other lipids, relies on acetyl-CoA for intracellular synthesis. Activating key enzymes in the mevalonate (MVA) synthesis pathway, such as HMG-CoA reductase (HMGCR), enables cholesterol biosynthesis. MVA is further modified to generate a variety of cholesterol for important biological processes such as membrane biosynthesis. Excess cholesterol is eliminated from the cell through ATP-binding cassette transporter A1 (ABCA1) [35]. In addition, low-density lipoproteins (LDLs) are taken up through membrane receptors (LDLRs), and high LDLRs levels promote LDL cholesterol-mediated breast cancer growth [36]. Reprogramming of cholesterol metabolism in tumors is mainly characterized by increased levels of intracellular cholesterol synthesis and abnormal metabolite accumulation [35]. This upregulation of cholesterol metabolism in both tumor cells and TME can promote oncogenic processes, such as tumor initiation, migration, and angiogenesis [37, 38].

Phospholipid (PL) synthesis, using DAG as a precursor, is enhanced in cancer, which regulates biological behaviors such as metastasis and drug resistance by modulating changes in membrane lipid composition and producing bioactive lipid second messengers [39]. Phosphatidylcholine (PC) is the predominant phospholipid in most cellular membranes. An increase in PC synthesis, along with elevated levels of choline cycle metabolites such as choline, phosphocholine (PCho), and glycerophosphocholine (GPC), has emerged as a significant hallmark of malignant transformation in tumors [40]. PC metabolic enzyme, choline kinase (ChoK), has been observed to be activated in various cancers [41]. Studies both in vitro and in vivo have shown that overexpression of ChoKα contributes to tumor progression, metastasis, and aggressiveness [42, 43].

In addition, PL catabolism is mediated by phospholipases (PLA2, C, and D), which can be recycled for PL biosynthesis and modulate various lipid-mediated signaling pathways promoting tumorigenesis. PL can also be hydrolyzed by PLC and PLD, producing DAG and phosphatidic acid (PA). This sustains the activity of key oncogenic signaling pathways involving PKC and mTOR [44]. Importantly, a significant portion of PL is hydrolyzed by PLA2, leading to the production of lysophosphatidylcholine (LPC) and AA. Subsequently, under catalysis of a series of enzymes, various lipid-derived mediators, including LPA, PGs, LTs, and S1P, are generated within tumor cells. LPC is catalyzed by lysophosphatidylcholine acyltransferases (LPCATs) to be reconverted into PC. Under the action of autotaxin (ATX), LPC is converted to LPA [45]. Similarly, AA participates in lipid mediator biosynthesis, producing prostaglandins (PGs) through cyclooxygenase (COX) and leukotrienes (LTs) through lipoxygenase (LOX). And sphingosine-1-phosphate (S1P) is also derived from sphingomyelin. These lipid-derived mediators are released extracellularly and act as crucial signaling molecules that mediate the crosstalk between the tumor and the TME for cancer progression [46].

Lipid storage in cancer

Increased uptake and endogenous synthesis of lipids in tumor cells lead to an increase in the cellular lipid pool. Acyl-CoA cholesterol acyltransferase (ACAT) converts free cholesterol to cholesteryl ester (CE) within the endoplasmic reticulum (ER) membrane, while excess intracellular FAs are ultimately converted into TAG by DGAT. These lipids are then stored as CE and TAG within lipid droplets (LD) in cells, reducing cell damage caused by peroxidation of free lipids within the cell [47, 48]. Lipids stored in LD can provide ATP response to metabolic stress by undergoing β-oxidation to produce acetyl-CoA. LDs serve as a critical reservoir of unsaturated FAs that cancer cells can use to maintain the function of cell membranes and organelles, particularly when there is an increased demand for lipids, such as during rapid oncogene-driven cell growth or a hypoxic environment [48]. Additionally, another key function of LDs is to protect cancer cells under ER stress and oxidative stress [49]. DGAT1, a key protein in lipid accumulation, promoting LDs formation and protecting cancer against

lipid peroxidation, has been found to play indispensable oncogenic roles in melanoma and glioblastoma [50, 51].

Lipolysis in cancer

Degradation of TAG in LD can be initiated by adipose triglyceride lipase (ATGL), hydrolyzing TAG to produce DAG. DAG is then hydrolyzed by hormone-sensitive lipase (HSL) and monoacylglycerol lipase (MAL) to release FFA. Given that lipid synthesis and LD accumulation are common metabolic characteristics of cancers, ATGL, the key enzyme for LD mobilization, is generally downregulated in most cancer cells [52]. Recent research suggests that enhanced ATGL expression exerts an anti-tumor effect in triple-negative breast cancer cells [53]. In hypoxic cancer cells, LD is significantly accumulated, which is resulted by the activation of hypoxia-inducible gene 2 (HIG2) to inhibit ATGL-mediated lipolysis [54, 55]. However, ATGL upregulation in tumor exhibits pro-tumor effects in some adipose-infiltrated cancers, including colorectal and breast cancer [56, 57]. In coculture systems, breast cancer cells exhibit increased proliferation and migration after acquiring FAs from adipocytes, which is dependent on the lipolysis induced by ATGL in both adipocytes and cancer cells [57]. Besides, ATGL also play a crucial role in the development of colon cancer driven by obesity [58]. These studies indicate that lipolysis acts as a double-edged sword in cancer progression, and the underlying mechanisms require further elucidation.

Lipid oxidation in cancer

As FAs uptake and storage increase, FAs catabolism in cancer cells is often enhanced. The survival and metastasis of cancer cells also rely on the uptake and consumption of FAs. FAO serves as an energy source for tumor cells under nutrient-deficient conditions. Carnitine palmitoyl transferase 1 (CPT1), the rate-limiting enzyme involved in mitochondrial FAO of LCFAs, mediates the entry of FAs into mitochondria. Once FAs enter the mitochondrial matrix, they are oxidized to generate acetyl-CoA, which enters the TCA cycle to produce ATP. The long-chain acyl-CoA synthase (ACSL) enzyme family plays an important role in FAO and lipids biosynthesis, facilitating the production of fatty acyl-CoA [59]. Tumors exhibit high FAO activity by upregulating CPT1A expression. Moreover, upregulation of CPT1A expression can promote EMT and stemness, leading to the invasive and metastatic capabilities of cancer cells [60, 61].

Lipid peroxidation (LPO) is prone to occur in PUFA-phospholipids (PUFA-PLs), resulting in the accumulation of lipid peroxidation within cells, which is caused by an imbalance in the ratio of intracellular PUFA to MUFA. This phenomenon is commonly associated with an increase in PUFA due to LD synthesis inhibition or a decrease in MUFA due to downregulation of enzyme activity involved in MUFA synthesis. LPO is significant in mediating ferroptosis and is often inhibited in progressing tumors [62, 63]. LDs, essential mediators of free unsaturated FA (especially PUFA) storage, regulate LPO and susceptibility to ferroptosis [64]. Upregulation of DGAT promotes LD synthesis in glioblastoma and gastric cancer cells. Inhibiting the formation of LDs by silencing DGATs can induce LPO and ferroptosis, thereby inhibiting cancer cell metastasis [50, 65]. Maintaining MUFA-phospholipid (MUFA-PL) levels in the cell membrane is critical for tumor cells to avoid ferroptosis. ASCL3, which is upregulated in various cancers, mainly catalyzes MUFA generation to form fatty acyl-CoA, promoting the synthesis of MUFA-PLs [59]. Furthermore, ACSL4 promotes the increase of membrane PUFA-PL levels by acting on PUFA, an essential therapeutic approach for tumor by increasing LPO and inducing ferroptosis [66]. Inhibition of the key enzyme SCD1 in gastrointestinal cancers reduces MUFA production, inducing ferroptosis and exerting anti-tumor effects [67, 68]. As research progresses, inducing the accumulation of lipid peroxides and promoting ferroptosis have become potential targets for anti-tumor therapy through lipid metabolism.

Oncogenic cues affecting tumor lipid metabolism

Activation of oncogenes and loss-function of tumor suppressor genes are the main causes of tumorigenesis. They also play an important role in reprogramming tumor metabolism by regulating lipid metabolic enzyme expression [4]. Sterol regulatory element-binding proteins (SREBPs) act as key upstream regulators of lipid metabolism. SREBP is a transcription factor that promotes DNL by upregulating key enzymes such as ACLY, FASN, and SCD, which are closely linked to tumor proliferation, apoptosis, and invasion [69]. Moreover, SREBP maintains intracellular cholesterol levels by inducing LDL receptor-mediated cholesterol uptake and inhibiting ABCA1-mediated cholesterol export in a mTORC1-dependent manner [70]. Downstream lipid reprogramming events are induced by SREBPs and mutations in oncogenes such as PI3K and MYC, as well as tumor suppressor genes such as p53 and PTEN (Fig. 2a).

PI3K mutation

The dysregulation of the PI3K-AKT signaling pathway is a frequent occurrence in cancer and leads to metabolic reprogramming, where SREBPs play a crucial role as downstream regulatory targets. This pathway can be activated by various upstream signaling events, such as receptor tyrosine kinase (RTK) signaling or oncogenic mutations in PIK3CA [71]. By increasing lipid

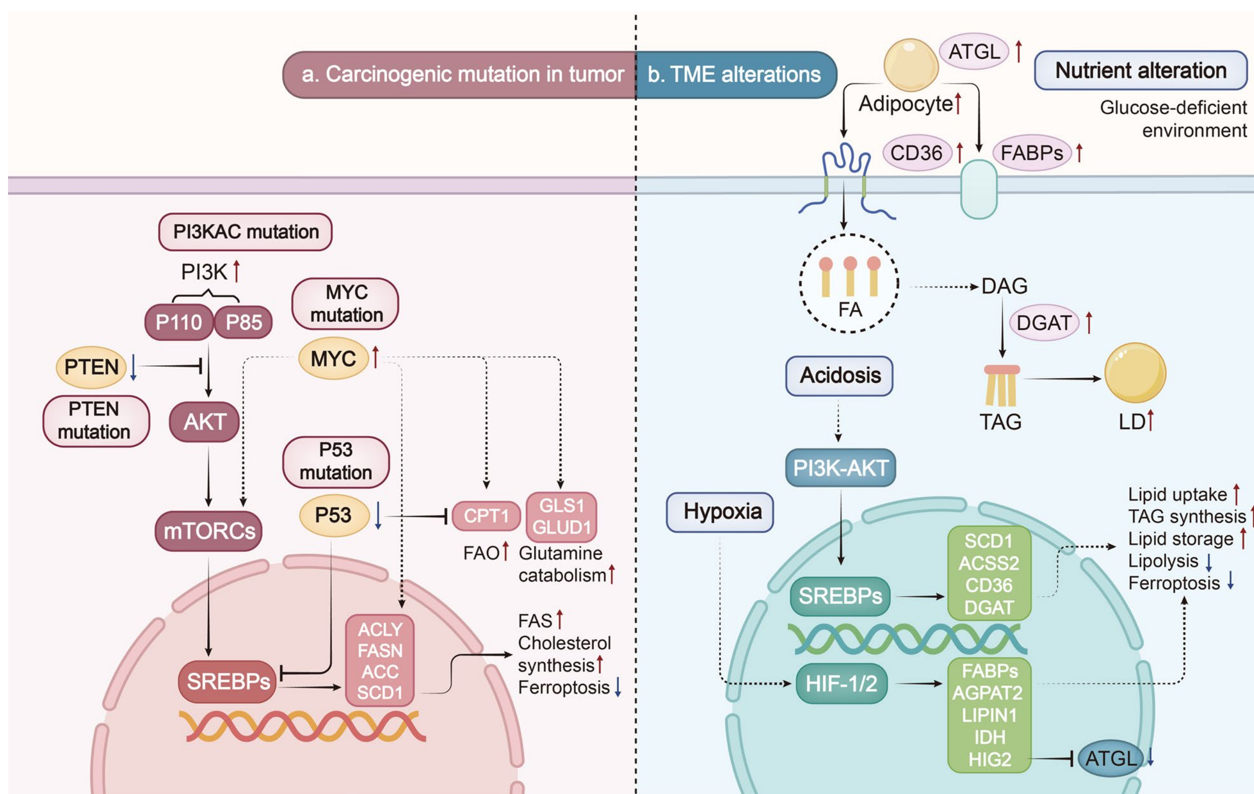

Fig. 2 Lipid metabolic alterations induced by oncogenic events and TME cues. Alterations in lipid metabolism in tumor cells are driven by oncogenic events and tumor environmental cues, such as hypoxia and nutritional deficiency conditions. **a** Activating mutations in oncogenes (such as MYC) and inactivation of tumor suppressor genes (such as p53 and PTEN) often occur in various tumor cells. Alterations in these genes subsequently upregulate the expression of key enzymes involved in lipid metabolism by regulating the PI3K-AKT-mTOR signaling pathway to activate transcriptional activity of SREBPs, or acting directly on key enzymes. As a consequence, lipid metabolism in tumor cells is enhanced. **b** TME encompasses various factors such as hypoxia, acidosis, and nutrient deficiency that promote tumorigenesis and cancer progression through reprogramming lipid metabolism in tumors. Lipid uptake, synthesis, and intracellular lipid accumulation are significantly upregulated in TME by activating key signaling pathways and enzymes

synthesis, this pathway promotes the occurrence and progression of liver cancer [72, 73]. The tumor suppressor PTEN is a critical negative regulator of the PI3K/AKT pathway, and its mutation can also activate this pathway [74]. Research has demonstrated that the loss of PTEN and the activation of PI3K/AKT lead to LD synthesis, contributing to prostate cancer progression [75]. In xenograft mice models of PIK3CA mutant breast cancer and PTEN-deficient prostate cancer, the excessive activation of the PI3K-AKT-mTOR signaling protects cancer cells from LPO and ferroptosis by SREBP1/SCD1-mediated MUFA synthesis [69]. Similarly, recent studies have shown that aspirin inhibits mTOR/SREBP-1/SCD1-mediated MUFA production and induces ferroptosis in PIK3CA mutant colorectal cancer [76]. In summary, the PI3K-AKT signaling may prove to be a potential therapeutic strategy for treating cancer as a metabolic disease.

P53 mutation

TP53, which encodes the tumor suppressor p53, is a commonly mutated oncogene in human cancers. p53 can bind directly to the promoter region of SREBP-1 and transcriptionally inhibit its expression, affecting downstream expression of key enzymes (ACLY, FASN) involved in lipogenesis [77]. Additionally, p53 suppresses the pentose phosphate pathway (PPP), which decreases NADPH production required for lipid synthesis [78, 79]. In breast cancer, p53 mutants have been shown to promote cancer progression by increasing cholesterol synthesis through enzymes involved in upregulation of the mevalonate pathway, highlighting the potential to target this pathway for p53-mutated tumors [80]. Moreover, the expression of genes key to FA synthesis (FASN, ELOVL6, and SCD1) is increased in p53-mutated tumors, while p53 transcription induces CPT1, which increases FAO and reduces intracellular lipid accumulation [81].

MYC mutation

MYC, a commonly activated oncogene in tumors, is known to promote transcriptional activation of genes involved in cell cycle, cell growth, and metabolism [82]. In addition to activating SREBP1, MYC directly regulates the expression of key enzymes involved in FA synthesis, such as ACLY, ACC, FASN, and SCD1, which have been shown to drive tumorigenesis in hepatocellular carcinoma (HCC) [83–85]. MYC also cooperates with SREBP2 to upregulate HMGCR for cholesterol metabolic reprogramming, contributing to the malignant phenotypes of tumor cells [86, 87]. Moreover, MYC-driven cancer cells exhibit enhanced glutamine utilization, with increased expression of key glutamine-metabolizing enzymes, including GLS1 and GLUD1, as well as the transporter protein SLC1A5 [88]. This augmented glutamine catabolism results in mitochondrial metabolic reprogramming to accommodate the replenishment requirements of the TCA cycle, supplying substrates for DNL, thereby sustaining cell vitality and growth [89]. What's more, breast cancer cells with MYC overexpression show increased dependence on FAO for bioenergetics. Inhibiting FAO markedly diminishes the energy metabolism of these cells, suggesting that targeting FAO could be a potential therapeutic strategy for breast cancer [90, 91].

Microenvironment factors affecting tumor lipid metabolism

Metabolic reprogramming of cancer cells is the result of a multifactorial process. Along with the activation of oncogenic signals caused by mutations in tumor cells, TME also plays a crucial role [92]. The TME encompasses various factors such as hypoxia, acidosis, and nutritional deficiencies, which promote tumor initiation and cancer progression by altering lipid metabolism in tumor cells (Fig. 2b).

Hypoxia

The rapid proliferation of solid tumors consumes a large amount of oxygen, leading to hypoxia as a typical feature of almost all TME [93]. The resulting hypoxia inhibits the pyruvate metabolic pathway of glucose, resulting in decreased citrate content in the TCA cycle. As citrate, the primary substrate for DNL, decreases, cancer cells turn to alternative carbon sources such as glutamate or acetate to produce acetyl-CoA for FA synthesis [2, 94]. Hypoxic tumor cells utilize glutamine and synthesize citrate under IDH1 catalysis, a process that relies on the expression of hypoxia-inducible factor (HIF1) [95, 96].

In addition to alterations in glucose metabolism, lipid metabolism also undergoes changes in hypoxic tumor cells. FA catabolism is dependent on oxygen, and tumor cells often inhibit FAO through various pathways. Hypoxia-activated HIF-1α and HIF-2α downregulate CPT-1 expression, which prevents FAs from entering the mitochondria for β-oxidation [97, 98]. As a result, FAs are redirected to LD storage, leading to increased lipid accumulation [99]. Additionally, HIF-1α upregulates FABPs expression in hypoxia, promoting FA uptake and lipid storage by regulating the expression of key enzymes involved in TAG synthesis [17, 100]. In clear cell renal cell carcinoma (ccRCC), hypoxia increases intracellular LD synthesis in a HIF-2α-dependent manner, which plays a crucial role in sustaining ER homeostasis and aggressive tumor behaviors [101]. Furthermore, HIF-1 upregulates the expression of low-density lipoprotein receptor-related protein 1 (LRP1) to promote lipoprotein endocytosis and the lipids storage in LDs, providing energy for cells during hypoxia [102, 103].

In summary, hypoxia induces genes involved in FA uptake, synthesis, and storage, leading to an overall increase in intracellular lipid content. The inhibition of key enzymes involved in FAO also supports lipid accumulation under hypoxia, and the accumulation of lipids in LDs helps sustain malignant behaviors of tumors [104].

Acidosis

TME is characterized by hypoxia and acidosis, both of which contribute to the metabolic reprogramming of tumor cells. Hypoxia results in lactate accumulation and H^+ build-up, which alter the metabolic pathways of cancer cells and promote tumor metastasis [105]. Lactate activates the expression of the SLC1A5 and GLS1 to promote glutamine transport and catabolism, which provides substrates for the TCA cycle [32]. In the absence of acetyl-CoA produced by glycolysis in an acidic microenvironment, tumors rely heavily on FAO to generate energy by converting LCFAs into acetyl-CoA and producing NADH and FADH2 [106]. Interestingly, in tumor cells, an acidic environment upregulates CD36 and DGAT expression, promoting exogenous lipid uptake and the formation of LDs, thereby promoting metastasis through a TGF-β2-dependent mechanism [107]. Acidosis also stimulates fatty acid synthesis (FAS) and promotes hepatocarcinogenesis through activating the PI3K/AKT pathway, upregulating SCD1, and promoting its binding to peroxisome proliferator activated receptor-α (PPARα) [108]. Additionally, an acidic TME triggers SREBP2 activation in tumors, leading to upregulation of the downstream key enzyme ACSS2, which provides suitable growth conditions for cancer cells in the acidic environment. These findings suggest that an acidic TME and SREBP2 activation is associated with reduced overall survival of cancer patients [109].

Nutrient alteration

The rapid proliferation of tumors requires continuous acquisition of nutrients from the microenvironment, resulting in a nutrient-deficient TME[105, 110]. In obese phenotypes, changes in metabolic spectra within tumor tissues result in the accumulation of lipids in adipocytes within the TME [111, 112]. Consequently, tumor cells must alter their metabolic patterns to enhance the utilization of lipids for energy supply to sustain their biological behaviors. In fat-rich TME, cancer cells can produce cytokines that induce ATGL-dependent lipolysis in the adipocytes surrounding the tumor, resulting in the release of FFAs [113]. These FFAs are then taken up by cancer cells via CD36 and FABP3/4 to form LDs, which act as energy sources for malignant cells. Moreover, lipid transfer from adipocytes to cancer cells can also be facilitated by extracellular vesicles (EVs) [114, 115]. Adipocytes in the TME have been shown to act as metabolic regulators that promote the growth and survival of colon cancer cells [116]. When co-cultured with breast cancer cells, the consumption of TAGs within adipocytes is increased, which in turn transfers adipocyte-derived FFAs to breast cancer cells, increasing CPT1A levels and driving FA metabolism in cancer cells [117].

Dietary factors affecting tumor lipid metabolism

Dietary interventions can change metabolite levels in the TME, which may then affect cancer cell metabolism to alter tumor growth [118]. Obesity and excessive high-fat diets (HFDs) are associated with increased overall and cancer-specific mortality, especially among patients with breast, colon and uterine cancer [119]. Excessive adipose expansion during obesity causes adipose dysfunction and inflammation to increase systemic levels of proinflammatory factors. Cancer-associated adipocytes can enter the TME to enhance pro-tumor effects [120]. In obese mouse models, HFDs increase the number of LGR5^{+} intestinal stem cells and activate the lipid metabolism transcription factor PPARγ for their tumorigenic potential [121]. Importantly, fat-mediated inflammatory signaling and the immunosuppressive microenvironment in tumors are the main causes of tumor metastasis [122]. For instance, HFD-induced obesity leads to CD8^{+} T cell exhaustion by reducing the production of granzymes and cytokines (IFN-γ and TNF-α), ultimately accelerating tumor growth in mouse models [123, 124]. Moreover, HFDs can induce lipid accumulation in prostate tumors in a SPREP-dependent manner, facilitating metastasis in mouse models [125]. Similarly, chronic HFDs alter biological behaviors, including angiogenesis and proliferation, in breast cancer [126].

Notably, different types of dietary lipids exhibit heterogeneity in driving the biological behavior of tumors. A study demonstrates that dietary palmitic acid, in contrast to OA or LA, enhances metastasis in oral carcinomas and melanoma in mouse models [127]. SFA intake is associated with an enhanced MYC signaling and poorer outcome in prostate cancer patients [128]. OA can also favor survival and chemotherapy resistance in gastric cancer [129]. Mechanistically, HFDs raise systemic FA levels, including SFAs and unsaturated FAs, which further enhances FAO, producing enough energy to facilitate tumor progression. In addition, two essential FAs: ALA (ω-3 PUFA) and LA (ω-6 PUFA), play proinflammatory and anti-inflammatory roles in tumors, respectively. In patients with metastatic colorectal cancer, primary tumors exhibit significantly elevated levels of ω-6 PUFAs and reduced levels of ω-3 PUFAs compared to those in patients with non-metastatic cancer [130]. Dietary LA stimulates invasion and peritoneal metastasis of gastric cancer through COX-1-catalyzed lipid metabolism [131]. Consequently, alterations in dietary lipid consumption, adopting a low-fat eating pattern or increasing ω-3 PUFAs intake, may represent a selective anti-tumor therapy.

Landscape and mechanisms of lipid metabolic reprogramming in tme

As cancer progresses, the TME also undergoes lipid metabolic reprogramming. It is worth noting that tumor cells play a significant role in modifying TME (e.g., acidosis, lipid accumulation) by producing metabolites and lipid-related signaling molecules. This in turn influences metabolic patterns and immune phenotype of TME cells, resulting in immune microenvironment remodeling [65]. For example, the secretion of lipids by CAFs in the TME promotes tumor progression by directly supplying energy sources to tumor cells. What's more, lipid metabolic reprogramming in CAFs also influences its own cytokine secretion function, which subsequently modulates the immune responses and promotes the formation of an immunosuppressive microenvironment. In addition, alterations in lipid metabolism patterns in immune cells also favor the construction of an immunosuppressive microenvironment, supporting tumor immune escape. Therefore, tumor progression is the result of a co-evolutionary process between tumor and TME. Moving forward, this section will focus on lipid metabolic alterations in TME cells and their interactions with tumor cells (Fig. 3).

Lipid metabolic reprogramming in CAFs

Cancer-associated fibroblasts (CAFs), an important stromal cell type in the TME, are activated by TGF-β and LPA signaling in TME [132, 133]. They synthesize and secrete lipids and bioactive lipid signaling molecules,

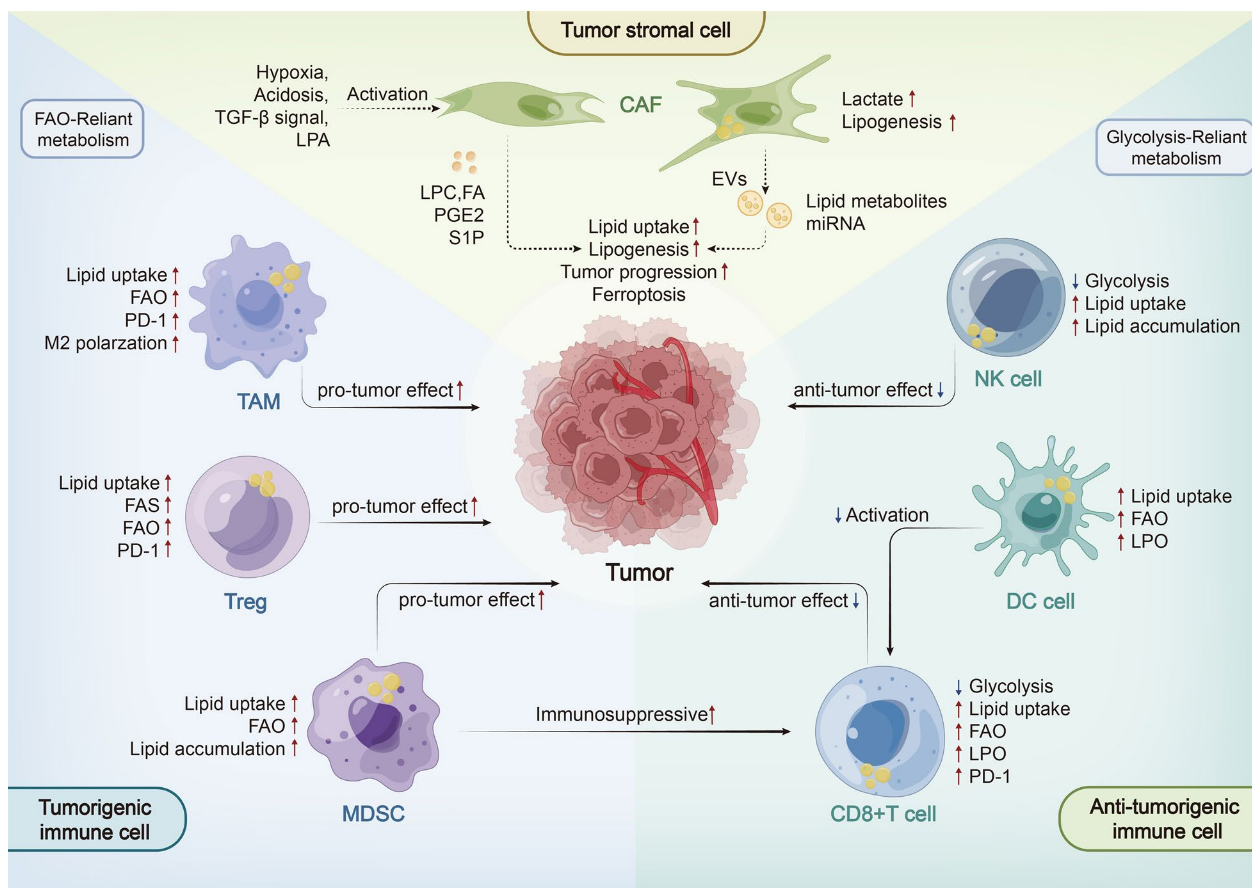

Fig. 3 Lipid metabolism landscape in TME. Tumor cells have the ability to educate TME cells into a pro-tumor phenotype by secreting metabolites and signaling molecules, such as cytokines and bioactive lipids, to TME, which further facilitates cancer progression. For instance, CAFs activated by tumor cells lead to increased levels of lipid synthesis, which serve as an essential energy source for tumor cells and induce the formation of an immunosuppressive microenvironment through secreting EVs and signaling molecules. Besides, tumor-infiltrating CD8$^+$ T cells and NK cells also exhibited increased lipid uptake and FAO. Similarly, lipid accumulation in TAMs also regulates their polarization and functional phenotypes. Increased lipid uptake and FAO in immunosuppressive cells, such as Tregs and MDSCs, further enhanced their pro-tumor effects. Taken together, lipid metabolic reprogramming facilitates crosstalk between tumor cells and TME cells, fueling tumor cells and changing functional phenotypes of TME cells

playing an essential role in tumor metabolic alteration, proliferation, invasion and immune responses [134]. To adapt to the TME, CAFs undergo lipid metabolic reprogramming characterized by an increase in lipid synthesis, storage, and secretion by upregulating key enzymes like FASN and SCD [135, 136]. This constructs a microenvironment with lipid accumulation, leading to metabolic reprogramming and biological behavior enhances in tumors [115, 137].

In the hypoxic and nutrient-poor microenvironment, CAFs upregulate SCD1 expression via HIF-1α, increasing the abundance of lipids such as OA in CAFs, resulting in promoting lung cancer growth [136, 138]. Therefore, targeting SCD1 in CAFs could be a promising therapeutic strategy. Recent metabolomics studies have shown that CAF-derived lipids enhance lipid uptake in tumor cells, promoting peritoneal metastasis of colorectal cancer [139]. This phenomenon also depends on the upregulation of CPT1 in CAFs, which enhances FAO and shapes the TME for colorectal cancer metastasis [140].

In addition, CAFs shape lipid metabolism and biological behavior of tumor cells by secreting biologically active lipid molecules and EVs containing small molecules and lipid metabolites [20, 141, 142]. Overexpressed biologically active lipids, such as LPC, in CAFs can be released into the TME and absorbed by tumor cells to promote tumor proliferation and migration through intracellular lipid metabolic reprogramming [135, 143]. Mechanistically, LPC is hydrolyzed by LPA in cancer cells, activating the AKT signaling pathway [144]. PGE2 and S1P in CAFs

also play vital roles in tumor progression in breast cancer and neuroblastoma [145–147]. What's more, a high concentration of proinflammatory cytokines secreted by CAFs supernatant can induce upregulation of cholesterol metabolism in prostate cancer cells, promoting androgen receptor therapy resistance [148]. miR-522, secreted from CAF-derived EVs, inhibits ferroptosis in cancer by targeting arachidonate lipoxygenase 15 (ALOX15) and blocking LPO [149]. In breast cancer, CAF enhances their exogenous lipid uptake capacity by inducing upregulation of FATP1 [150, 151]. Similarly, CAFs promotes colon cancer cells to absorb lipids secreted from CAFs through CD36, thereby promoting cancer cell migration [135]. Lactate secreted by CAF induces lipid metabolic reprogramming in prostate cancer, leading to the LD formation and mobilization, concurrently enhancing tumor invasiveness [31]. These evidences suggest that the signaling molecules and metabolites secreted by CAFs play an essential role in tumor progression and may become promising therapeutic targets in future [152].

Overall, the crosstalk between CAFs and cancer cells is mediated by lipid metabolic reprogramming that contributes to cancer progression, metastasis, and therapeutic resistance. Moreover, recent studies have shown that lipid metabolic reprogramming of CAFs also plays an important role in remodeling the tumor immune microenvironment. For example, $CD36^+$ CAFs recruit MDSCs through upregulating MIF expression, thus promoting immune escape in HCC. Inhibitors targeting to CD36 can restore the anti-tumor immune response in HCC and synergistically enhance the anti-tumor effect of anti-PD-1 therapy [153].

Lipid metabolic reprogramming in immune cells

Lipids are critical metabolites that support the biological activities of immune cells. Under normal conditions, immune cells with anti-tumor activity, such as effector $CD8^+$ T cells, NK cells, and M1 macrophages, depend on glycolysis for their maturation and function, whereas immune-regulatory cells such as Tregs, M2 macrophages, and MDSCs rely on FAO to exert their tumor immune suppression effects [115]. When tumors occur, lipid metabolism of tumor cells and stromal cells, such as adipocytes and CAFs, contributes significantly to the establishment of a TME characterized by low glucose and high lipid accumulation [115, 137, 154]. In such a TME, immune cells display increased immunosuppressive effects by regulating their lipid metabolism patterns, and subsequently promoting tumor progression [65]. For instance, lipid accumulation and enhanced FAO in TAMs contributed to its polarization to the M2 phenotype, which blocked anti-tumor T cell responses and supported the immunosuppressive function of T cells [155]. Increased uptake of oxidized lipids and enhanced lipid peroxidation in $CD8^+$ tumor-infiltrating lymphocytes (TILs) lead to their immune dysfunction, whereas lipid peroxidation resolution restored the functionalities of $CD8^+$ TILs in vivo [11] (Table 1).

$CD8^+$ T cells

$CD8^+$ TILs are an important component of anti-tumor immune cells, but their cytotoxic effects change to an exhausted state as cancer progresses [156–158]. In response to the limited nutrients and glucose in the TME, $CD8^+$ TILs experience a significant reduction in glycolytic activity. To sustain their anti-tumor functions, $CD8^+$ TILs undergo metabolic adaptation and promote FAO as an alternative energy source [159, 160]. However, excessively elevated lipid metabolism can lead to lipid peroxidation and ROS accumulation within the cell, further impairing their anti-tumor effects [161] (Fig. 4a).

$CD8^+$ TILs often undergo metabolic transitions to adapt to the hypoxia, glucose deficiency and lipid accumulation in the TME. This transition involves converting glycolysis to FAO, maximizing their activity to maintain their anti-tumor function. For instance, in a mouse model of obesity-associated breast cancer, $CD8^+$ TILs downregulate glycolytic activity and enhance FAO [162]. Additionally, $CD8^+$ T cells in MC38 colorectal cancer cell line and B16 melanoma cell line-bearing mice models show an FAO increase with the upregulation of CPT1 [163–165]. PD-1 signaling plays a crucial role in this process by affecting the PI3K and ERK pathways [166]. Enhanced PD-1 signaling in $CD8^+$ TILs promotes metabolic transition by STAT3 activation-mediated upregulation of FAO [162]. Similarly, the IL-9/STAT3 signaling maintains the anti-tumor effect by upregulating FAO activity, decreasing intracellular LPO and resisting ferroptosis in $CD8^+$ Tc9 (cytotoxic T lymphocyte subset 9) cells [165]. In addition, PPAR signaling also activates FAO in $CD8^+$ TILs. When TME changed to a state of hypoxia, glucose deficiency, or lipid accumulation, the PPARα signaling in $CD8^+$ TILs is activated, and the FAO within the cell is enhanced [163]. The PPAR agonist bezafibrate upregulates CPT1 to increase FAO, leading to enhanced anti-tumor effects during anti-PD-1 therapy in animal models [163, 164]. Interestingly, elevated tumor-intrinsic lipid metabolism can competitively inhibit T cells, leading to a decrease in lipid metabolism levels [167, 168]. These findings highlight that an appropriate increase of FAO in $CD8^+$ TILs can enhance their cytotoxic effects, especially when combined with anti-PD-1 therapy.

Lipid accumulation is a common metabolic alteration in the TME. Extensive studies have shown that excessive lipid accumulation is observed in exhausted $CD8^+$ TILs, where the fatty acids receptor is always upregulated.

Table 1 Lipid metabolism in immune cells

Immune cell	Lipid metabolic alteration	Effect on immune cells	Mechanism	Treatment Strategy	Reference
$CD8^+$ T cells	FAO↑	Maintained anti-tumor function through FAO upregulation	Promoted switch from glycolysis to FAO by PD-1; Activated the expression of PPAR, STAT3 signaling	Promoting FAO and related signals; Inhibiting metabolic conversion through PD-1 blockade	[162–166]
	Lipid uptake↑ LPO↑	Impaired $CD8^+$ T cell function for tumor progression	CD36 upregulation; Increased lipid accumulation for ferroptosis	Targeting CD36; Degrading lipid peroxides	[11, 161, 169–171]
Treg cells	Lipid uptake↑	Enhanced the immunosuppression effect	CD36 upregulation;	Targeting CD36	[8, 175]
	FAS↑ FAO↑	Elevated the level of Treg cell Enhanced the immunosuppression effect	Activated the expression of SREBP, PI3K and PD-1; FASN upregulation;	Targeting SREBP and PD-1	[175–179]
TAMs	Lipid uptake↑ FAS↑	Released pro-tumorigenic cytokines Enhanced the immunosuppression effect	CD36 upregulation; Increased LD accumulation	Targeting CD36	[155, 187–190, 192–194]
	FAO↑	Increased M2-like polarization; Enhanced the immunosuppression effect	Activated the expression of PPAR signaling; Enhanced the rate of FAO	Targeting FAO	[9, 187, 188, 196]
DCs	Lipid uptake↑ FAO ↑	Reduced the ability of T cell stimulation	Atg5 downregulation; CD36 and CPT1 upregulation;	Targeting FAO and CD36; PD-1 blockade	[199–201, 203]
	LPO↑	Impaired DC function for tumor progression	Activated the expression of XBP1; Lipid peroxide accumulation	Degrading lipid peroxides	[202]
NK cells	Lipid uptake↑ LPO↑	Impaired NK cell function for tumor progression	CD36 upregulation; Activated the expression of PPAR signaling; Increased lipid peroxide accumulation	Degrading lipid peroxides	[12, 207–210]
MDSCs	Lipid uptake↑	Enhanced the immunosuppression effect	FATPs, VLDLR and CD36 upregulation; Activated the expression of STAT3;	Targeting FTAPs and CD36	[10, 218–221]
	FAO↑	Enhanced the immunosuppression effect	CPT1 upregulation	Targeting FAO	[222]

Specifically, CD36 expression on $CD8^+$ TILs has been linked to tumor progression and poor survival rates in cancer patients [169]. In mice models of melanoma, colorectal cancer, and pancreatic ductal adenocarcinoma (PDAC), $CD8^+$ TILs have been reported to upregulate CD36 expression in order to facilitate extracellular lipid uptake [11, 169, 170]. However, excessive lipid accumulation can lead to elevated levels of intracellular cholesterol, LCFA, and ox-LDL, which in turn resulting in $CD8^+$ T cell exhaustion. Accumulated lipids, particularly oxidized low-density lipoprotein (ox-LDL), can increase intracellular LPO levels, ultimately resulting in ferroptosis and reducing the production of anti-tumor factors such as IFN-γ and TNF-α by activating p38, thereby impairing anti-tumor immune responses [11, 169]. Furthermore, LCFAs accumulation in $CD8^+$ T cells can impair mitochondrial function and reduce FAO, thereby suppressing the cytotoxic effects of $CD8^+$ T cells in PDAC [170].Increased cholesterol levels in $CD8^+$ T cells are also strongly associated with its functional exhaustion [161, 171], resulting from increased PD-1 and ER stress [161]. Therefore, inhibiting lipid accumulation in $CD8^+$ T cells, such as degrading lipid peroxides by glutathione peroxidase 4 (GPX4), is a feasible strategy for sensitizing immunotherapy [11].

Intriguingly, in contrast to the previous findings, ACAT1 inhibition has been shown to enhance the anti-tumor effect of $CD8^+$ T cells by increasing free cholesterol in the cytoplasm, which promotes membrane synthesis [172]. These results, along with other studies, suggest that the impact of cholesterol and other lipids on $CD8^+$ T cell function is largely dependent on their intracellular levels. Taken together, it can be concluded that optimal levels of lipids are necessary to maintain intracellular FAO and biological function, thereby sustaining the

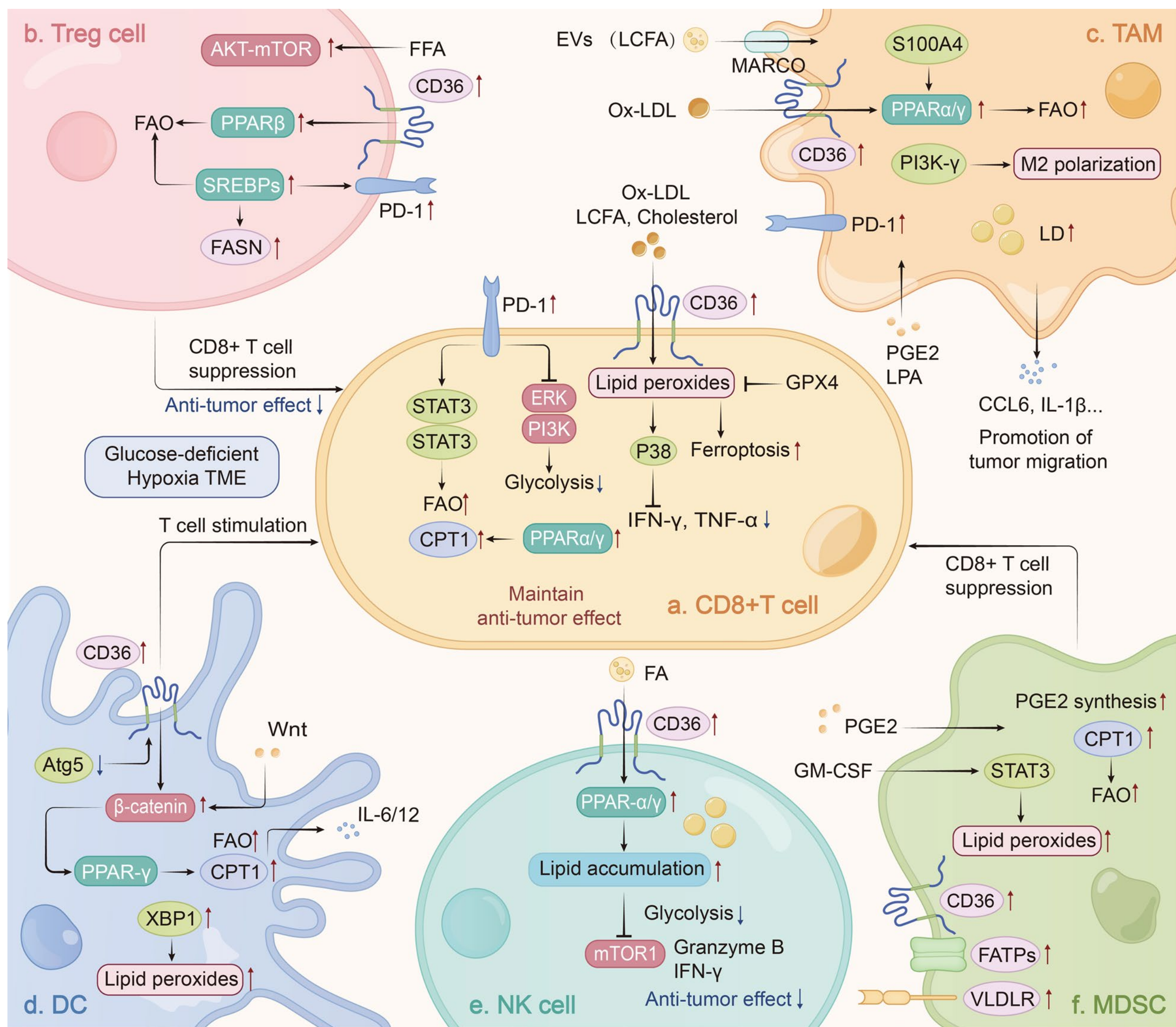

Fig. 4 Mechanism of lipid metabolic reprogramming in immune cells. A hypoxic, glucose-deficient, lipid-rich TME often educates immune cells into an immunosuppressive and pro-tumor phenotype by reprogramming their lipid metabolism. Immune cells in the TME undergo lipid metabolism reprogramming by directly absorbing excess lipids in the TME or enhancing their own lipid uptake, synthesis, and oxidation. Overexpression of PD-1 and CD36 on CD8^{+} TILs promotes metabolic transition by activating STAT3 or PPARs, which results in enhanced FAO (**a**). In Tregs cells, lipid metabolism is enhanced by CD36-PPARβ signaling, AKT-mTORC1 signaling, and SREBPs-mediated overexpression of FASN (**b**). TAMs can use lipids directly in TME or uptake exosomes containing LCFAs. FAO in TAMs is also enhanced by CD36-PPARs signaling (**c**). In DCs, NK cells, and MDSCs, CD36-PPARs signaling also plays a critical role in modulating their lipid metabolism (**d**–**f**)

effector state of CD8^{+} T cells, whereas excessive levels of lipids can lead to T cell exhaustion in the TME.

Treg cells

Regulatory T (Treg) cells in the TME dominate in weakening anti-tumor responses through secreting cytokines and expressing cell surface inhibitory receptors [173]. In fact, the overall lipid metabolism in Treg cells is upregulated, including lipid uptake, FAS, and FAO, which ultimately contributes to the immunosuppressive effect [174] (Fig. 4b).

Increased lipid uptake through the upregulation of CD36 is a prominent feature of Treg cells in the TME. This has been observed in mice models of colorectal cancer, melanoma, and glioblastoma, where upregulation of CD36 in Treg cells promotes lipid metabolism under environmental stresses [8, 175]. CD36-mediated intracellular lipid accumulation activates the PPARβ signaling pathway, which regulates mitochondrial metabolism

and further enhances the immunosuppressive function of Treg cells in tumor [8]. Therefore, targeting CD36 in Treg cells can be an effective approach to restore effective anti-tumor immune responses.

Increased lipid synthesis, including FA and cholesterol, is the predominant metabolic alteration in tumor-infiltrating Treg cells, which is facilitated by the action of SREBPs and their target genes [176]. FASN-mediated DNL contributes to the functional maturation of Treg cells, while PD-1 expression in tumor-infiltrating Treg cells is also elevated, dependent on SREBP activation [176, 177]. Additionally, Treg cells rely on FAO for oxidative phosphorylation to fulfill their functions [175, 178]. Specifically, Treg cells enhance FA and cholesterol metabolism via AKT-mTORC1 signaling, promoting cell proliferation and inducing the expression of critical immune suppression molecules, including CTLA-4 and ICOSs [179]. Consequently, targeting lipid metabolism in Treg cells, such as CD36 and SREBP, may be a promising way to enhance the efficacy of cancer immunotherapy, worthy of further study [8, 176].

TAMs

Tumor-associated macrophages (TAMs), which represent another important component of TME, mainly rely on lipids metabolism to maintain their differentiation and function. TAMs are primarily divided into anti-tumor M1 and pro-tumor M2 phenotypes, M1 macrophages use fatty acids to synthesize inflammatory mediators and obtain most ATP from aerobic glycolysis, while M2 macrophages enhance FAO by fuel fatty acids to obtain ATP [180]. The TME contains various signaling molecules that can alter lipid metabolism in TAMs, including increased lipid uptake, FAS, and FAO, which promote TAM polarization to the pro-tumor M2 phenotype. This polarization exerts immunosuppressive effects, promoting tumor growth, metastasis, and angiogenesis [181] (Fig. 4c).

Lipid metabolites or signaling molecules in TME regulate differentiation and polarization of macrophages, exerting immunosuppressive effects [182]. Inflammation-related cancers exhibit increased levels of PGE2 and LPA, which promote the differentiation of monocytes into immunosuppressive TAMs phenotype [183, 184]. Furthermore, tumor cells and adipocytes release significant amounts of lipid-rich exosomes to TME, leading to the differentiation of TAMs toward the M2 phenotype [185, 186].

Lipid transport proteins, particularly CD36, play a crucial role in lipid accumulation within TAMs, which further affect the activation of TAMs [187, 188]. In liver metastasis mouse models, CD36 was upregulated in tumor-infiltrating TAMs [189], and CD36 knockout resulted in decreased lipid accumulation in TAMs [187]. Moreover, the elevated macrophage receptor for collagenous structures (MARCO) on TAMs also promotes lipid accumulation, which is induced by IL-1β in prostate cancer cells. CD36 in TAMs mainly mediates extracellular lipid uptake, especially ox-LDL, and the internalization of tumor cell-released lipids in EVs [155, 189, 190]. Lipid-loaded TAMs then release pro-tumorigenic cytokines, including CCL6, to TME, and finally promotes cancer cell migration [190]. Mechanically, lipid accumulation in TAMs leads to increased expression of PI3K-γ, which play a critical role in TAM polarization [155]. Loss of CD36 in TAMs can restore cytotoxic effects of $CD8^+$ T cells and inhibit the growth of metastatic tumors in liver [189].

In addition to lipid uptake, TAMs also exhibit a phenotype with enhanced lipid biosynthesis, which contributes to the secretion of tumor-promoting cytokines and ROS response. Evidence has shown that inhibiting FASN in TAMs can significantly reduce extracellular tumor-promoting cytokines and hinder tumor progression [191]. In addition, continuous FAS activation induced by SERBPs is a major cause for maintaining the activity of M2-like TAMs in the Treg-mediated immunosuppressive microenvironment [192]. Activation of lipid uptake and synthesis promotes the formation of LDs, which further enhances their tumor-promoting functions. Inhibiting LD formation leads to a shift in TAM phenotype from M2 to M1, which may be an effective strategy to counteract TAM-mediated immunosuppression [193, 194].

An increased FAO is also very common in TAMs, which helps maintain their pro-tumorigenic functions. M2 macrophages rely on enhanced FAO instead of glycolysis for energy. High levels of FAO promoted mitochondrial oxidative phosphorylation, production of ROS, and phosphorylation of STAT6, promoting activation and transcription of genes that regulate TAMs generation and function [187]. For example, FAO is critical for M2-induced HCC migration, increasing ROS and secretion of IL-1β [195]. Mechanistically, the high rate of FAO in M2 macrophages attributes to the activation of the PPARγ [9, 188, 196]. TAMs exhibit downregulated expression of RIPK3 in HCC, which significantly inhibits caspase1-mediated PPAR cleavage[9]. Furthermore, elevated S100A4 can significantly activate PPARγ and increase FAO levels [188]. Inhibiting FAO or PPARγ signaling pathway in TAM impedes their polarization toward a pro-tumorigenic M2 phenotype and inhibits tumor progression [187, 196]. Therefore, inhibiting FAO may be a useful way to modulate TAMs polarization to an anti-tumorigenic phenotype, thus enhancing anti-tumor immune responses.

Targeting M2-like TAMs also presents a promising therapeutic strategy for cancer treatment. Compared to M1-like TAMs, M2-like TAMs express higher levels of PD-1. Therefore, combining anti-PD-1 therapy with lipid metabolism inhibitors may selectively attack M2-like TAMs, improving the effectiveness and sensitivity of therapy [20, 197].

DCs

Dendritic cells (DCs) are the primary antigen-presenting cells that activate $CD8^+$ T cells and mediate anti-tumor immune responses. Lipid metabolic alterations of DCs in TME, such as increased lipid uptake, lipid accumulation and enhanced FAO, can decrease their antigen presentation capacity and facilitate immune evasion in tumors [198] (Fig. 4d).

Increased lipid uptake in DCs leads to lipid accumulation and FAO promotion, which impairs their ability to stimulate T cells [199, 200]. In tumor-bearing mice, an upregulation of fatty acids receptor is observed in DCs within the tumor, resulting in a significant increase in intracellular lipid levels compared to peripheral blood DCs [199]. Research has found that increased CD36 expression was found in DCs in TME due to the absence of the autophagy gene Atg5. Restoring Atg5 expression and blocking CD36 in DCs may effectively reduce lipid accumulation [201]. Moreover, lipid-laden DCs have a profound defect in their ability to process and present soluble antigens [199]. Similarly, XBP1-mediated lipid peroxide accumulation in tumor-associated DCs can induce ER stress and inhibit antigen presentation function of DCs, thus indirectly hindering its anti-tumor effect [202]. Elevated FAO level mediated by CPT1A is also an essential metabolic feature of tumor-associated DCs, which ultimately leads to the secretion of immune-suppressive cytokines, such as IL-6 or IL-12, promoting Treg cell aggregation to TME. Mechanically, intracellular β-catenin-PPARγ activated by extracellular Wnt5a contributed to this process [203]. Blocking lipid accumulation and FAO in tumor-associated DCs may enhance their anti-tumor efficacy.

NK cells

Natural killer (NK) cells, a particular type of T cells, play a crucial role in protective immunity against tumors and viral infections. They break infected cells or tumor cells via secreting perforin and granzyme [204]. Acidosis and nutrient-deficient TME are associated with the dysfunction of NK cells [205, 206]. Similarly, lipid-rich microenvironments let lipid accumulated within NK cells, ultimately impairing their anti-tumor functions (Fig. 4e).

Lipid accumulation in NK cells is the main cause of its dysfunction for killing tumor cells. Notably, an increased lipid accumulation and high CD36 expression in splenic NK cells isolated from surgery-treated tumor-bearing mice were observed [12]. Similarly, another study reported that individuals with obesity were deficient in NK cell numbers compared to lean individuals [207]. Besides, NK cells can directly take up lipids-rich EVs secreted from lung mesenchymal cells, which leads to lipid accumulation within the cells [208]. As a consequence, lipid-laden NK cells exhibit decreased production of granzyme B and IFN-γ, which ultimately results in a diminished anti-tumor effect [12, 207, 209]. In particular, increased FA levels in the lymphoma environment are also found to be related to NK cells dysfunction [209]. Further study indicated lipid accumulation in NK cells is driven by PPARα/δ signaling pathway under lipotoxic obese environment. Inhibiting PPARα/δ or blocking the lipids transportation can reverse NK cell metabolic paralysis and restore its cytotoxicity [207]. However, recent research on HCC suggested a potentially beneficial role for cholesterol accumulation in NK cells, as it promotes membrane lipid rafts formation and enhances anti-tumor effects [210].These findings are controversial as to the role of different lipids in NK cells, requiring more high-quality research to explore.

MDSCs

Myeloid-derived suppressor cells (MDSCs), divided into mononuclear MDSCs (M-MDSC) and polymorphonuclear MDSCs (PMN-MDSC), play an important role in shaping the immunosuppressive microenvironment [211]. It has been well demonstrated that increased lipid uptake and FAO in MDSCs can promote its production of immune-suppressive cytokines that inhibit cytotoxic effects of $CD8^+$ T cells [212] (Fig. 4f).

Bioactive lipid signaling factors in TME promotes the realization of immune cells function. Specifically, in breast and colon cancer, studies have identified PGE2 as a crucial factor in activating MDSCs in TME [213, 214]. Mechanistically, tumor-derived PGE2 induces nuclear accumulation of p50 NF-κB in M-MDSCs, leading to NO-mediated immune suppression [215]. Therefore, blocking PGE2 has been proposed as a therapeutic strategy to prevent immune suppression of MDSCs and restore its anti-tumor effects in TME [215, 216].

In addition to lipid signaling factors, lipid metabolic reprogramming of MDSCs, characterized by increased lipid uptake and FAO, is essential in regulating their functions. Importantly, exogenous FA uptake promotes their ability to suppress the activity $CD8^+$ T cell, facilitating tumor progression [211, 217, 218]. Notably, unsaturated FAs have a stronger effect on MDSC suppression, as MDSCs treat with LA exhibited more substantial suppression than those treated with palmitic acid [219].

CD36, FATPs, and VLDLR expression are upregulated in tumor-activated PMN-MDSCs. Inhibition of CD36 can reduce the immunosuppressive function of MDSCs [218]. Similarly, FATP2 can also be overexpressed in PMN-MDSCs, induced by tumor cell-derived GM-CSF and the activation of STAT3 signaling [10, 220]. It promotes intracellular PGE2 synthesis and exerts tumor-promoting effects [220]. Inhibiting FATP2 in MDSCs enhances anti-PD-L1 tumor immunotherapy by upregulating CD107a and decreasing PD-L1 expression on $CD8^{+}$ TILs [221]. In addition, Mouse models showed that tumor-infiltrating MDSCs had increased FAO levels, along with upregulation of CPT1, and increased oxygen consumption. Inhibition of FAO combined with low-dose chemotherapy can restrain the immunosuppressive effects of MDSCs and induce significant anti-tumor effects [222]. Therefore, targeting the lipid metabolism of MDSCs may sensitize the effects of cancer immunotherapy.

Strategies for tumor comprehensive therapy by targeting lipid metabolism

Based on the comprehensive understanding of lipid metabolism in tumors and TME established in the previous text, targeting lipid metabolism holds promise as a multi-dimensional approach that can act on both tumor cells and TME cells, resulting in improved therapeutic outcomes. However, due to the plasticity of lipid metabolism, cancer cells can switch to an alternative pathway when one metabolic pathway is blocked. This, to some extent, hinders the anti-tumor efficacy of monotherapy [94, 223]. Notably, it can be effectively combined with tumor chemotherapy and targeted therapy to enhance anti-tumor efficacy in recent studies. Furthermore, targeting CD36 or CPT1 in combination with immunotherapy has shown promising results in enhancing anti-tumor immune responses. These findings provide valuable insights for optimizing therapeutic strategy for cancer patients (Fig. 5).

Advances in targeting lipid metabolism combined with chemotherapy and targeted therapy

As described above, the dysregulated lipid metabolism in tumor cells provides energy support for tumor progression, playing an essential role in membrane synthesis and signal transduction. This shift in lipid metabolism, including the lipid uptake from the extracellular microenvironment, increased lipogenesis, and the increase in intracellular LD storage, correlates with the metastatic potential of tumor cells [224], the acquisition of stem cell-like properties [225], and the development of resistance to cancer chemotherapy [226, 227]. This may interfere with chemotherapy and targeted therapy in tumors. Therefore, aberrant lipid metabolism has become a potential target for treating drug-resistant cancer. Combination therapy can sensitize tumor cells to drugs, demonstrating a therapeutic effect superior to monotherapy [227]. Combination therapy also compensates for the insufficient efficacy of single-target lipid metabolism inhibitors. A considerable amount of preclinical research and clinical trials are currently focusing on novel strategies to enhance therapeutic effects by combining targeted lipid metabolism therapy with conventional chemotherapy and targeted therapy, even radiotherapy (Fig. 5a; Table 2).

Targeting lipid uptake

Tumor cells exhibit a propensity for lipid uptake to support biosynthesis, energy production, and lipid storage in LDs. Consequently, inhibiting lipid uptake has emerged as a promising therapeutic strategy in oncology. Considerable preclinical evidence suggests that targeting the fatty acid receptor CD36 can be effective against various types of cancer [4, 15, 228, 229]. Particularly, CD36-mediated metabolic reprogramming in breast cancer, has been linked to resistance to HER2-targeted therapies. Recent clinical studies have confirmed that higher CD36 expression correlates with poorer outcomes in early-stage $HER2^{+}$ breast cancer patients undergoing trastuzumab-lapatinib therapy [230]. Furthermore, JC63.1C, an anti-CD36 monoclonal antibody, was found to resensitize lapatinib-resistant xenograft tumors to HER2-targeted therapy [231], providing a novel direction for combinatorial treatment strategies in breast cancer. In addition, studies in leukemia models showed that the FA6.152 monoclonal anti-CD36 or the CD36 inhibitor SSO, when used in conjunction with chemotherapy drugs such as Ara-C or doxorubicin, led to a significant extension in survival [232, 233]. In PDAC, CD36 siRNA notably increased the efficacy of gemcitabine treatment [234].

Inhibiting FABPs has also demonstrated promising anti-tumor effects. FABP5 inhibitors, namely SBFI-102/103, were identified as novel targets in prostate cancer and were shown to enhance the tumor-suppressing effects of paclitaxel [235, 236]. FABP4 inhibitor BMS309403, was also found to boost the efficacy of carboplatin by inhibiting tumor metastasis in in vivo ovarian cancer models [237]. In another study, a mouse model of melanoma showed that inhibiting FATP2, another critical lipid metabolism transporter, in PMN-MDSCs using lipofermata, led to enhanced tumor regression when combined with BRAF/MEK inhibitor [238]. Taken together, these findings suggest that targeting lipid uptake by inhibiting fatty acid transporters is a promising new strategy to overcome therapy resistance in cancer treatment.

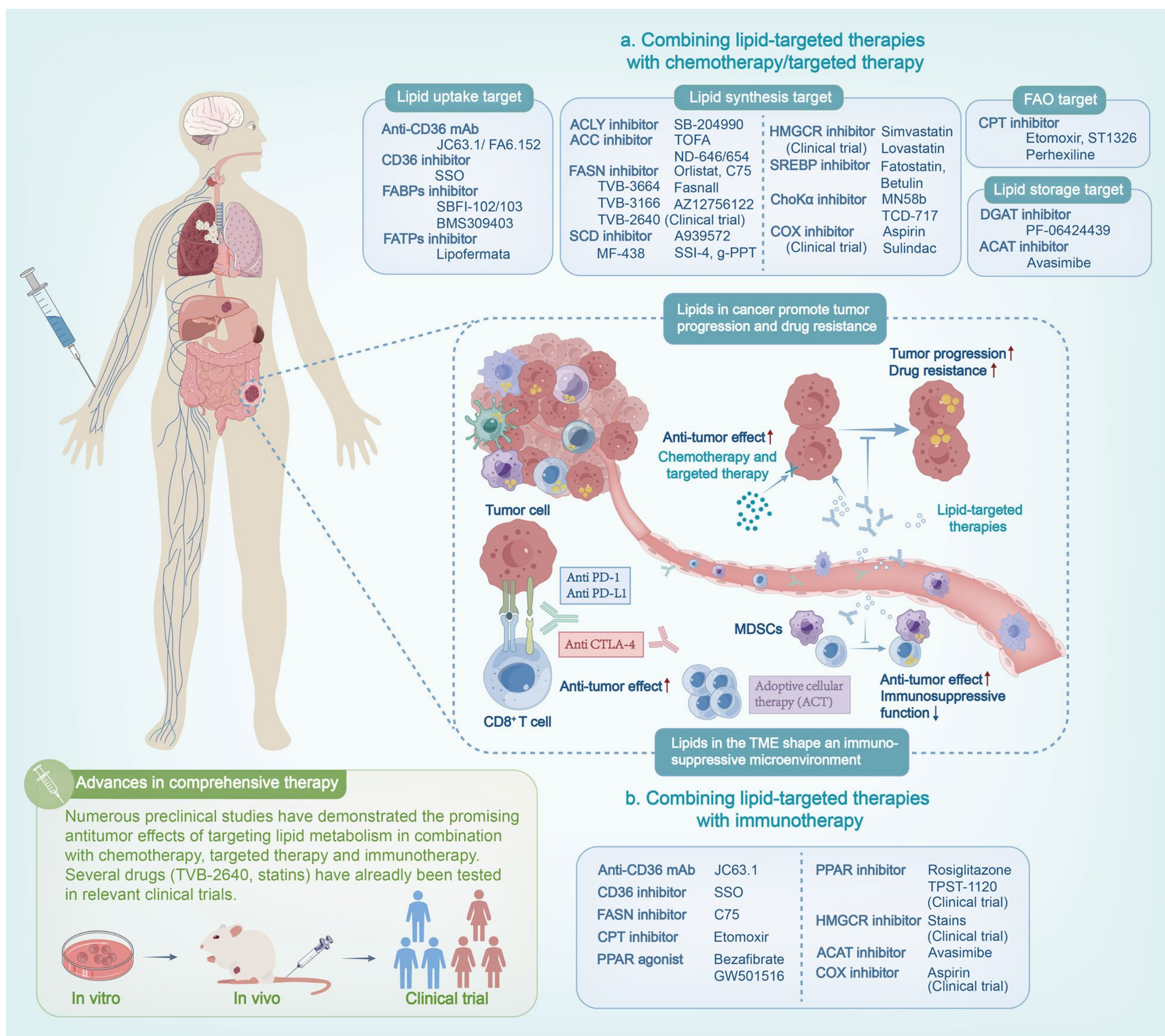

Fig. 5 Lipid-targeted therapy in combination with chemotherapy, targeted therapy and immunotherapy. Lipid metabolism reprogramming within tumors not only propels tumor progression and drug resistance, but also play a crucial role in shaping the immunosuppressive microenvironment. This provides a theoretical foundation for the comprehensive treatment strategies by targeting tumor lipid metabolism. In numerous preclinical studies, inhibitors of lipid metabolism have shown significant anti-tumor effects in combination with chemotherapy, targeted therapy and immunotherapy, which is superior to a single-target treatment. The targets of these inhibitors primarily include lipid uptake (CD36, FABPs, FATPs), lipid synthesis (ACLY, ACCs, FASN, SCDs, SERBP, HMGCR, ChoK, COX), FAO (CPT1, PPAR), and lipid storage in LDs (DGAT, ACAT). These findings provide valuable insights for optimizing therapeutic strategy for cancer patients by combination lipid-targeted therapy with present anti-tumor therapy

Targeting lipid synthesis

Increased lipid synthesis, inclusive of fatty acids and cholesterol, is a characteristic feature of tumors. Consequently, targeting key enzymes in these pathways is emerging as a potential therapeutic strategy for cancer, particularly in conjunction with chemotherapy and targeted therapy. ACLY, a key enzyme in the production of acetyl-CoA, serving as a substrate for DNL, supports tumor growth and confers resistance to vemurafenib in melanoma treatment. In tumor-bearing mice model, although vemurafenib exerted minimal effects on tumor growth, the combination of SB-204990 and vemurafenib exhibited a significantly more suppressive effect [239]. Similarly, in vitro results suggested that combining SB-204990 could be an effective strategy for treating cisplatin-resistant ovarian cancer [240]. In addition, ACCs,

Table 2 Combining lipid-targeted therapies with chemotherapy and targeted therapy

Target	Treatment	Phase	Tumor type	Combined treatment	Reference
CD36	JC63.1 (anti-CD36)	In vivo	Breast cancer	Lapatinib (HER2/EGFR inhibitor)	[231]
	FA6.152 (anti-CD36)	In vivo	Leukemia	Ara-C	[232]
	SSO (CD36 inhibitor)	In vivo	Leukemia	Ara-C, Doxorubicin, Etoposide, SN-38, Irinotecan, Dasatinib	[233]
FABPs	SBFI-102/103 (FABP5 inhibitor)	In vivo	Prostate cancer	Taxane	[236]
	BMS309403 (FABP4 inhibitor)	In vivo	Ovarian cancer	Carboplatin	[237]
FATPs	Lipofermata (FABP2 inhibitor)	In vivo	Melanoma	PLX4720 (BRAFi) PD0325901 (MEKi)	[238]
ACLY	SB-204990	In vivo	Melanoma	Vemurafenib (BRAFi)	[239]
		In vitro	Ovarian cancer	Cisplatin	[240]
ACC	TOFA	In vivo	HNSCC	Cetuximab	[241]
	ND-646	In vivo	NSCLC	Carboplatin	[242]
	ND-654	In vivo	HCC	Sorafenib	[243]
FASN	TVB-2640	Phase II	$HER2^+$ Breast cancer	Taxane or trastuzumab	NCT03179904
		Phase II	Astrocytoma	Bevacizumab	NCT03032484 [258]
		Phase III	Glioblastoma	Bevacizumab	NCT05118776
		Phase I	NSCLC, ovarian, and breast cancer	Taxane	NCT02223247 [257]
	Orlistat	In vivo	Pancreatic cancer	Gemcitabine	[249]
		In vivo	Prostate cancer	Radiotherapy	[247]
		In vivo	Ovarian cancer	Cisplatin	[248]
		In vitro	HCC	Sorafenib	[245, 246]
		In vivo	NSCLC	Gefitinib (EGFRi)	[250]
	C75	In vivo	Breast cancer	Cetuximab	[319]
		In vivo	Gastrointestinal stromal tumors (GIST)	Imatinib	[320]
		In vivo	Breast cancer	CYH33 (PI3Ki)	[253]
	TVB-3664	In vivo	HCC	Cabozantinib, Sorafenib	[251]
		In vivo	Lung adenocarcinoma	MRTX849 (KRASi)	[252]
	TVB-3166	In vivo	Ovarian, prostate and pancreatic cancer	Taxane	[254]
	Fasnall	In vivo	$HER2^+$ Breast cancer	Carboplatin	[255]
	AZ12756122	In vitro	NSCLC	Osimertinib	[256]
SCD	A939572	In vitro	Glioblastoma	Temozolomide	[262]
		In vivo	ccRCC	Temsirolimus (mTORi)	[261]
	SSI-4	In vivo	HCC	Sorafenib	[263]
	g-PPT	In vivo	NSCLC	Gefitinib	[264]
	MF-438	In vitro	Melanoma	Vemurafenib, Binimetinib	[260]
		In vitro	Lung cancer	Cisplatin	[265]
HMGCR	Simvastatin	Phase II	NSCLC	Gefitinib	NCT00452244 [275]
		Phase II	Breast cancer	Fluorouracil, adriamycin, and cyclophosphamide	NCT04418089 [276]
		Phase III	Prostate cancer	ADT	NCT03127631 [278]
		In vitro	Endometrial cancer	Metformin	[271]
		In vivo	Renal cell carcinoma	Everolimus	[270]
		In vitro	Glioblastoma	Temozolomide	[272]
	Lovastatin	In vivo	Gallbladder cancer	Cisplatin	[273]
		In vitro	Nasopharyngeal carcinoma	Cisplatin, cyclophosphamide, doxorubicin and paclitaxel	[274]

Table 2 (continued)

Target	Treatment	Phase	Tumor type	Combined treatment	Reference
SREBP	Fatostatin	In vivo	Melanoma	Vemurafenib	[266]
		In vivo	Prostate cancer	Taxane	[321]
	Betulin	In vivo	HCC	Sorafenib	[267]
ChoK	MN58b TCD-717	In vivo In vitro	Colorectal cancer, PDAC	5-flurouracil	[279, 280]
COX	Aspirin	Phase II	ER+ breast cancer	ACT	NCT04038489
	Sulindac	Phase II	Colorectal cancer	Erlotinib	NCT01187901
CPT	Etomoxir	In vivo	Leukemia	Ara-C	[284]
		In vivo	Glioblastoma	Temozolomide	[322]
		In vivo	HCC	Antiangiogenic drug	[287]
		In vivo	Gastric cancer	5-fluorouracil	[285]
		In vivo	Nasopharyngeal carcinoma	Radiotherapy	[286]
		In vitro	Breast cancer	Radiotherapy	[323]
	Perhexiline	In vivo	Colorectal and gastric cancer	Oxaliplatin	[14]
		In vivo	PDAC	Gemcitabine	[289]
		In vivo	Ovarian cancer	Cisplatin	[290]
		In vitro	Breast cancer	Paclitaxel	[291]
	ST1326	In vivo	Leukemia	ABT199 (Bcl-2 inhibitor)	[324]
DGAT	PF-06424439	In vitro	Colorectal cancer	5-fluorouracil	[297]
		In vitro	Breast cancer	Cisplatin, radiotherapy	[298, 299]
ACAT	Avasimibe	In vivo	Leukemia	Imatinib	[325]
		In vivo	Breast cancer	Doxorubicin	[326]
		In vivo	Melanoma	Paclitaxel	[303]
		In vivo	PDAC	Gemcitabine	[304]
		In vitro	Biliary tract cancer	Gemcitabine	[305]

which catalyze the conversion of acetyl-CoA to malonyl-CoA, the initial step in fatty acid synthesis, are upregulated in cetuximab-treated head and neck squamous cell carcinoma (HNSCC) by the continuously activated AMPK pathway, suggesting a possible mechanism refers to the cetuximab resistance. A combination of cetuximab and TOFA, an ACC inhibitor, resulted in notable growth inhibition of cetuximab-resistant HNSCC xenografts in vivo [241]. Another ACC inhibitor, ND-646, when combined with carboplatin, could also significantly inhibit tumor growth in preclinical non-small cell lung cancer (NSCLC) models [242]. Similarly, the combination of sorafenib and a liver-specific ACC inhibitor (ND-654) effectively decreased tumor proliferation in vivo [243]. However, clinical trials assessing the efficacy of targeting ACC in tumors are currently scarce. Recent clinical trials have supported the use of an ACC inhibitor (Firsocostat) for treating nonalcoholic steatohepatitis (NCT02856555, NCT03987074) [244].

Palmitic acid synthesis, another rate-limiting step in DNL, is facilitated by FASN. Deregulation in the expression and activity of FASN carries significant implications for therapeutic response. FASN inhibitors, such as the anti-obesity drug Orlistat, have shown significant antitumor effects in various cancers [13]. Recent studies have underscored the efficacy of combining FASN inhibitors with other treatment strategies. Preclinical evidence suggests Orlistat's ability to reverse sorafenib resistance in HCC, thus illuminating new avenues for combined HCC treatment [245, 246]. Moreover, in prostate cancer, the combination of Orlistat and radiotherapy significantly reduces the activity of the NF-κB pathway, and inhibits cancer progression [247]. Preclinical research on pancreatic cancer, NSCLC, and ovarian cancer has shown that combining Orlistat with chemotherapy and targeted treatment significantly enhances anti-tumor effects [248–250]. Despite Orlistat being an FDA-approved therapy, there are currently no registered clinical trials examining its role in cancer. Another FASN inhibitor, TVB-3664, exhibits synergistic therapeutic effects when combined with TKI, as shown in an HCC mouse model [251]. A separate in vivo study using a lung adenocarcinoma xenograft model demonstrated the anti-tumor effects of combining TVB-3664 with a KRAS inhibitor [252]. The

PI3K pathway, frequently hyperactive in tumor, plays crucial roles in both malignant and immune cells. The co-administration of the PI3K inhibitor (CYH33) with the FASN inhibitor (C75) has been found to synergistically inhibit tumor growth while enhancing host immunity [253]. Other FASN inhibitors like TVB-3166, Fasnall, and AZ12756122 also promote enhanced anti-tumor effects in combination therapies [254–256]. However, these inhibitors often present challenges related to poor pharmacokinetics, selectivity issues, and toxicity, rendering their clinical applicability uncertain. Notably, TVB-2640, considered the most promising FASN inhibitor, has been approved for multiple clinical studies.

When combined with paclitaxel, TVB-2640 has shown significant efficacy in clinical trials, including in patients with KRAS mutation in NSCLC, ovarian cancer and breast cancer, as compared to monotherapy (NCT02223247)[257]. In a phase II trial for relapsed high-grade astrocytoma, TVB-2640 was identified as a well-tolerated oral medication that could be safely administered in combination with bevacizumab. The positive safety profile and promising response rates endorse the initiation of a larger multicenter trial for TVB-2640 in conjunction with bevacizumab for astrocytoma (NCT03032484) [258]. Currently, a phase III clinical trial is underway to evaluate the combination of TVB-2640 and bevacizumab for the treatment of glioblastoma (NCT05118776). Furthermore, a phase II trial has been conducted to assess the efficacy of TVB-2640 in combination with trastuzumab and paclitaxel in patients with $HER2^{+}$ metastatic breast cancer resistant to trastuzumab-based therapy (NCT03179904).

Targeting SCD1, the most critical enzyme in MUFA synthesis, has become the focus of many studies. SCD1 inhibitors, such as MF-438 and CAY10566, have been found to alter the composition of membrane PLs, leading to LPO and ferroptosis [259]. In vitro studies of BRAF-mutated melanoma have supported the role of MF-438 as a promising therapeutic target, especially when used in combination with MAPK inhibitors [260]. In ccRCC cells, the SCD1 inhibitor A939572 induces apoptosis and synergistically inhibits tumor growth when combined with temsirolimus, an mTOR inhibitor [261]. A range of SCD inhibitors is now available (e.g., A939572, SSI-4, g-PPT, MF-438), and most of these have been shown in preclinical models to produce stronger anti-tumor effects when combined with chemotherapy and targeted therapies [262–265]. However, few of these inhibitors have been translated into clinical trials, and none are currently being explored for their effects on cancer. SREBPs, key upstream regulators of lipid synthesis, are being considered as potential therapeutic targets, which can suppress the generation of key enzymes in lipid synthesis at the transcription level. Combining an SREBP inhibitor (fatostatin) with vemurafenib therapy enhances the therapy response in melanoma-bearing mice models, increasing membrane lipid polyunsaturation and lipid peroxidation [266]. Moreover, another preclinical study showed that the inhibition of SREBP-1 facilitated the anti-tumor effects of Sorafenib on HCC cells and xenograft tumors [267]. Importantly, a clinical trial focusing on head and neck cancer patients undergoing cisplatin chemotherapy demonstrated that dietary intake enriched with ω-3 FAs could prolong survival (NCT05101889) [268]. This also presents a potential novel dietary adjunctive therapeutic strategy.

Targeting cholesterol also provides a promising way to improve the sensitivity of anti-tumor drugs. Multiple studies have reported that the inhibition of cholesterol synthesis and uptake can notably impede proliferation and invasion in cancer. Statins, a type of HMGCR inhibitor, have effectively inhibited cholesterol in clinical trials [269]. A retrospective cohort study indicated that regular use of statins could lead to longer progression-free survival (PFS) in ccRCC patients prescribed with an mTOR inhibitor, everolimus, compared to those without statins. This finding has been confirmed in tumor xenograft models [270]. Mechanistically, the use of statins could represent a form of drug repositioning to enhance the efficacy of mTOR inhibitors. Similarly, statins combined with traditional chemotherapy have demonstrated promising results in preclinical models of endometrial, gallbladder cancer, nasopharyngeal carcinoma, and glioblastoma [271–274]. In an early-phase II trial of NSCLC, simvastatin showed potential to improve the efficacy of gefitinib in a subgroup of gefitinib-resistant NSCLC patients (NCT00452244) [275]. Moreover, a recent study on locally advanced breast cancer suggested that combining simvastatin with neoadjuvant chemotherapy improved therapeutic responses in patients. Although no statistically significant difference was documented, there was a trend toward better activity and tolerability (NCT04418089) [276]. However, a phase III trial in advanced gastric cancer reported no significant advantage of simvastatin plus capecitabine-cisplatin over placebo plus capecitabine-cisplatin (NCT01099085) [277]. The efficacy of statin combinations needs to be further validated in clinical trials for specific types of cancer. Currently, a phase III clinical trial is underway for prostate cancer patients, evaluating the combination of simvastatin with androgen deprivation therapy (ADT), with promising results anticipated (NCT03127631) [278].

PL metabolism and lipid-derived mediators (e.g., PGE2 and LPA) are crucial in tumor progression and drug resistance, suggesting new strategies for comprehensive therapy. ChoK, the key enzyme for PCho

phosphorylation, is overexpressed in various tumors. ChoKα inhibitors, MN58b and TCD-717, have shown effective anti-tumor activity combined with 5-fluorouracil in mouse xenograft models of colorectal cancer [279]. Similarly, MN58b synergizes with gemcitabine, 5-fluorouracil and oxaliplatin in preclinical studies of PDAC [280]. TCD-717 has entered Phase I trials as a novel anti-tumor strategy, but no data are available yet (NCT01215864). Furthermore, other key enzymes in PL metabolism, including PLC and D, have been demonstrated as potential anti-tumor targets in some preclinical studies. D609, a PLC inhibitor, can induce proliferation arrest and cell differentiation in breast cancer cells [281]. Similarly, targeted inhibition of PLD effectively suppresses tumor growth and metastasis in mouse model [282]. Notably, inhibiting bioactive lipids, especially through PGE2 pathway by using COX inhibitors, has shown efficacy in various tumors, including gastrointestinal cancer [283]. Several clinical trials have evaluated the therapeutic potential of COX inhibitors in combination therapies, highlighting their significance in treatment regimen (NCT04038489) (NCT01187901).

Targeting FAO

FAO, which involves the key rate-limiting enzyme CPT, has emerged as a promising metabolic therapeutic target for cancer. Etomoxir, the most commonly used CPT inhibitor in preclinical research, has shown notable efficacy when combined with chemotherapy and targeted treatments, functioning through the inhibition of mitochondrial FAO. For example, blocking CPT1 with etomoxir significantly enhances the cytotoxicity of Ara-C against drug-resistant leukemia cells [284]. Likewise, numerous in vitro preclinical studies have indicated a promising future for etomoxir when combined with traditional chemotherapy and radiotherapy [285, 286]. Moreover, antiangiogenic drug (AAD)-induced tumor hypoxia initiates FAO reprogramming, which stimulates cancer cell proliferation in HCC therapy. The combination of AAD and the FAO inhibitor etomoxir can resensitize drug-resistant tumor cells and enhance anti-tumor effects [287]. However, few clinical studies have used etomoxir for anti-cancer treatment due to its clear hepatotoxicity [288]. Perhexiline, another CPT inhibitor, when combined with oxaliplatin, significantly suppressed the progression of gastrointestinal cancer in cell-based xenograft and patient-derived xenograft models. In preclinical models of PDAC, ovarian, and breast cancer, perhexiline combined with chemotherapy has demonstrated potential application value [289–291]. Notably, perhexiline has been approved for angina treatment in Australia and Asia, therefore it could be translated quite safely into anti-tumor trials. While clinical trials for anti-tumor treatment have not yet been conducted with CPT inhibitors like etomoxir, perhexiline, and ST1326, substantial preclinical evidence provides promising therapeutic strategies [14, 292].

Targeting lipid storage

LDs are storage organelles characterized by a lipid core containing neutral lipids. They play a fundamental role in tumor cells and are associated with tumor aggressiveness and therapy resistance [293–295]. For example, LD accumulation drives cell death resistance to 5-fluorouracil and oxaliplatin treatments both in vitro and in vivo. Mechanistically, LD accumulation impairs caspase cascade activation and ER stress responses [295]. Inhibition of LD synthesis has been shown to upregulate LPO, indicating its potential as a cancer therapy. Numerous studies have linked DGAT to the progression of several cancers, such as gastric cancer, which is dependent on promoting lipid storage in LDs [107, 129, 296]. The DGAT inhibitor, PF-06424439, has been confirmed in vitro studies of colorectal and breast cancer to have a positive role in enhancing the anti-tumor effects of 5-fluorouracil, cisplatin, and even radiotherapy [297–299]. Additionally, inhibition of CE formation has also been identified as a promising approach to suppress tumor proliferation and metastasis. Avasimibe, an ACAT-1 inhibitor, elevates the level of free cholesterol in pancreatic, colorectal, and liver cancer cells, inducing ER stress and resulting in cancer cell apoptosis [300–302]. Furthermore, avasimibe was combined with chemotherapy (paclitaxel and the immunoadjuvant αGC), leading to enhanced CTL responses by facilitating the formation of T cell receptors and anti-tumor effects in B16 melanoma xenograft models [303]. The combination of avasimibe and gemcitabine demonstrated a strong synergistic effect in suppressing PDAC and biliary tract cancer in vitro and tumor growth in vivo [304, 305]. However, to date, no inhibitors designed to target DGAT and ACAT have been tested in clinical trials in cancer patients.

Advances in targeting lipid metabolism combined with immunotherapy

Cancer immunotherapies, including checkpoint inhibitors and adoptive cell transfer (ACT) [306], which activate the immune system to recognize and attack cancer cells, have obtained durable clinical responses. Immune checkpoint inhibitors (ICIs) are monoclonal antibodies and comprise anti-programmed cell death protein 1 (PD-1), anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), and anti-programmed death-ligand 1 (PD-L1), which targets immune inhibitory pathways known as checkpoints. It is important to note that ICIs are not believed to kill tumor cells directly. Rather, they mediate

their anti-tumor effects indirectly by stimulating T cells and enhancing their functions, making ICIs more effective and less toxic than traditional systemic immune therapies [307, 308]. Current studies increasingly focus on the role of lipid metabolic reprogramming in immune cells on immunotherapy. Building on the previously mentioned understanding, it has been noted that immune cells within the TME amplify their immunosuppressive effects by altering their lipid metabolism patterns, which subsequently promotes tumor progression. As an illustration, disrupting PD-L1 palmitoylation makes cancer cells more susceptible to T cell-mediated destruction, thereby inhibiting tumor growth [309, 310]. This suggests a theoretical foundation for modifying the immunosuppressive TME through the targeting of lipid metabolism. Moreover, several metabolism-modulating drugs such as statins and bezafibrate have been shown to obstruct cancer development [164, 311], indicating a novel therapeutic strategy that combines metabolism-regulating agents with immunotherapy for the treatment of cancer. Thus, we aim to summarize promising therapeutic targets within various lipid metabolism pathways including lipid uptake, synthesis, and FAO, in relation to immunotherapy (Fig. 5b; Table 3).

As a critical regulator of lipid metabolism in immune cells, CD36 significantly influences their anti-tumor immune responses within the TME. Suppressing CD36 in $CD8^+$ T cells reduces intracellular lipid accumulation and reinstates their anti-tumor activity [169], while targeting CD36 in Treg cells mitigates their immunosuppressive effects [8]. Combined, these strategies can synergistically augment the efficacy of anti-PD-1 therapy. The potency of this conclusion has been substantiated through the conjunction of JC63.1 and anti-PD-1 mAb in the melanoma-bearing mice model. Similarly, CD36 inhibitor SSO synergizes with anti-PD-1 immunotherapy by restoring anti-tumor T cell responses in HCC. This combination treatment exhibits marked anti-tumor efficacy with decreased Tregs and MDSCs and increased IFN-γ^+ and granzyme B^+ $CD8^+$ T cells [153]. In addition, directing the intervention toward CD36 in TAMs can also decrease their internal lipid accumulation and affect their functional phenotypes [187]. In gastric cancer, PD-L1 blockade augments the expression of FABP4/5 and lipid uptake of tissue-resident memory T cells (Trm), thereby extending their lifespan and enhancing their anti-tumor effects [168]. Furthermore, FATP2 is a vital regulator of the immunosuppressive function of PMN-MDSCs, which mediates its effect via regulation of lipid accumulation and subsequent synthesis of PGE2. A combination treatment involving lipofermata and a CTLA4 antibody in TC-1 and LLC tumor-bearing mice demonstrated a synergistic tumor-suppressive effect compared to treatment with either agent alone. Mechanistically, the anti-tumor effect was attributed to a significant infiltration of $CD8^+$ T cells within the tumors, achieved by inhibiting PMN-MDSCs [10]. The inhibition of FATP2 expression in MDSCs, in combination with anti-PD-L1 therapy, can also significantly enhance the anti-tumor effect through the regulation of ROS in MDSCs [221]. Therefore, targeting lipid uptake presents an effective approach to potentiate cancer immunotherapy, which has demonstrated superior anti-tumor efficacy in mouse models.

Apart from lipid uptake, FAS and FAO also play critical roles in tumor-associated immune cells and serve as potential targets for combination immunotherapy. Tumor-infiltrating Treg cells display heightened PD-1 expression, which is dependent on the activation of SREBP, revealing a potential strategy for targeting Treg cell lipid metabolism for cancer immunotherapy [176]. An intervention known as C57, which targets FASN in TAMs, can reduce its secretion of pro-tumor inflammatory factors and exert a tumor-suppressive effect [191]. Additionally, CYH33, in combination with C75, induces immune activation and enhances anti-tumor immunity, providing a rationale for the concurrent targeting of PI3K and FASN in breast cancer treatment [253]. A combination of the CPT1 inhibitor etomoxir with ACT suppresses the immunosuppressive function of tumor-infiltrating MDSCs, leading to significant anti-tumor effects [222]. In the TME, etomoxir can inhibit the FAO of TAMs, reduce CD47-mediated anti-phagocytosis, and promote anti-tumor immunity in glioblastoma and hematological tumors [187, 312]. Additionally, a preclinical study involving MC38 colon tumor-bearing mice demonstrated that the PPARγ coactivator 1-α (PGC-1α)/PPAR agonist, bezafibrate, could elevate the levels of CPT1, enhance FAO, and preserve the population of $CD8^+$ TILs in TME. This mechanism thus aids in the facilitation of anti-PD-L1 therapy [164]. In lung cancer models, bezafibrate further amplified the effects of PD-L1 blockade by fostering the expansion of effector T cells within the TME [313]. Similarly, GW501516, another PPAR agonist, improved the potency of ACT by modifying T cell metabolism and cytokine expression in B16 melanoma-bearing mouse models [314]. Strikingly, current clinical trials are evaluating the efficacy of combining PD-1 blockade with PPARs inhibitors, such as rosiglitazone and TPST-1120 (NCT03829436, NCT04114136), in various cancer. The latter study primarily focuses on the proliferation of T cells and the enhancement of anti-tumor immunity. In summary, the strategic targeting of FAO synthesis and oxidation, along with immunotherapy, represents a promising approach for precision therapy.

Table 3 Combining lipid-targeted therapies with immunotherapy

Target	Treatment	Phase	Tumor type	Effects on immune cells	Combined treatment	Reference
CD36	JC63.1 (Anti-CD36)	In vivo	B16 melanoma lung metastatic model	Reduced ferroptosis and enhanced anti-tumor function in CD8+ T cells	Anti-PD-1 Ab	[169]
		In vivo	YUMM1.7 melanoma-bearing mice model	Reduced accumulation and promoted apoptosis in Treg cells Increased accumulation in CD8+ TILs	Anti-PD-1 Ab	[8]
	SSO	In vivo	HCC murine models	Decreased Tregs and MDSCs Increased IFN-γ+ and granzyme B+ CD8+ T cells	Anti-PD-1 Ab	[153]
FATP2	Lipofermata	In vivo	TC-1 and LLC tumor-bearing mice model	Promoted anti-tumor effect of CD8+ TILs	Anti-CTLA4 Ab	[10]
		In vivo	B16 melanoma and LLC tumor-bearing mice model	Activated T cells and inhibited suppressive role of MDSCs	Anti-PD-L1 Ab	[221]
FASN	C75	In vitro	TAMs coculture with TPC-1 thyroid tumor	Reduced extracellular cytokine levels from TAMs through inhibition of lipid biosynthesis	NA	[191]
CPT	Etomoxir	In vitro	TAMs coculture with various tumor cell lines	Suppressed pro-tumor function of TAMs through inhibition of FAO	NA	[187]
		In vivo	Lewis lung and MC38 colon tumor-bearing mice	Increased number of adoptively transferred OT-1 T cells infiltrating the tumors and cells producing IFN-γ	ACT	[222]
		In vivo	GL261 glioblastoma-bearing mice model	Boost TAM phagocytosis and anti-tumor effect	Anti-CD47 Ab	[312]
PPAR	Bezafibrate (PGC-1α/PPAR agonist)	In vivo	MC38 colon tumor-bearing mice	Enhanced proliferation during the early phase and inhibited apoptosis of the effector T cells	Anti-PD-1 Ab	[164]
		In vivo	Lewis lung tumor-bearing mice	Maintained survival and functional capacity of CD8+ TILs	Anti-PD-L1 Ab	[313]
	GW501516 (PPAR agonist)	In vivo	B16 melanoma-bearing mice	Activated the expression of T-bet and IFN-γ level in CD8+ T cells	ACT	[314]
	Rosiglitazone (PPARγ inhibitor)	Phase II	Solid Tumor Malignancies	NA	Nivolumab, Pembrolizumab	NCT04114136
	TPST-1120 (PPARα inhibitor)	Phase I	Advanced Cancers	NA	Nivolumab	NCT03829436
HMGCR	Statin	In vivo	MOC1 oral tumor-bearing mice	Activated effector T cells Shifted macrophages from M2 to M1	Anti-PD-1 Ab	[315]
		Prospective cohort	Pleural mesothelioma, NSCLC	NA	Nivolumab	[311]
		Retrospective study	NSCLC	NA	Nivolumab, Pembrolizumab	[316]
		Prospective cohort	NSCLC	NA	PD-1/PD-L1 inhibitors	NCT05636592
PSK9	Evolocumab	In vivo	MC38 colon tumor-bearing mice	Boost the number of active IFN-γ+ CTLs	Anti-PD-1 Ab	[317]

Table 3 (continued)

Target	Treatment	Phase	Tumor type	Effects on immune cells	Combined treatment	Reference
ACAT	Avasimibe	In vivo	B16 melanoma and lung tumor-bearing mice	Enhanced anti-tumor effect and cytokine production of $CD8^+$ T cells	Anti-PD-L1 Ab	[172]
		In vivo	B16 melanoma-bearing mice	Increased tumor cell apoptosis and T cell effect	ACT	[303]
		Tissue	HCC	Enhanced expansion of cytolytic and non-cytolytic antigen-specific $CD8^+$ T cells	Nivolumab	[318]
COX	Asprin	Phase II	MSI-H colorectal cancer	NA	Anti-PD-1 Ab	NCT03638297

Currently, cholesterol is a subject of keen interest in the field of tumor immunotherapy. Particularly, inhibitors of HMGCR, such as statins, have demonstrated potential as therapeutic targets. Studies conducted in mice models have shown that daily oral administration of simvastatin or lovastatin enhances tumor control and prolongs survival when combined with PD-1 blockade. These findings suggest T cell activation and the transition from M2 to M1 macrophage predominance as possible mechanisms underlying combination therapy [315]. Furthermore, statins have exhibited potential to enhance the effects of immunotherapy in two clinical studies conducted on NSCLC and pleural mesothelioma patients [311, 316]. Currently, a prospective clinical study (NCT05636592) is underway to investigate the treatment of NSCLC using a combination of statins and PD-1/PD-L1 inhibitors. Moreover, inhibiting PCSK9, a key protein in the regulation of cholesterol metabolism, can boost the response of tumors to immune checkpoint therapy [317]. Avasimibe inhibiting ACAT can block cholesterol ester synthesis and LD formation, then enhance the anti-tumor effect of $CD8^+$ TILs by increasing membrane synthesis and intracellular free cholesterol levels [172]. Furthermore, ACAT inhibition can enhance the in vitro sensitivity of $CD8^+$ T cells to PD-1 blockade in HBV-related HCC [318]. In a preclinical study conducted on MC38 colon tumor-bearing mice, the combination of avasimibe and an anti-PD-1 antibody displayed superior efficacy in controlling tumor progression compared to either monotherapy, resulting in a significant anti-tumor effect [172]. Notably, a recent Phase II clinical trial was conducted to investigate the efficacy of a COX inhibitor combined with PD-1 antibody in treating MSI-H colorectal cancer (NCT03638297). There is substantial preclinical evidence supporting the feasibility of targeting lipid metabolism in conjunction with immunotherapy. Anticipation is building for future clinical trials to further validate and translate these potential targets into novel treatment strategies for cancer patients.

Conclusions and perspectives

Lipid play a critical role in cancer progression by serving as energy sources, membrane structures, and signaling molecules. Tumor cells often undergo lipid metabolic reprogramming, characterized by increased lipid uptake, lipid synthesis, fatty acid oxidation, and lipid storage, to survive and develop under hypoxic and nutrient-deficient conditions. Gene mutations and environmental factors (hypoxia, acidosis, and nutritional deficiency) are important drivers to promote metabolic reprogramming in tumor cells. Metabolic reprogramming of tumor cells will further remodel the TME, affecting lipid metabolism and functional phenotypes of TME cells. Among them, lipid metabolic reprogramming of CAFs, Treg cells, $CD8^+$ T cells, and TAMs plays an important role in shaping the tumor immunosuppressive microenvironment, leading to tumor immune escape and therapeutic resistance, ultimately promoting tumor progression. Based on the above facts, targeting lipid metabolism holds a promising multidimensional therapeutic approach for cancer. However, drugs targeting metabolic pathways are currently in the preclinical stage, even though there is strong evidence that combining metabolic inhibitors with chemotherapy or immunotherapy can significantly enhance their antitumor efficacy in animal models. Given the complex connections between different metabolites, the development of useful drugs targeting tumor metabolic pathways still has a long way to go.

Abbreviations

FAO Fatty acid oxidation
TME Tumor microenvironment
CAFs Cancer-associated fibroblasts
Tregs Regulatory T cells
TAMs Tumor-associated macrophages

MDSCs	Myeloid-derived suppressor cells
NK cells	Natural killer cells
TAG	Triacylglycerols
FA	Fatty acid
DNL	De novo lipogenesis
PL	Phospholipid
FATP	Fatty acid transport protein
FABP	Fatty acid-binding protein
ACLY	ATP-citrate lyase
ACSS	Acetyl-CoA synthetase
ACC	Acetyl-CoA carboxylases
FASN	Fatty acid synthase
SFA	Saturated fatty acid
MUFA	Monounsaturated fatty acid
PUFA	Polyunsaturated fatty acid
ELOVLs	Elongation of very-long-chain fatty acids gene family
SCD	Stearoyl-CoA desaturase
FADS	Fatty acid desaturase
OA	Oleic acid
LA	Linoleic acid
ALA	Alpha-linolenic acid
AA	Arachidonic acid
AdA	Adrenic acid
GLS	Glutaminase
GLUD	Glutamate dehydrogenase
IDH	Isocitrate dehydrogenase
LCFA	Long-chain fatty acid
GPAT	Glycerol-3-phosphate acyltransferase
LPA	Lysophosphatidic acid
DAG	Diacylglycerol
DGAT	Diacylglycerol acyltransferase
MVA	Mevalonate
HMGCR	HMG-CoA reductase
ABCA1	ATP-binding cassette transporter A1
LDLR	Low-density lipoprotein receptor
PC	Phosphatidylcholine
PCho	Phosphocholine
GPC	Glycerophosphocholine
ChoK	Choline kinase
PA	Phosphatidic acid
LPC	Lysophosphatidylcholine
LPCATs	Lysophosphatidylcholine acyltransferase
ATX	Autotaxin
PG	Prostaglandin
COX	Cyclooxygenase
LT	Leukotriene
LOX	Lipoxygenase
S1P	Sphingosine-1-phosphate
ACAT	Acyl-CoA cholesterol acyltransferase
ER	Endoplasmic reticulum
LD	Lipid droplet
ATGL	Adipose triglyceride lipase
HSL	Hormone-sensitive lipase
MAL	Monoacylglycerol lipase
HIG2	Hypoxia-inducible gene 2
CPT	Carnitine palmitoyl transferase
ACSL	The long-chain acyl-CoA synthase enzyme family
LPO	Lipid peroxidation
PUFA-PL	PUFA-phospholipid
MUFA-PL	MUFA-phospholipid
SREBP	Sterol regulatory element-binding protein
RTK	Receptor tyrosine kinase
PPP	Pentose phosphate pathway
HCC	Hepatocellular carcinoma
HIF	Hypoxia-inducible factor
ccRCC	Clear cell renal cell carcinoma
LRP1	Low-density lipoprotein receptor-related protein 1
FAS	Fatty acid synthesis
PPAR	Peroxisome proliferator activated receptor
HFD	High-fat diet
EVs	Extracellular vesicles
ALOX15	Arachidonate lipoxygenase 15
$CD8^+$ TILs	$CD8^+$ tumor-infiltrating lymphocytes
ox-LDL	Oxidized low-density lipoprotein
PDAC	Pancreatic ductal adenocarcinoma
GPX4	Glutathione peroxidase 4
MARCO	Macrophage receptor for collagenous structures
ICI	Immune checkpoint inhibitor
M-MDSC	Mononuclear MDSC
PMN-MDSC	Polymorphonuclear MDSC
NSCLC	Non-small cell lung cancer
HNSCC	Neck squamous cell carcinoma
ADT	Androgen deprivation therapy
AAD	Antiangiogenic drug
ACT	Adoptive cell transfer
PD-1	Programmed cell death protein 1
CTLA-4	Cytotoxic T-lymphocyte-associated protein 4
PD-L1	Programmed death-ligand 1
PGC-1α	PPARγ coactivator 1-α

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JLY and JW designed the outline. HRJ, JW, ZJW, and MJX participated in literature searches and drafted the manuscript. HRJ, JW, MJX, and BHX designed the figures and tables. JW, JLY, and KD supervised and edited the manuscript. All authors read and approved the final manuscript.

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