

Review

The role of lipid metabolic interactions in reshaping the tumor microenvironment

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Abstract

The tumor microenvironment (TME), which encompasses the extracellular matrix, cancer-associated fibroblasts, endothelial cells, pericytes, and immune cells, is intimately connected to tumor development and metastasis. TME is widely heterogeneous, and metabolic interactions among the different components contribute to reshaping TME. Lipid metabolism, referring to lipid uptake, synthesis, transport, and lipolysis, is essential for maintaining cellular homeostasis. The availability of nutrients in the TME constantly changes during tumor progression, and tumor cells must reprogram lipid metabolism to maintain their rapid proliferation, survival, invasion, and metastatic potential. The interactions of lipid metabolism among tumor cells and other cell subtypes reshape the microenvironment into a niche suitable for tumor development. In this review, we present the featured lipid metabolic interactions within the TME of different cancer types and discuss how targeting abnormal lipid metabolic pathways could be a promising strategy for cancer therapeutics.

Key words tumor microenvironment, lipid metabolic interaction, tumor immunotherapy

Introduction

Tumor microenvironment (TME) refers to the interior environment surrounding tumor cells and includes the extracellular matrix (ECM), cancer-associated fibroblasts (CAFs), endothelial cells (ECs), pericytes, and immune cells. The TME is highly heterogeneous and closely associated with tumor occurrence, development, and metastasis [1]. Among these factors, the interactions between different cell subtypes play crucial roles in tumor development. The ECM regulates tumor cell proliferation, migration, and invasion through interactions with cells. CAFs, the most prominent stromal cells in the TME, promote tumor cell growth and invasion by secreting growth factors and cytokines and contributing to immune evasion. ECs are key players in tumor angiogenesis, providing essential nutrients and oxygen to tumors while also being involved in metastasis and immune escape. Pericytes affect blood

vessel stability and permeability, influencing immune cell infiltration and drug delivery within the TME. Additionally, immune cells such as tumor-infiltrating lymphocytes (TILs), macrophages, and dendritic cells play dual roles in tumor immune surveillance and evasion. TILs are an adaptive immune response against tumor growth. Understanding the specific roles of these cell subtypes in various cancer types is crucial for developing new therapeutic strategies [2].

An important feature of the TME is metabolic reprogramming, including changes in lipid metabolism. This reprogramming helps tumor cells adapt to challenges in the microenvironment, such as hypoxia, acidity, and nutrient deficiencies. The purpose of these adaptations includes facilitating angiogenesis and enhancing tumor cell growth, invasion, and metastasis [3]. The interactions between carcinogenic signals and the environment select favorable meta-

bolic pathways and carcinogenic characteristics for tumor cells [4].

Lipids are important components of the cell membrane structure and participate in various biological activities [5]. Lipids not only are used for energy storage and metabolism but also play important roles as signaling molecules for many cellular activities. Lipid metabolic reprogramming has been well recognized as a hallmark of cancer. In cholesterol metabolism, tumor cells break through metabolic homeostatic regulation by increasing the expression of low-density lipoprotein receptor (LDLR); moreover, cholesterol synthases (such as HMG-CoA reductase) are activated to increase endogenous synthesis. However, normal cells rely heavily on negative feedback inhibition to maintain metabolic balance. In terms of fatty acid (FA) metabolism, tumor cells upregulate CD36 and other transporters to augment FA uptake, thus rapidly replenishing the membrane components and energy required for proliferation, while the level of FA intake is significantly lower in normal cells. Importantly, variations in metabolic products also contribute to malignancy, which is exemplified by arachidonic acid (AA) metabolism. Tumor cells convert AA into proinflammatory mediators, such as prostaglandin E₂, to drive immunosuppression and metastasis, whereas normal cells tend to produce anti-inflammatory products such as lipoxin. These differences in lipid metabolism between cancer cells and normal cells are closely related to the intricacies of the tumor microenvironment [6–8]. Cancer cells undergo metabolic interactions with diverse compo-

nents of the TME to support rapid proliferation, invasion, and metastasis (Figures 1 and 2).

Breast Cancer and TME

Breast cancer (BC) is the most common type of cancer in women [9]. Breast cancer can be classified into four types on the basis of molecular subtype: HR positive/HER-2 negative, HR positive/HER-2 positive, HR negative/HER-2 positive, and triple-negative breast cancer (TNBC) [10]. The factors that influence the development of breast cancer are genetic and nongenetic. Nongenetic risk factors include age, obesity, the use of exogenous female hormones, alcohol consumption, and reproductive factors, among others [11].

Lipid metabolism reprogramming plays a significant role in the initiation and progression of breast cancer [12]. On the one hand, breast tumor cells reprogram TME metabolism in a paracrine- or autocrine-dependent manner. On the other hand, the heterogeneity of the TME affects the process of tumor occurrence and development. Compared with that in normal breast tissue, lipid metabolism in breast cancer cells substantially differs.

Adipocytes in BC

The dynamic interactions between breast tumor cells and related adipose cells promote the progression of breast cancer. The metabolites produced by adipocytes can stimulate the growth of tumor cells. Adipocytes increase the expression levels of featuring

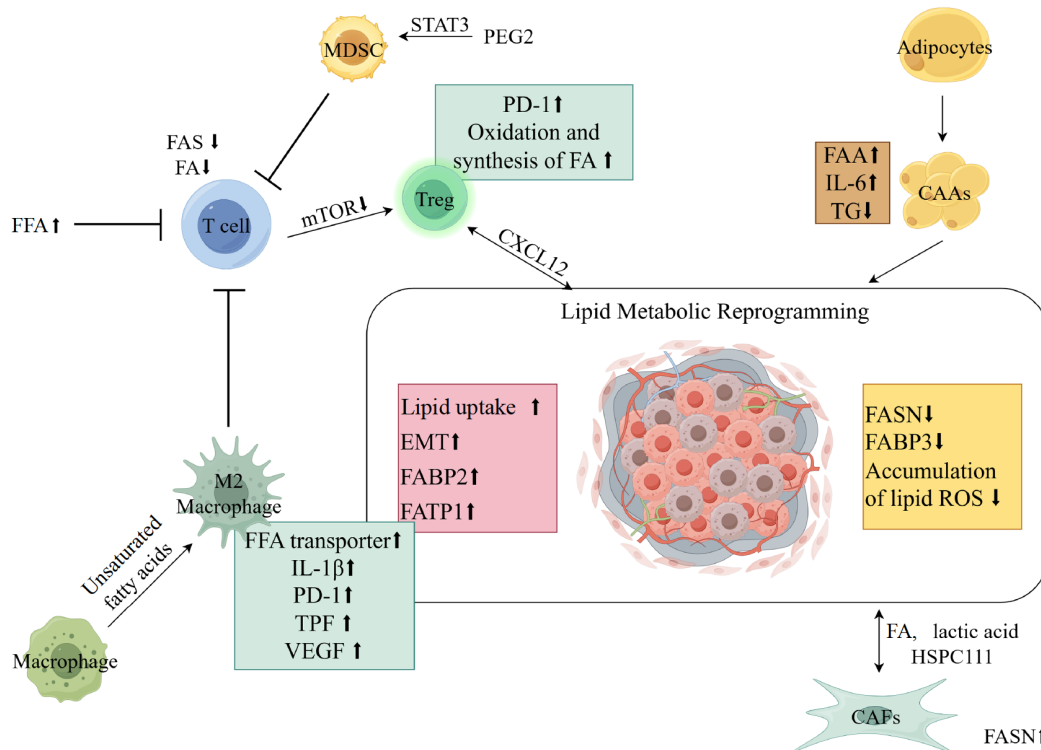


Figure 1. Lipid metabolism interactions in the tumor microenvironment Tumor cells adapt to adverse conditions in the TME through reprogramming of lipid metabolism, leading to aberrant signaling pathways. Additionally, the secretion of fatty acids by tumor cells into the microenvironment can cause changes in the phenotype and function of nontumor cells, and reprogrammed stromal cells can reshape the ECM by secreting paracrine signals. The dynamic interaction between tumor cells and the TME promotes the formation of a microenvironment conducive to angiogenesis, tumor invasion, and tumor immune evasion. EMT, epithelial-mesenchymal transition; FFA, free fatty acid; FABP, fatty acid-binding protein; FAS, fatty acid synthase; FATP, fatty acid transport protein; HSPC111, hematopoietic stem progenitor cell 111; IL, interleukin; mTOR, mammalian target of rapamycin; PD, programmed cell death protein; PGE₂, prostaglandin E₂; ROS, reactive oxygen species; STAT3, signal transducer and activator of transcription 3; TG, triglyceride; TPF, taxane/platinum/5-fluorouracil; VEGF, vascular endothelial growth factor.

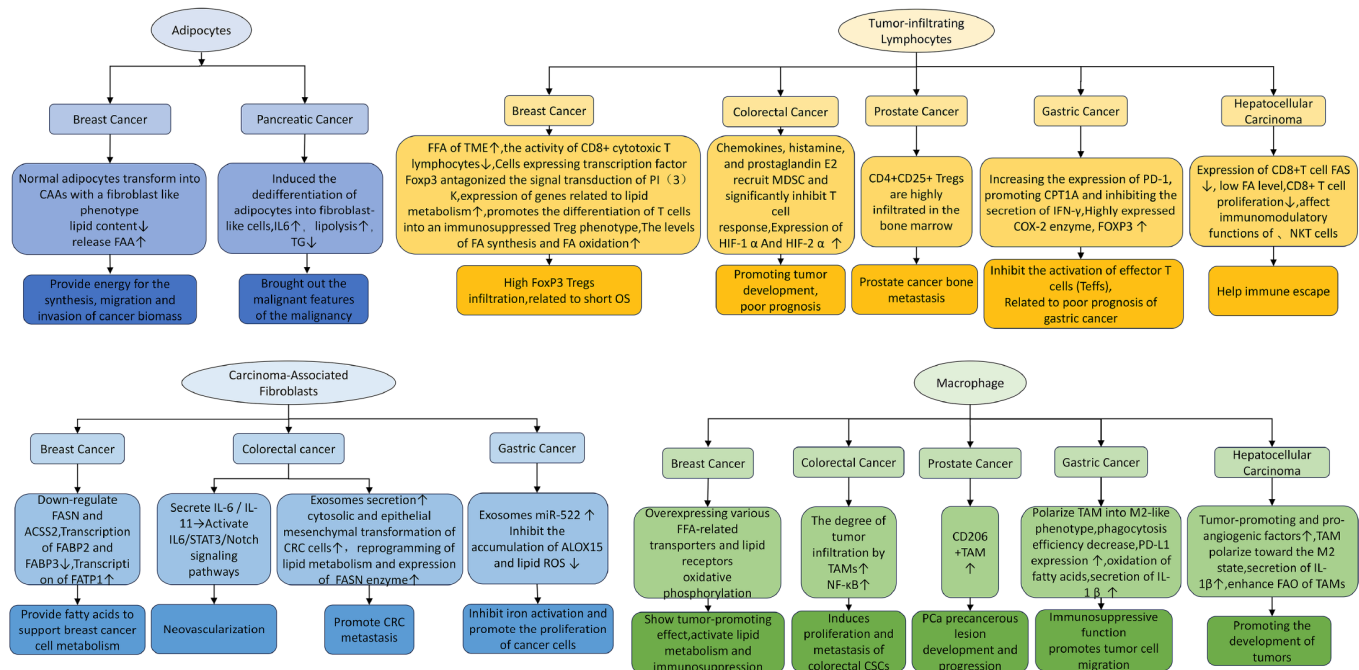


Figure 2. Functions and mechanisms of lipid metabolic interactions between cancer cells and other cell subsets in the TME ACS2, acyl-coenzyme A synthetase short-chain family member 2; ALOX, arachidonic acid lipoxygenase 15; CAAs, cancer-associated adipocytes; CAFs, carcinoma-associated fibroblasts; CPT1A, carnitine palmitoyltransferase 1A; CRC, colorectal cancer; CSCs, cancer stem cells; FFA, free fatty acid; FABP, fatty acid binding protein; FASN, fatty acid synthase; FATP, fatty acid transporter; FOXP3, forkhead box protein P3; HIF, hypoxia-inducible factor; IL, interleukin; MDSCs, myeloid-derived suppressor cells; NKT cells, natural killer T cells; OS, overall survival; PCA, prostate cancer; PD-1, programmed cell death protein 1; PD-L1, programmed death ligand 1; STAT, signal transducer and activator of transcription; TAMs, tumor-associated macrophages; Teffs, effector T cells; TG, triglyceride.

jumonji and AT-rich interaction domain 2 (JARID2) in breast cancer cells via leptin secretion, which is facilitated by the Janus kinase 2 (JAK2)/signal transducer and activator of transcription 3 (STAT3) signaling cascade. JARID2 can transcriptionally repress a series of tumor suppressor genes and simultaneously enhance lipid metabolism in breast cancer cells [13]. Mammary adipose cells secrete oleic acid, which, in conjunction with acyl-CoA synthetase long-chain family member 3 (ACSL3), safeguards breast cancer cells from undergoing ferroptosis [14]. Notably, stearoyl-CoA desaturase-1 (SCD1), a key enzyme regulating the SFA/MUFA ratio, has been demonstrated to modulate lipid membrane composition and confer ferroptosis resistance in breast cancer cells through the SFA/MUFA metabolic pathway [15–18]. These findings suggest that a coordinated mechanism involving both secreted oleic acid and endogenous SCD1-mediated lipid remodeling is involved in protection against ferroptosis. The metabolic processes of adipocytes themselves are concurrently regulated by tumor cells. Creatine derived from adipocytes promotes obesity-driven breast cancer progression. Cancer cells in the obese microenvironment upregulate acyl CoA synthetase Bubblegum family member 1 (Acsbg1), which enhances ATP production through oxidative phosphorylation and facilitates the influx of adipocyte-derived creatine into the TME via the creatine transporter Slc6a8 [19]. TGFβ signaling in breast cancer cells drives the expression of metabolism-regulating signaling molecule C (FAM3C) in adipocytes. Overexpression of FAM3C significantly reduces cell death in breast cancer cells and fibrosis within the TME [20]. The interaction between cancer-associated adipocytes (CAAs) and breast tumor cells reshapes the microenvironment into a favorable state for tumor proliferation, angiogenesis,

infiltration, and metastasis.

CAFs in BC

CAFs are the predominant stromal cells in the TME. They constitute a heterogeneous and plastic population that is involved in the metabolic reprogramming of tumor cells mediated through various pathways, leading to the deregulation of lipid metabolism [21]. Prostaglandin E2 (PGE2) is a biologically active lipid mediator that promotes tumor progression and is associated with poor patient prognosis. PGE2 inhibits the proliferation and activation of CAFs to limit the growth of primary breast tumors but paradoxically promotes metastasis [22]. Exosomes derived from CAFs carry miR-454-3p, which targets acyl-CoA synthetase long-chain family member 4 (ACSL4) in breast cancer cells to inhibit lipid metabolism and ferroptosis [23].

Macrophages in BC

M2-like macrophages are closely related to the metastasis of breast cancer [24]. Lipid-related macrophages (LAMs) exhibit the typical functional characteristics of M2-like macrophages and display active lipid metabolism and immunosuppressive functions via the overexpression of various FFA-related transporters and lipid receptors. The increase in LAM infiltration in the tumor-adipose microenvironment is correlated with a shorter survival rate in breast cancer patients [25]. Importantly, LAMs are positively costained with alveolar macrophage (AM) markers such as Siglec-F and display similar enrichment of genes related to lipid metabolism. This similarity suggests a potential relationship between LAMs and AMs in the context of lung metastasis in patients with breast cancer

[26]. Deficiency in myeloid neutral ceramidase (NcDase), which catalyzes the conversion of ceramide to sphingosine, triggers the reprogramming of tumor-associated macrophages (TAMs) into an immunosuppressive phenotype. In preclinical breast cancer models, this reprogramming ultimately results in T-cell exhaustion. Specifically, TAMs are identified via markers such as CD11b and F4/80, which are commonly used to distinguish macrophages from other immune cells within the tumor microenvironment [27]. Lipid accumulation and lipolysis facilitated by fatty acid binding proteins (FABPs) in TAMs accelerate the metastasis of breast cancer [28].

TILs in BC

TILs are related to improvements in the survival of patients with various tumor subtypes. During the activation process, different lymphocyte subtypes exhibit metabolic heterogeneity. Effector T lymphocytes (Teffs) typically exhibit a high degree of glycolysis to meet their increased energy demands, whereas regulatory T cells (Tregs) display increased lipid oxidation rates [29]. Importantly, recent studies have highlighted the complex interplay between lipid metabolism and the function of CD8⁺ T cells within the TME. The accumulation of free fatty acids (FFAs) in the TME has been shown to exert immunosuppressive effects on cytotoxic CD8⁺ T lymphocytes, decreasing their activity and efficacy [30,31]. Elevated FFA levels can promote lipid uptake and peroxidation in CD8⁺ T cells, leading to ferroptosis and functional impairment [31]. In contrast, Tregs utilize lipids efficiently through fatty acid oxidation, which is essential for their immunosuppressive functions. The inhibition of lipid synthesis and metabolic signaling pathways in Tregs, such as those regulated by sterol regulatory element binding proteins (SREBPs), has been shown to enhance the antitumor immune response by reducing Treg-mediated immunosuppression [32].

Cancer stem (-like) cells in BC

Cancer stem (-like) cells (CSCs) represent a population of quiescent self-renewing cells characterized by the expression of CD44/CD24 markers [33]. These cells are present in primary tumors and can drive invasive tumor phenotypes, contributing to the unfavorable prognosis of TNBC [34].

Lipid metabolism is considered a key factor in the proper functioning of pathways involved in determining the fate of CSCs [35]. The increased lipogenesis in breast CSCs (BCSCs) is associated with abnormal expression of lipid enzymes such as FASN and SCD1, which are highly involved in maintaining their self-renewal and proliferative capabilities. Overexpression of key enzymes involved in *de novo* fatty acid synthesis, such as ATP-citrate lyase (ACLY), in breast cancer cells leads to increased expression of stemness factors and the transcription factor SNAIL, which in turn promotes epithelial-mesenchymal transition (EMT) and cancer stemness [36]. Inhibition of the fatty acid synthesis pathway suppresses the stemness of CSCs. For example, pyruvium pamoate (PP) induces cytotoxic effects and prevents metastasis in CSCs by impairing the metabolic flux of glucose into cholesterol and fatty acid synthesis [34]. The small natural compound resveratrol can induce apoptosis in CSCs by downregulating the *FASN* gene and increasing the expression of the apoptosis-promoting genes *DAPK2* and *BNIP3* [37]. The JAK/STAT signaling pathway regulates lipid metabolism, promoting BCSC and cancer chemoresistance. Inhibition of JAK/STAT3 signaling blocks the self-renewal of BCSCs and the expression of many lipid metabolism genes, including carnitine

palmitoyl transferase 1B (CPT1B) [38].

PGE2 signaling enhances intrinsic tumor-initiating ability and promotes and enhances the CSC phenotype [39]. The Wnt pathway is involved in regulating cell proliferation and differentiation and determining cell fate. Celecoxib inhibits CSCs by suppressing PGE2 synthesis and downregulating Wnt pathway activity, resulting in chemotherapeutic sensitivity, inhibition of EMT, and weakening of metastasis and tumorigenesis [40].

Gangliosides, a type of sphingolipid, participate in cell-to-cell communication and play an immunomodulatory role. In tumor cells that overexpress gangliosides, the functions of T cells and B cells are inhibited, which promotes tumor cell immune system escape [41]. Studies have shown that the ganglioside GD2 can be used as a cell surface marker of CSCs in BC and that GD3 synthase (GD3S) can be used as a potential therapeutic target of CSCs [42,43]. Inhibiting GD3S can attenuate the EMT of CSCs and tumor cell proliferation and metastasis.

Colorectal Cancer and TME

Colorectal cancer (CRC) is a common malignant tumor of the digestive system. CRC has the second-highest mortality rate among all cancers worldwide and has become a major public health problem [9].

The risk of CRC is driven mainly by environmental factors, especially diet. Changes in CRC cellular metabolism are suggested to be the earliest trigger for malignant cell transformation [44]. Altered lipid metabolism in CRC is characterized mainly by the upregulation of lipogenesis involving *ab initio* synthesis of fatty acids (FAs) and triglycerides, increased lipid uptake and abundance, and dependence on FAs [45,46]. Changes in total lipid content and differential expression of genes encoding lipogenesis-related enzymes are observed in tumor tissues compared with normal tissues [47].

Excessive intake of dietary fats is considered a risk factor for the formation and/or exacerbation of tumor precursors, such as adenomatous polyps, and the development of colorectal tumors is associated with increased bile acid levels. Excess dietary fats alter the overall pool of bile acids, thereby activating or limiting the intestinal and hepatic cross-signaling of the bile acid receptor farnesoid X receptor (FXR). FXR is a major regulator of bile acid-mediated effects and the occurrence of colorectal tumors [48].

Cancer-associated fibroblasts in CRC

Because of their extensive interactions with cancer cells, CAFs play a key role in cancer progression by promoting ECM deposition and remodeling, EMT, invasion, metastasis, and treatment resistance [49].

Notch is a cell surface receptor that mediates signaling pathways between adjacent cells [50,51]. The IL6/STAT3/Notch axis plays an important role in the interaction between mesenchymal stem cells and tumor cells in colon cancer [52]. Stromal cell-derived exosomes promote Notch activation by activating STAT1 [53]. Notch signaling is a major regulator of neovascularization, a critical aspect of tumor development. In colon cancer, activation of Notch signals tumor metastasis [54]. Notch signaling is also involved in regulating fibroblast activation. In CRC, Notch signaling mediates the conversion of bone marrow-derived stromal cells (BMSCs) into activated fibroblasts.

CAFs secrete factors that contribute to angiogenesis and tumor

invasion. They are markers for detecting colorectal tumor progression; therefore, their role in characterizing colorectal tumors is important. Hu *et al.* [55] reported that CAFs can directly secrete exosomes to increase the stemness and EMT of CRC cells, promoting CRC metastasis and chemoresistance. Gong *et al.* [56] also demonstrated that reprogramming of lipid metabolism and increased expression of the FASN enzyme in CAFs lead to lipid production and promote the migration of colorectal adenocarcinoma cells. Furthermore, knocking down FASN in CAFs or blocking CD36 *in vivo* with monoclonal antibodies eliminates the migratory nature of CRC cells. According to Heichler *et al.* [57], CAFs secrete IL-6/IL-11 to promote tumor development by activating the STAT3 signaling pathway. Zhang *et al.* [58] reported that the cancer-derived exosome HSPC111 promotes lipid metabolism reprogramming in CAFs to promote CRC liver metastasis.

Tumor-associated macrophages in CRC

The differentiation of tumor-associated macrophages (TAMs) has been detected in a few cancer models and is regulated by relevant Notch signaling. However, there is a lack of evidence regarding the expression profile of Notch receptors and ligands in TAMs associated with different types of cancer [59,60].

The degree of tumor infiltration by TAMs is strongly associated with poor patient prognosis. Tumor cells can recruit macrophages by secreting major spectral regulators of macrophage survival, differentiation, and chemotaxis [61]. TAMs that highly express PGE2 also promote the survival and growth of CSCs. PGE2 activates NF- κ B through the EP4-phosphatidylinositol 3-kinase (PI3K) and EP4-protein kinase A signaling pathways, thus inducing the proliferation and migration of colorectal CSCs [62].

TILs in CRC

TILs are strongly associated with CRC prognosis. The accumulation of Tregs is positively associated with good prognosis in some patients with chronic inflammatory infiltration [63,64]. In contrast to breast cancer, high levels of FOXP3⁺ Treg infiltration result in improved survival in patients with mismatch repair-proficient CRC [65]. According to Hanke *et al.* [66], high levels of FOXP3⁺ Treg infiltration in early lymph node-negative CRC are associated with a good prognosis. Vlad *et al.* [67] reported that increased FOXP3⁺ Treg density is associated with improved survival in patients with CRC and suggested that this density could be an independent prognostic factor. In right-sided colorectal cancer, aberrant activation of phospholipase α 2-IVa/AA signaling mediates immunosuppressive effects by secreting IL-17A and adenosine to induce CD39⁺ $\gamma\delta$ Treg production [68]. Berntsson *et al.* [69] reported prolonged survival in CRC patients with B-cell infiltration, which may also be associated with good prognosis in CRC patients.

Gastric Cancer and TME

Gastric cancer (GC) is a highly heterogeneous and invasive malignant tumor. Differences in lipid metabolism pathways between GC and normal gastric tissues have been reported. These differences are closely related to the growth, metabolism, metastasis, and prognosis of GC [70,71]. The typical characteristics of lipid metabolism in gastric cancer include increased lipid synthesis and increased β -oxidation and oxidative decomposition of FAs, which depend on the *de novo* biosynthetic pathway of lipids [72]. SREBP, ACLY, SCD, FASN, and acetyl coenzyme A carboxylase

(ACC) are regulatory factors of lipid metabolism in GC.

CAFs in GC

CAFs play a key role in gastric cancer by secreting a variety of cytokines and matrix metalloproteinases to promote the proliferation, invasion and metastasis of tumor cells. CAFs secrete exosomal miR-522 to inhibit ferroptosis in gastric tumor cells by targeting ALOX15 and blocking the accumulation of lipid ROS [73].

CAFs participate in the development of drug resistance in GC [74,75]. miR-149, which targets PGE2 and IL-6, mediates the crosstalk between tumor cells and CAFs in GC and promotes the proliferation of gastric tumor cells [76]. Cisplatin and paclitaxel activate ubiquitin-specific protease 7/heterogeneous ribonucleoprotein A1 signaling to increase the secretion of CAF-derived miR-522. This activation results in the inhibition of ALOX15 and a reduction in lipid ROS accumulation in tumor cells, ultimately decreasing chemosensitivity [73].

TILs in GC

The distribution of TILs in gastric cancer patients is closely related to patient prognosis. Specific T-cell subsets, such as Tregs and memory T cells, are associated with immune evasion and poor prognosis in patients with gastric cancer. Tregs promote tumor immune evasion by enhancing lipid biosynthesis and FOXP3 expression.

The functions of activated CD8⁺ T cells in GC depend on the synthesis of lipids, including FAs and cholesterol. PI3K and mTOR regulate this process through the SREBP and LXR transcription factors [77]. In the hypoxic hypoglycemic TME of GC, FA accumulation leads to the overexpression of the fatty acid translocase CD36 and oxidized low-density lipoprotein (ox-LDL). ox-LDL promotes p38 phosphorylation in a CD36-dependent manner, resulting in lipid peroxidation and ferroptosis, which damages CD8⁺ TIL cytotoxicity and inhibits the tumor immune response [78]. In GC, TILs overexpress 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase (HMGCR) and accumulate large amounts of cholesterol in the plasma membrane of CD8⁺ T cells, which activates ER-XBP1, induces TGF- β , VEGF, and Kyn, and promotes high expression of immune checkpoints, such as PD-1, PD-3, and PD-8, leading to CD8⁺ T-cell exhaustion and GC cell immune escape [79,80].

Infiltrated FOXP3⁺ Tregs are associated with poor prognosis in GC patients. Tregs have enhanced lipid biosynthesis, with advantages in the tumor environment depending on supplementary energy pathways involving lipid metabolism, which mainly rely on the FAO pathway [81]. FAO can inhibit the activation of TefFs by increasing the expression of PD-1, promoting carnitine palmitoyl transferase (CPT1A), and attenuating the secretion of IFN- γ [82]. Tregs are CD4⁺ T cells that express FOXP3, which acts as the main regulatory factor for the development and function of Tregs. FOXP3 can increase fatty acid uptake, oxidative phosphorylation (OXPHOS), and FAO [83]. Tregs express the enzyme cyclooxygenase-2 (COX-2) and produce PGE2, which mediates immunosuppression in the TME. High expression of FOXP3⁺ also inhibits the proliferation of autologous CD4⁺CD25⁻ T cells [84,85].

Tissue-resident memory T (Trm) cells account for 30% of the TILs in the TME of gastric adenocarcinoma and are associated with a good prognosis. Trm cells rely mainly on lipid uptake and metabolism to maintain survival. The lipid uptake capacity of

gastric adenocarcinoma cells surpasses that of Trm cells, resulting in the apoptosis of the latter. Targeting PD-1 can increase the expression of fatty acid binding protein 4 (Fabp4) and Fabp5 in Trm cells while inhibiting their expression in gastric adenocarcinoma cells, thereby increasing lipid uptake by Trm cells [86]. Blocking PD-L1 on tumor cells may be important in determining antitumor immunity processes.

Other cells with a role in GC progression

Adipocytes play a significant role in promoting GC progression by reprogramming FA metabolism in the TME. Through the action of phosphatidylinositol transfer protein cytoplasmic 1 (PITPNC1), adipocytes facilitate the reprogramming of FA metabolism, which supports the enhanced growth and metastasis of GC cells, particularly in the omentum, a common site for GC metastasis. [87]. The conversion of adipocytes into CAFs further contributes to the malignant behavior of GC. Upon interaction with GC cells, adipocytes undergo a phenotypic switch into CAFs, which actively participate in promoting tumor progression by secreting proinflammatory cytokines, ECM components, and growth factors that stimulate GC cell invasion and peritoneal metastasis [88]. This adipocyte-to-CAF conversion facilitates remodeling of the TME, creating a more permissive environment for GC progression and invasion. The crosstalk between GC cells and adipocytes highlights the role of the omental fat depot as a crucial player in GC metastasis, particularly in advanced stages of the disease.

Mesenchymal stem cells (MSCs) in the GC TME contribute significantly to the resistance of GC cells to chemotherapy. MSCs promote the stemness of GC cells via FAO, a key metabolic pathway that supports the survival of CSCs under metabolic stress. FAO enhances mitochondrial respiration and provides energy for the maintenance of the CSC phenotype, increasing the capacity of GC cells to survive chemotherapeutic treatments [89]. This metabolic shift not only aids in the survival of GC cells but also confers increased resistance to conventional chemotherapy, leading to a poor prognosis for patients. MSCs also secrete cytokines and growth factors that contribute to the maintenance of the CSC niche, further promoting drug resistance and tumor relapse. The role of MSCs in GC underscores the importance of targeting metabolic reprogramming and the stem cell niche to overcome chemoresistance and improve treatment outcomes in GC.

In addition to their role in regulating immune responses, DCs in the GC TME exhibit altered lipid metabolism that impairs their immune-stimulating functions. Lipid metabolism alterations in DCs reduce their ability to present antigens effectively, compromising the activation of T cells and weakening the overall antitumor immune response. This metabolic dysregulation in DCs is associated with poor tumor staging and prognosis in GC patients, as the impaired immune response allows tumor cells to escape immune surveillance and progress unchecked [90]. The altered lipid metabolism in DCs can be linked to the unique metabolic demands of TME, which favor immune suppression and tumor progression. This dysfunction of DCs highlights the complex interplay between metabolism and immunity in GC and points to the potential of targeting lipid metabolism pathways to enhance immune function and improve patient outcomes.

The reprogramming of lipid metabolism in various cell types within the GC TME, including adipocytes, MSCs, and DCs, plays a crucial role in promoting tumor progression, metastasis, and drug

resistance. Adipocytes facilitate GC metastasis through FA metabolism reprogramming and conversion into CAFs, whereas MSCs support GC cell stemness and chemoresistance through fatty acid oxidation. Additionally, DCs in GC exhibit metabolic alterations that impair their immune function, contributing to immune evasion and poor prognosis. Understanding these metabolic pathways and their interactions in the GC TME provides new insights into the mechanisms driving GC progression and offers potential therapeutic targets to improve treatment outcomes.

Hepatocellular Carcinoma and TME

Hepatocellular carcinoma (HCC) has the sixth highest incidence rate and is one of the leading causes of cancer-related deaths worldwide [9]. The TME of HCC is associated with different metabolic disorders, including abnormal lipid metabolism, an area that has attracted extensive attention in recent years [91].

Lipid metabolism is closely related to the development of HCC. Nonalcoholic fatty liver disease is characterized by dyslipidemia, increased oxidative stress, ROS production, and mitochondrial alterations, which cause inflammatory responses that can further progress to HCC [92]. Cholesterol induces fatty acid accumulation in the liver, leading to insulin resistance, lipotoxicity, hepatocyte damage, and the inhibition of AMPK, leading to hepatic fibrosis. Enhanced cholesterol synthesis in hepatocytes results in excess free cholesterol forming cholesterol crystals, which can activate nucleotide-binding oligomerization domain-like receptor protein 3 (NLRP3). This leads to subsequent hepatocyte inflammation and scorching, which is a process of tissue repair leading to fibrosis and HCC [93]. In addition, adipose tissue can induce insulin resistance and trigger chronic low-level inflammation in various organs through the secretion of leptin, adiponectin, resistin, and numerous inflammatory cytokines, which promote the occurrence and development of HCC [94].

Lipid metabolism is also associated with poor prognosis in patients with HCC. The family of lipid metabolism regulators, lysophosphatidylcholine acyltransferases (LPCATs), increases the structural stability of cell membranes, protects tumor cells, and facilitates cancer development and metastasis. Hypermethylation of many CpG sites of LPCATs is associated with poor prognosis [95]. SREBP-1 upregulation in HCC promotes the synthesis of FAs associated with the upregulation of ACLY, FASN, and SCD in HCC. This change increases cholesterol uptake by HCC cells and regulates mitochondrial FAO [96].

Dendritic cells in HCC

The inhibition of fatty acid synthesis in dendritic cells (DCs) in HCC affects the endoplasmic reticulum (ER) and Golgi apparatus, which reduces the antigen-presenting capacity of DCs [97]. Specifically, the ability of lipid-containing DCs to process and present antigens is reduced [98]. Cross-presentation is directly regulated by oxidized lipid accumulation in DCs. Lipid oxide can block cross-presentation by reducing the expression of the peptide-MHC class I complex on cell surfaces [99]. The HCC TME is helpful in shaping the functional phenotype of DCs in the presence of lipid droplets (LDs) and predicting the diversity of LD types in healthy and sick individuals [96].

TAMs in HCC

TAMs play a crucial role in HCC [100]. Most TAMs polarize toward

the M2 state and promote HCC progression by secreting tumor-promoting and proangiogenic factors and inhibiting the activation of tumor-infiltrating T cells [101]. M2 monocyte-derived macrophages (MDMs) promote HCC cell migration in an FAO-dependent manner by increasing IL-1 β secretion [102]. Lipid loading by macrophages is associated with increased tumor killing and inflammatory capacity. Receptor-interacting protein kinase 3 (RIPK3) is a serine/threonine kinase whose expression is downregulated in TAMs isolated from mouse and human HCC samples. RIPK3 deficiency has been shown to increase FAO in TAMs through the ROS-caspase2-PPAR pathway, thereby promoting M2 polarization in TAMs [103]. Additionally, macrophages are associated with the development of HCC in obese individuals. Debebe *et al.* [104] reported that the Wnt/ β -linked protein, a novel signal generated by steatosis-induced macrophage infiltration, promotes the growth of tumor progenitor cells.

Kupffer cells become foam cells after the uptake of oxidized low-density lipoprotein (OxLDL). Together with macrophages recruited by activated hepatocytes, these cells promote the formation of a TME conducive to tumor immune escape by producing large amounts of cytokines, chemokines, and growth factors and triggering the release of suppressive immune checkpoint proteins by T cells [93].

TILs in HCC

The low number of CD8⁺ T cells in HCC tissues may be related to the inhibition of CD8⁺ T cell proliferation by lipids. Additionally, the expression of multiple FASs in CD8⁺ T cells in liver cancer tissues is downregulated, and FA levels are low [96]. Natural killer T (NKT) cells mainly recognize lipid antigens; thus, the immunomodulatory functions of HCC cells may be affected once lipid metabolism is altered [96,105]. The promyelocytic leukemia zinc finger (*PLZF*) gene is a cell type-specific master regulator that controls invariant natural killer T (iNKT) cell development and effector functions. iNKT cells increase lipid biosynthesis upon activation and are synergistically promoted by PPAR γ and PLZF through increased transcription of *Srebf1*, which encodes SREBP1. CD8⁺ T, NKT, and Th17 cells in the nonalcoholic fatty liver disease microenvironment facilitate immune escape, whereas the number of CD4⁺ T cells with antitumor effects is reduced.

Other cells involved in HCC progression

Abnormal lipid metabolism in MDSCs, neutrophils, and natural killer (NK) cells contributes to tumor progression. Enhanced FAO promotes the immunosuppressive function of tumor-infiltrating MDSCs, whereas FAS affects neutrophils. Additionally, low-level MSCs increase adipogenesis and accelerate HCC growth by activating the AKT/mTOR/SREBP1 pathway through YAP signaling.

Lipid Metabolism-targeted Therapeutic Strategies for Cancer Treatment

Tumor cells exhibit distinct biological features characterized by their dependency on lipid metabolism, with aberrant lipid metabolic pathways driving tumor proliferation, metastasis, and immune evasion. Targeting lipid metabolism may exert therapeutic effects through direct tumor cell killing, remodeling of the immunosuppressive tumor microenvironment, or synergistic effects with other therapeutic modalities. Currently, numerous preclinical studies are exploring combinatorial approaches that integrate lipid metabo-

lism-targeting interventions (such as the inhibition of fatty acid synthesis, cholesterol uptake, lipid droplet accumulation, or phospholipid metabolism) with conventional therapies to increase treatment efficacy and mitigate drug resistance (Table 1).

In the fatty acid metabolic pathway, key therapeutic targets include FASN, ACC, and CPT1. The FASN inhibitor TVB-2640 has been extensively evaluated in clinical trials, with dose-limiting toxicity (DLT) primarily manifesting as reversible dermatologic and ocular effects [8,106]. Notably, TVB-2640 has demonstrated a manageable safety profile when combined with bevacizumab in clinical studies targeting astrocytoma [107]. In combination with paclitaxel, TVB-2640 has demonstrated significant therapeutic efficacy in solid tumors, including KRAS-mutant lung cancer, ovarian cancer, and breast cancer [106]. MK-1775 synergistically inhibits tumor progression and enhances anti-PD-1 therapy efficacy by suppressing the PI3K/AKT/mTOR pathway, thereby downregulating FASN-mediated fatty acid synthesis, blocking fatty acid oxidation in TAMs, and promoting IRF-mediated CXCL10/11 secretion to increase CD8⁺ T cell infiltration [108]. The acetyl-CoA carboxylase (ACC) inhibitor ND-646 functions as an allosteric regulator to effectively suppress *de novo* fatty acid synthesis in non-small cell lung cancer (NSCLC), resulting in significant inhibition of pulmonary tumor growth as a monotherapy or in combination with carboplatin [109]. Resistance to antiangiogenic drugs (AADs) arises from hypoxia-induced metabolic reprogramming toward FAO in tumors, which fuels cancer cell proliferation through CPT1A-dependent activation of the FAO pathway. Combination therapy targeting both angiogenesis and CPT1A (e.g., etomoxir) effectively reverses this resistance mechanism by disrupting FAO dependency, thereby significantly enhancing antitumor efficacy [110].

In the cholesterol metabolic pathway, the antitumor responses of CD8⁺ T cells can be augmented by the modulation of cholesterol metabolism. Inhibition of cholesterol esterification in T cells via the cholesterol acyltransferase ACAT1 enhances effector functions and promotes CD8⁺ T cell proliferation. Avasimibe, an ACAT1 inhibitor originally developed for atherosclerosis treatment, elevates plasma membrane cholesterol levels in CD8⁺ T cells, thereby strengthening TCR signaling and immunological synapse formation. This mechanism confers robust antitumor activity in murine melanoma models, with synergistic efficacy observed when avasimibe is combined with anti-PD-1 therapy [111]. The tumor-intrinsic vacuolar-type H⁺-ATPase subunit ATP6V0A1 promotes cholesterol uptake and 24-hydroxycholesterol (24-OHC) production in CRC cells via RAB-GEF1-dependent endosomal maturation. This metabolic reprogramming suppresses antitumor immunity by inhibiting memory CD8⁺ T cell function through the liver X receptor (LXR)-transforming growth factor-beta 1 (TGF- β 1) axis. The ATP6V0A1 inhibitor daclatasvir effectively reversed this immunosuppressive phenotype, thereby inhibiting tumor growth in preclinical models [112]. Statins, such as simvastatin, inhibit hydroxymethylglutaryl-coenzyme A reductase (HMGCoAR), thereby exerting pleiotropic antitumor effects by suppressing cholesterol biosynthesis pathways [113]. The nuclear receptor retinoic acid receptor-related orphan receptor gamma (ROR γ) serves as a critical therapeutic target driving cholesterol biosynthesis programs in TNBC. Pharmacological inhibition of ROR γ effectively suppresses tumor growth and synergizes with statins to enhance antitumor efficacy [114].

In phospholipid metabolism pathways, long noncoding RNA (lncRPM) sustains BCSC stemness and chemotherapy resistance

Table 1. Comprehensive summary of lipid metabolism-targeted cancer therapeutics

Metabolic pathway	Target	Drug/ Intervention	Mechanism	Efficacy & combination strategies	Ref.
Fatty acid metabolism	FASN	TVB-2640	Inhibits <i>de novo</i> fatty acid synthesis	Combination with paclitaxel shows significant efficacy in KRAS-mutant lung, ovarian and breast cancers	[106,107]
		MK-1775	Inhibits PI3K/AKT/mTOR pathway, downregulates FASN expression, blocks FAO in TAMs, enhances CD8 ⁺ T cell infiltration	Synergizes with anti-PD-1 to suppress tumor progression	[108]
	ACC	ND-646	Allosteric ACC inhibitor blocking malonyl-CoA production	Significantly inhibits NSCLC growth alone or combined with carboplatin	[109]
	CPT1A	Etomoxir	Inhibits FAO	Reverses anti-angiogenic therapy resistance, synergizes with vascular targeting	[110]
Cholesterol metabolism	ACAT1	Avasimibe	Inhibits cholesterol esterification, increases CD8 ⁺ T cell membrane cholesterol	Enhances TCR signaling and immune synapse formation, synergizes with anti-PD-1	[111]
	ATP6V0A1	Daclatasvir	Inhibits endosomal maturation, blocks cholesterol uptake and 24-OHC generation	Reverses LXR-TGF- β 1-mediated immunosuppression; suppresses colorectal cancer growth	[112]
	HMGCoAR	Simvastatin	Inhibits cholesterol biosynthesis	Multifaceted antitumor effects, synergizes with ROR γ inhibitors	[113,114]
Phospholipid metabolism	PLA2G16	Giripladib	Inhibits PLA2G16-mediated phospholipid metabolism and PI3K/AKT/Wnt/Hippo pathways	Combination with doxorubicin/cisplatin/tamoxifen eliminates BCSCs and reverses chemo-resistance	[115]
	Lp-PLA2	Darapladib	Inhibits Lp-PLA2, induces ferroptosis and modulates phosphatidylethanolamine metabolism	Synergizes with GPX4 inhibitors to suppress gastric, esophageal, lung and breast cancers	[116]
Lipid uptake & storage	FATP2	Lipofermata	Blocks lipid uptake	Reverses age-related resistance to BRAF/MEK inhibitors in melanoma	[117]
	FABP4	BMS309403	Inhibits FABP4-mediated fatty acid transport	Reduces ovarian cancer metastatic burden and enhances carboplatin sensitivity	[118]
	PPAR γ /Nur77	ST-CY14	Blocks PPAR γ -Nur77 interaction, stabilizes Nur77 protein	Inhibits aberrant lipid metabolism and metastasis in breast cancer	[119]
	CD36	CD36 inhibitor	Blocks fatty acid uptake, reduces T cell lipotoxicity	Restores CD8 ⁺ T cell function and synergizes with anti-PD-1	[120]
	DGAT2	PF-06424439	Inhibits lipid droplet formation	Enhances radiosensitivity in breast cancer and reverses cancer stem cell properties	[121]

FASN, fatty acid synthase; NSCLC, non-small cell lung cancer; TAMs, tumor-associated macrophages; FAO, fatty acid oxidation; ACC, acetyl-CoA carboxylase; CPT1A, carnitine palmitoyltransferase 1A; TCR, T-cell receptor; LXR, liver X receptor; TGF- β 1, transforming growth factor beta 1; HMGCoAR, 3-hydroxy-3-methylglutaryl-CoA reductase; ROR γ , retinoic acid receptor-related orphan receptor gamma; BCSCs, breast cancer stem cells; Lp-PLA2, lipoprotein-associated phospholipase A2; GPX4, glutathione peroxidase 4; FATP2, fatty acid transport protein 2; FABP4, fatty acid-binding protein 4; PPAR γ , peroxisome proliferator-activated receptor gamma; EMT, epithelial-mesenchymal transition.

by activating phospholipase A2 group 16 (PLA2G16)-mediated phospholipid metabolism, as well as the PI3K/AKT, Wnt/ β -catenin, and Hippo/YAP signaling pathways. Giripladib, a cytosolic phospholipase A2 (cPLA2) inhibitor evaluated in clinical trials for chronic osteoarthritis, exhibits enhanced therapeutic efficacy when combined with standard-of-care agents such as doxorubicin, cisplatin, or tamoxifen [115]. Lipoprotein-associated phospholipase A2 (Lp-PLA2) regulates intracellular phospholipid metabolism and confers resistance to ferroptosis, a form of iron-dependent cell death. Darapladib, an Lp-PLA2 inhibitor, synergizes with glutathione peroxidase 4 (GPX4) inhibitors to induce ferroptosis and modulate phosphatidylethanolamine (PE) metabolism, thereby effectively suppressing tumor growth in gastric, esophageal, and lung adenocarcinoma and breast cancers [116].

In lipid uptake and storage, key targets include CD36, FABPs, and diacylglycerol acyltransferase (DGAT). Enhanced resistance to targeted therapies (BRAF and MEK inhibitors) in elderly melanoma patients arises from lipid secretion by senescent fibroblasts, which drives tumor cells to overexpress fatty acid transport protein 2 (FATP2) for excessive lipid uptake. Blocking FATP2 suppresses lipid accumulation, restores mitochondrial metabolism, and reverses age-related drug resistance [117]. Small-molecule inhibitors of FABP4, such as BMS309403, significantly reduce the metastatic tumor burden and increase the sensitivity of cancer cells to carboplatin, thereby offering a novel metabolic targeting strategy for ovarian cancer metastasis [118]. In fatty acid uptake, the binding of PPAR γ to the orphan nuclear receptor Nur77 promotes Nur77 ubiquitination and degradation, leading to aberrant fatty acid

uptake during breast cancer progression. ST-CY14, a small-molecule inhibitor that blocks the Nur77-PPAR γ interaction, stabilizes Nur77 protein levels, effectively suppressing dysregulated lipid metabolism and tumor growth/metastasis in breast cancer, thereby offering an innovative therapeutic strategy for targeting fatty acid uptake disorders [119]. CD36-mediated fatty acid uptake induces lipid peroxidation and ferroptosis in tumor-infiltrating CD8 $^{+}$ T cells, leading to their dysfunction. Blocking CD36 or inhibiting ferroptosis restores their antitumor activity, with synergistic efficacy when combined with anti-PD-1 therapy [120]. In lipid droplet (LD) storage, PF-06424439, a diacylglycerol acyltransferase 2 (DGAT2) inhibitor, reduces LD biogenesis by blocking DGAT2 activity, thereby increasing radiosensitivity in breast cancer cells. When combined with radiotherapy (RT), it downregulates lipid metabolism and EMT-related genes, reverses CSC traits, and significantly improves RT efficacy [121] (Table 1).

On the basis of current research progress and the challenges associated with tumor drug resistance, future strategies may include the development of dual-pathway inhibitors and other combination therapies, the optimization of treatment regimens, and the exploration of synergistic mechanisms between metabolic interventions and immunotherapy. Additionally, novel delivery systems such as lipid nanoparticles targeting the tumor microenvironment could be engineered to achieve precise targeting and enhance therapeutic efficacy [122–124].

Discussion and Prospects

Cellular metabolism reprogramming is a primary characteristic of various cancers. Changes in lipid metabolism in the TME can be beneficial to the migration, invasion, and metastasis of tumor cells. The regulation of lipid metabolism, including lipid uptake, synthesis, and hydrolysis, is essential for maintaining cellular homeostasis. Cancer cells coordinate the activation of lipid synthesis metabolism and its associated signaling networks for the formation of biomembranes, energy metabolism, and the formation of second messengers.

Among the tumors discussed above, we found that tumor tissues are biased toward increased levels of lipid metabolism, such as increased lipid *de novo* synthesis, increased β -oxidation and oxidative catabolism of FAs, increased lipid uptake and abundance, and increased dependence on FAs. This reprogramming is particularly pronounced in gastrointestinal tract tumors, such as colorectal, gastric, and hepatocellular carcinomas. Reprogrammed lipid metabolism provides energy for tumor development and induces ECM changes in the TME, affecting cell signals; causing adverse reactions such as insulin resistance, lipotoxicity, and normal tissue damage; and further promoting tumor growth, infiltration, invasion, and metastasis. Moreover, they promote the expression of immune checkpoint molecules and ECM remodeling, indirectly affecting the recruitment and activity of immune cells. Cancer-stromal interactions are strengthened in the process of tumor progression.

On the one hand, the heterogeneity of tumor cell lipid metabolism is mediated by abnormal oncogenic signaling within cells, such as stimulating oncogenic mutation signal transduction components. This signaling can directly increase the activity of metabolic enzymes or transcription factors, thereby increasing the expression of metabolic regulatory factors. Lipid metabolism is also influenced by external factors of the TME, including hypoxia, acidosis, various

growth factors, chemokines, leukocyte interleukins, colony-stimulating factors, transcription factors, and lipid molecules.

On the other hand, the reprogramming of lipid metabolism leads to aberrant signaling pathways in cancer cells, and the secretion of fatty acids into the microenvironment can cause phenotypic and functional changes in nontumor cells, thereby influencing the development process of tumors. The dynamic interactions between tumor cells and the TME reshape the tumor microenvironment into an environment suitable for tumor growth, infiltration, invasion, and metastasis.

Importantly, in addition to the abovementioned tumors, other malignancies (e.g., non-small cell lung cancer, prostate cancer, and glioma) also exhibit features of abnormal lipid metabolism. For example, lung cancer cells can increase monounsaturated fatty acid synthesis by upregulating stearoyl-CoA desaturase (SCD1) to maintain membrane fluidity [125]. Prostate cancer relies on FASN to provide a lipid raft signaling platform [126]. A more detailed summary of these therapeutic strategies and their immunological implications is provided in Tables 2 and 3.

However, the existing evidence has not yet clarified whether these metabolic alterations constitute the core driving mechanism, and the interaction network with TME needs to be further analyzed. Future studies need to further distinguish between tissue-specific metabolic patterns and universal regulatory laws.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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Table 2. Direct inhibitors of lipid metabolism in cancer

Compound	Target	Regulatory mechanism	Cancer type	Ref.
Statins	HMGCR	Inhibits HMGCR, rate limiting enzymes in the metabolic pathway of mevalonate	Breast cancer, prostate cancer	[127,128]
Celecoxib	COX-2	Significantly reduces the number of liposomes and the production of PGE2 in IBC cells	Breast cancer	[129]
5-LOX inhibitor	5-LOX	Inhibits 5-LOX pathway to reduce the production of leukotrienes	Colorectal cancer	[130]
Disulfiram	ALDH, Cu	Inhibits ALDH and chelates Cu inducing ROS production and inhibits the ROS-NF-κB pathway to induce apoptosis	Breast cancer, pancreatic cancer	[131–136]
Tepoxalin (TPX), Erlotinib (ERB)	COX-2, 5-LOX, EGFR	Inhibits the expression of COX-2, 5-LOX, EGFR and VEGF-C to promote the apoptosis and anti-proliferation	Gastric cancer	[137]
Kaempferol, Kaempferide	SCD1, the structural protein of lipid droplets	Inhibits the expression of lipogenic and adipogenic proteins, lipid droplet proteins, and oxidative stress-related proteins to attenuate lipid accumulation and oxidative stress	Hepatocellular carcinoma	[138]
Orlistat	FASN	Blocks the thioesterase domain of FASN, decreasing the proliferation of PC cells and enhancing apoptosis	Pancreatic cancer	[139]
Etomoxir	CPT1	Inhibits CPT1 to reduce FAO, suppressing low pH-induced PC invasion	Pancreatic cancer	[140]
Nanoformulation of avasimibe (a potent ACAT-1 inhibitor)	ACAT-1	Inhibits ACAT-1 to reduce cholesterol ester storage in lipid droplets and increase intracellular free cholesterol levels, leading to apoptosis and inhibition of proliferation	Pancreatic cancer	[140]
Yarrow SFE (Yarrow obtained by Supercritical Fluid Technology)	SREBF1, FASN, SCD1	Downregulates SREBF1, FASN and SCD to reduce accumulation of lipid droplets and inhibition of cellular invasion	Pancreatic cancer	[141]
PPNP formulation	FASN, ACC, lipin, Cox-2	Suppresses excessive lipid synthesis and reduces FASN, ACC, lipin and Cox-2 protein levels	Pancreatic cancer	[142]
Natural compounds including flavonoids, alkaloids, and saponins	SREBP-1, AMPK, HMGCR	Targets SREBP-1 to regulate lipid metabolism, targets AMPK to influence lipid metabolism, regulates lipid metabolism-induced ferroptosis in cancer cells, targets HMGCR to influence lipid metabolism, and others	Gastric cancer	[143]
Solid lipid-nanoparticle formulation of miR-125 + Afa/SLN-KL coated with mitochondrial targeting K peptide and EGFR-directed L ligand	–	Disrupts metabolic reprogramming, interrupts the supply of cholesterol and triglycerides, alleviates the “Warburg effect” of tumors, and intensifies energy expenditure in the tumor microenvironment, thereby inhibiting tumor proliferation and aggressiveness	Gastric cancer	[144]
Curcumin	FASN, AKT, STAT3	Targets binding to FASN, AKT, STAT3, downregulates FASN to reduce lipid synthesis, and regulates IL-6/JAK/STAT3 and IL-1β/NF-κB pathways, and PI3K/AKT pathway to inhibit metabolic disorders and the occurrence of EMT	Hepatocellular carcinoma	[145]
Diosmetin (DSM)	–	Inhibits fatty acid biosynthesis and glycerides metabolism pathways	Hepatocellular carcinoma	[146]

HMGCR, 3-hydroxy-3-methylglutaryl-coenzyme A reductase; COX-2, cyclooxygenase-2; 5-LOX, 5-lipoxygenase; ALDH, aldehyde dehydrogenase; EGFR, epidermal growth factor receptor; VEGF-C, vascular endothelial growth factor-C; SCD-1, stearoyl-CoA desaturase 1 (a lipogenic protein); FASN, fatty acid synthase; PC, pancreatic cancer; CPT1, carnitine palmitoyltransferase 1; FAO, fatty acid oxidation; ATAT-1, acyl-CoA cholesterol acyltransferase 1; SREBP-1, sterol regulatory element-binding protein 1; SCD, stearoyl-CoA desaturase; ACC, acetyl-coenzyme A carboxylase; AMPK, adenosine monophosphate activated protein kinase; AKT, protein kinase B; STAT3, signal transducer and activator of transcription; PI3K, phosphatidylinositol 3-kinases; IL, interleukin; JAK, Janus kinase; NF-κB, nuclear factor-kappa B; PPNP, paclitaxel-poly (lactic-coglycolic acid) nanoparticle.

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Table 3. Indirect inhibitors of lipid metabolism in cancer

Compound	Target	Regulatory mechanism	Cancer type	Ref.
Biguanides	mTOR	Activates AMPK, inhibiting mTOR signal transduction, and reduces the expression of FAS	Breast cancer, colorectal cancer, prostate cancer	[147]
Betulinic acid	STAT3	Interfers with the binding of HIF-1 α and STAT3 to VEGF promoter in hypoxic PC-3 cells	Breast cancer, colorectal cancer, prostate cancer	[148]
Tamoxifen, Fluvastatin	AKT	Inhibits PI3K/AKT/mTOR pathway	Breast cancer	[149]
Everolimus, Temsirolimus	mTOR	Inhibits PI3K/AKT/mTOR pathway	Breast cancer	[149]
Alpelisib	PI3K	Reduces AKT signaling and targets PI3K/AKT/mTOR pathway	Breast cancer	[150,151]
lapatinib	HER2	Inhibits HER2 kinase activity, reducing FASN tyrosine phosphorylation and FASN enzyme activity, which further downregulates HER2 signal transduction and inhibits breast cancer invasion	Breast cancer	[151]
C75	HER2	Inhibits HER2 protein and mRNA expression, resulting in reduced phospholipid synthesis	Breast cancer	[152]
Oslitha	STAT3, NF- κ B	Inhibits STAT3, NF- κ B, STAT3, and NF- κ B related gene expression	Colorectal cancer	[153]
GSI	γ -secretase	Inhibits Notch pathway	Colorectal cancer	[154]
ZLDI-8	ADAM17	Inhibits the proliferation of CRC cells by inhibiting Notch signaling pathway	Colorectal cancer	[155]
Metformin	AMPK	Activates AMPK/p53/miR-23a/FOXA1 pathway to induce apoptosis	Hepatocellular carcinoma	[156]
Cisplatin, Pclitaxel	USP7	Activates USP7/hnRNPA1 signaling pathway and increases the secretion of CAF-derived miR-522, inhibiting ALOX15, reducing the accumulation of lipid ROS in tumor cells, and ultimately reducing chemical sensitivity	Gastric cancer	[73]
Apatinib	PI3k, AKT	Inhibits glycolysis and reduce amino acid metabolism through MAPK and PI3K/AKT/mTOR signaling	Hepatocellular carcinoma	[157]
Everolimus (RAD001), Rhein	PI3k, AKT, mTOR	Inhibits PI3K/AKT/mTOR pathway activation to reduce tumor weight and volume	Gastric cancer	[158]
Tanshinone IIA (TSN)	p53	Induces ferroptosis in GC cells through p53 mediated downregulation of SLC7A11	Gastric cancer	[159]
Loganetin, 5-Fluorouracil	–	Downregulates the Wnt/ β -catenin pathway	Gastric cancer	[160]
Cetuximab	–	Promotes DR4 recruitment and DISC formation in lipid rafts to increase the sensitivity of gastric cancer cells to TRAIL inducing GC cells apoptosis	Gastric cancer	[161]
Naringenin	p53	Regulates antioxidant enzymes and scavenges free radicals to weaken LP, inhibiting NDEA-hepatogenesis and precancerous lesions, and induces rapid accumulation of p53, arresting hepatoma cells in G1/G2 and G2/M phases	Hepatocellular carcinoma	[162]
CPI-613 (Devimistat)	AMPK	Activates AMPK signaling in PC cells to increase phosphorylation levels with ACC and reduces lipid metabolism, promoting apoptosis	Pancreatic cancer	[163,164]
Zalcitabine	TFAM	Induces oxidative mtDNA damage and degradation of mitochondrial transcription factor TFAM, activating DNA damage sensing CGAS-STING1 pathway to induce autophagy and subsequently autophagy-dependent iron death	Pancreatic cancer	[163]
Novobiocin (Nov) derivative XN4	TF, TFR, NOX4	Promotes the accumulation of Fe ²⁺ in GC cells by upregulating TF and TFR, and induces ferroptosis in GC cells by upregulating NOX4 expression	Gastric cancer	[165]
Chrysin	CBR1	Inhibits CBR1 to drive ROS-dependent autophagy, which leads to degradation of FTH1 and increases intracellular free iron levels	Pancreatic cancer	[166]

(Continued)

Compound	Target	Regulatory mechanism	Cancer type	Ref.
Romidepsin, Tamoxifen	FOXM1	Dwnregulates of FOXM1 expression and induction of reactive oxygen species/lipid peroxidation to synergistic induction of PC cell aging	Pancreatic cancer	[167]
Astaxanthin (AST)	AMPK, mTOR	Activates the AMPK, inhibits mTOR, and triggers signals that initiate autophagosome formation	Gastric cancer	[168]
Silybum marianum total extract (STE), silymarin (Sm), and silibinin (Sb)	HGF, c-Met, PI3K, AKT, mTOR, Wnt, β -catenin, AFR	Suppresses oxidative stress, HCC cell proliferation, HGF/cMET, Wnt/ β -catenin, and PI3K/AKT/mTOR signaling pathways	Hepatocellular carcinoma	[169]
Sorafenib	SLC7A11, HBXIP	Enhances oxidative stress-induced HCC ferroptosis by blocking cystine/glutamate reverse transporter SLC7A11-dependent glutathione (GSH) synthesis and inhibiting HBXIP/SCD axis in hepatocellular carcinoma	Hepatocellular carcinoma	[170]
Hypericin(HP)	PKAC α	Binds directly to PKAC α , activates PKA/AMPK signaling to reduce apoptosis in hepatocytes, and attenuates lipid accumulation to reduce oxidative stress, enhance lipid oxidation and inhibit adipogenesis	Hepatocellular carcinoma	[171]

mTOR, mammalian target of rapamycin; AMPK, adenosine monophosphate-activated protein kinase; FAS, fatty acid synthase; STAT3, signal transducer and activator of transcription 3; HIF-1 α , hypoxia-inducible factor-1 α ; PI3K, phosphatidylinositol 3-kinase; AKT, protein kinase B; HER2, human epidermal growth factor receptor 2; FASN, fatty acid synthase; NF- κ B, nuclear factor-kappa B; ADAM17, a disintegrin and metalloproteinase 17; USP7, ubiquitin-specific protease 7; hnRNPA1, heteroribonucleoprotein A1; MAPK, mitogen-activated protein kinase; GC, gastric cancer; DR4, death receptor 4; DISC, death-inducing signaling complex; TRAIL, tumor necrosis factor-related apoptosis-inducing ligand; LP, lipid peroxidation; CGAS, cyclic GMP-AMP synthase; STING1, stimulator of interferon response cGAMP interactor 1; TFAM, mitochondrial transcription factor A; TF, transferrin; TFR, transferrin receptor; NOX4, nicotinamide adenine dinucleotide phosphate oxidase 4; CBR1, human carbonyl reductase 1; FTH1, ferritin heavy polypeptide 1; HGF, hepatocyte growth factor; c-MET, the receptor of HGF; Wnt, Wingless-type MMTV integration site family; AFP, a strategic signaling molecule implicated in numerous sides of tumor biology; HBXIP, the oncoprotein hepatitis B X-interacting protein; PKAC α , protein kinase A catalytic subunit α .

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