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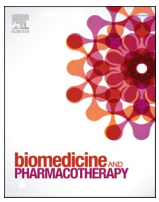

Review

Targeting fatty acid uptake and metabolism in cancer cells: A promising strategy for cancer treatment

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ABSTRACT

Despite scientific development, cancer is still a fatal disease. The development of cancer is thought to be significantly influenced by fatty acids. Several mechanisms that control fatty acid absorption and metabolism are reported to be altered in cancer cells to support their survival. Cancer cells can use *de novo* synthesis or uptake of extracellular fatty acid if one method is restricted. This factor makes it more difficult to target one pathway while failing to treat the disease properly. Side effects may also arise if several inhibitors simultaneously target many targets. If a viable inhibitor could work on several routes, the number of negative effects might be reduced. Comparative investigations against cell viability have found several potent natural and manmade substances. In this review, we discuss the complex roles that fatty acids play in the development of tumors and the progression of cancer, newly discovered and potentially effective natural and synthetic compounds that block the uptake and metabolism of fatty acids, the adverse side effects that can occur when multiple inhibitors are used to treat cancer, and emerging therapeutic approaches.

1. Introduction

Fatty acids contribute to the cellular lipid pool to maintain homeostasis in cellular biochemical processes like forming the biological membrane and maintaining membrane fluidity, acting as secondary messengers in signaling pathways, and serving as energy storage. Fatty acids are the fundamental component of many lipid species, including phospholipids, sphingolipids, diacylglycerol (DAG), triacylglycerol (TAG), etc. [1,2]. It is abundantly clear that fatty acids play a role in carcinogenesis since they are required for energy during metabolic stress conditions in rapidly proliferating cancer cells, which rely on external absorption and de novo fatty acid production [3,4]. This review will look at the various roles that fatty acids play in the development of tumors and the progression of cancer, as well as recently discovered and potential natural and synthetic compounds that block the uptake and metabolism of fatty acids and their side effects when used in combination with other inhibitors to treat cancer.

2. Sources of fatty acids in cancer cells

Mammalian cells obtain fatty acids through direct uptake from the surrounding microenvironment or *de novo* synthesis using nutrients, e.g., glucose, glutamine, etc. Lipidomic remodeling of cancer cells, such as modulating fatty acid transport and metabolism, storing lipid droplets, and de novo lipogenesis, is a well-known metabolic hallmark [5]. Although pathways driving specific lipid phenotypes are unclear.

Abbreviations: AMPK, AMP-activated protein kinase; EET, Epoxyeicosatrienoic acid; FASN, fatty acid synthase; COX, cyclooxygenase; CPT1, Carnitine palmitoyltransferase 1; IL, Interleukin; MMP, matrix metalloproteinase; mTOR, mammalian target of rapamycin; mTORC, mammalian target of rapamycin complex; PIP_3, Triphosphorylated PI(3−5)P3; PI3K, phosphoinositide 3-kinase; SCD-1, Stearoyl-CoA desaturase-1; SREBP, Sterol regulatory element-binding protein; TCA, Tricarboxylic acid; ALA, α-Linolenic acid,18:3n-3; MUFA, mono-unsaturated fatty acid; ARA, arachidonic acid, 20:4n-6; FADS, fatty acid desaturase; LA, linoleic acid,18:2n-6; ELOVL, elongation of very long-chain fatty acid protein; OA, oleic acid, 18:1n-9; PLA_2, phospholipase A_2; $cPLA_{2,}$, cytoplasmic PLA_2; $iPLA_{2,}$, Ca^{2+}-independent PLA_2; EMT, epithelial-mesenchymal transition; DAG, diacylglycerol; TAG, triacylglycerol; PGE, prostaglandin E; PRDX6, peroxiredoxin 6; PA, palmitic acid,16:0; ACC, AMPK-mediated acetyl-CoA carboxylase; DGLA, dihomo-γ-linolenic acid; LKB1, Liver kinase 1; RSL3, (1 S,3 R)-RSL-3; FIN, ferroptosis inducing agent; PE, phosphatidylethanolamine.

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Endothelial cells predominantly take in and metabolize fatty acids based on the length, number, and position of double bonds in the chain [6]. Essential fatty acids and their long-chain polyunsaturated fatty acids (LCPUFAs) and their derivatives, such as arachidonic acid,20:4n-6 (ARA), eicosapentaenoic acid,20:5n-3 (EPA), docosahexaenoic acid, 22:6n-3 (DHA) play essential roles in human health and disease [6,7].

Furthermore, one kind of n-3 and n-6 fatty acids interfere with the metabolism of the other. For example, an excess of n-6 fatty acids can limit the metabolism of n-3 fatty acids, potentially leading to a deficiency of n-3 LCPUFA metabolites [6–8]. Endothelial cells metabolize ARA through three main pathways: cyclooxygenase (COX), lipoxygenase, and cytochrome P450. The COX pathway generates primary metabolites like PGI_2, prostaglandin E_2 (PGE_2), TxA_2, and 12-hydroxyheptadecatrienoic acid. Lipoxygenase produces 12- and 15-hydroxy eicosatetraenoic acids. Epoxyeicosatrienoic acids (EETs), particularly 14,15- and 11,12-EETs, are significant metabolites synthesized through cytochrome P450. PGE_2 and TxA_2 are vital for vascular balance. PGI_2 acts as a vasodilator and platelet aggregation inhibitor, while TxA_2 constricts vessels and activates platelets. An imbalance in PGI_2 or TxA_2 production is linked to thrombotic and cardiovascular disorders. PGI_2's protective effects involve inhibiting platelet activation and leukocyte adhesion, enhancing cell survival through Bcl-2 upregulation, and activating the PI3-kinase-Akt pathway [9]. N-6 LCPUFAs produce pro-inflammatory eicosanoids in acute inflammatory responses.

On the other hand, n-3 LCPUFAs generate anti-inflammatory or neutral eicosanoids. Eicosanoids derived from ARA, an n-6 LCPUFA, regulate various processes such as cellular membrane composition, inflammation, coagulation, and vascular balance. Additionally, ARA-triggered cytokines and adipokines contribute significantly to metabolism and inflammation control. Another n-6 long-chain fatty acid, linoleic acid,18:2n-6 (LA), promotes inflammation by elevating inflammatory markers like TNF-α, MCP-1, VCAM-1, and ICAM-1. This effect is achieved through the activation of NF-κB and activator protein 1. Furthermore, LA also impacts the release of nitric oxide. These fatty acids play distinct roles in mediating inflammatory and metabolic responses within the body [6–9]. Both eicosapentaenoic and docosahexaenoic acids, types of n-3 fatty acids, compete with ARA in forming pro-inflammatory compounds like leukotrienes and prostaglandins. They also affect cytokine production. Beyond competing with n-6 fatty acids, n-3 fatty acids inhibit the generation of inflammatory markers such as C reactive protein, TNFα, matrix metalloproteinases (MMP)− 2 and MMP-9, and tissue inhibitors of MMP.

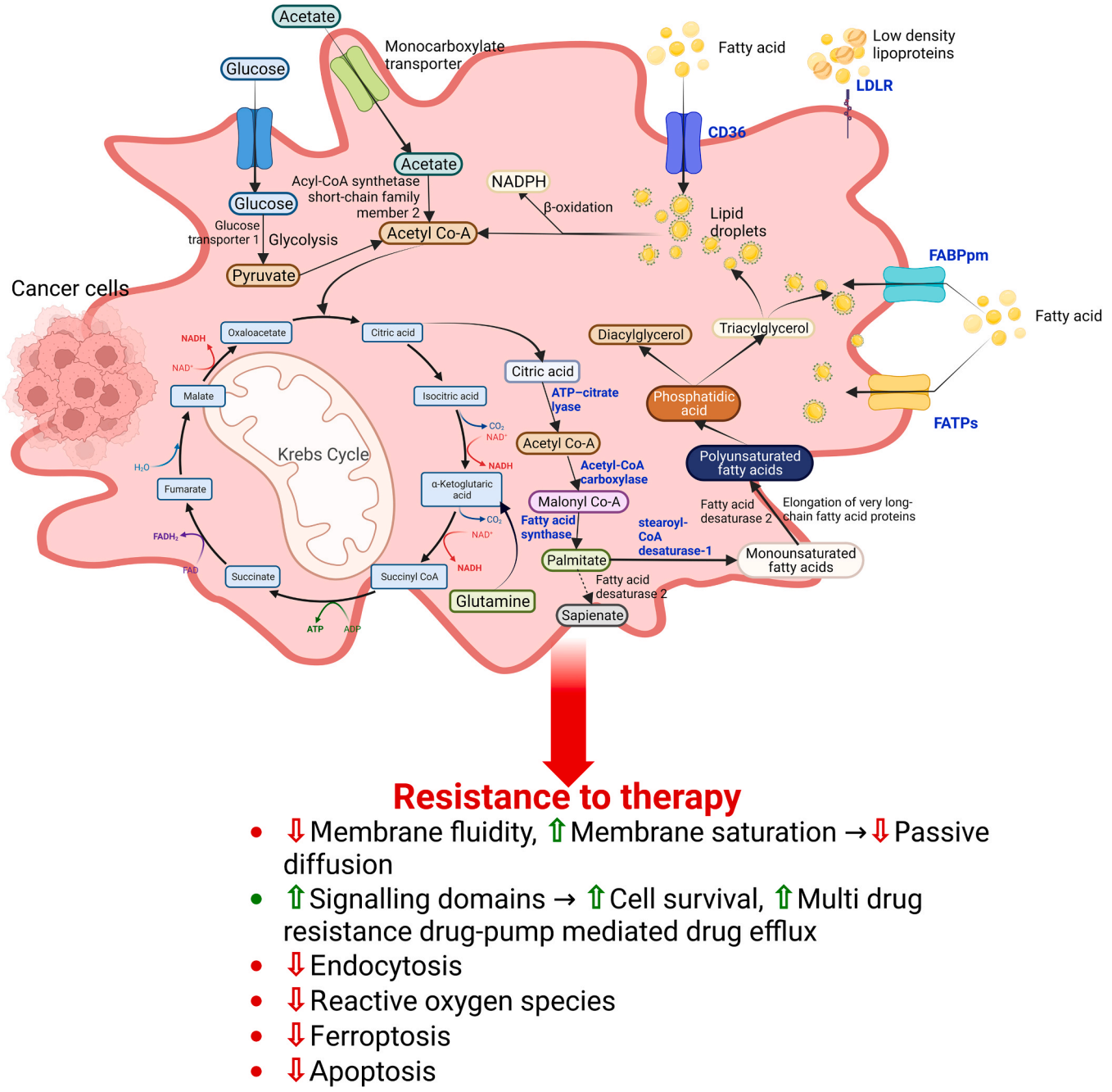
Moreover, n-3 fatty acids have the potential to act as a therapeutic tool by inhibiting COX-2 expression. This is particularly valuable since COX-2 overexpression is implicated in various inflammatory and degenerative conditions, including cancer [4,7–9]. Cancer cells overexpress fatty acid translocase (FAT/CD36), fatty acid transport protein family (FATPs), and plasma membrane fatty acid-binding proteins (FABPpm) to facilitate exogenous fatty acid uptake [7,10]. Fatty acid uptake and storage in lipid droplets, along with altered fatty acid oxidation products due to higher expression of CD36, are correlated with poor prognosis across various cancer types [11–13]. FAT/CD36 supports tumor growth by promoting lipidomic remodeling [13]. FAT/CD36 plays a vital role in cancer microenvironment metabolic crosstalk by shifting the allegiance of cancer cells towards exogenous lipid uptake.

Interestingly metastatic dissemination of various cancer cells e.g. kidney, gastric, colon, breast, prostate and ovarian cancer cells, preferably home to adipose tissue located in periglandular regions and visceral omentum [14], which might activate endogenous lipolysis of triglycerides to produce free fatty acids that could be subsequently secreted and taken up by metastatic cells overexpressing FABP4 and potentiate AMP-activated protein kinase (AMPK) to culminate β-oxidation through carnitine palmitoyl transferase 1 (CPT1) and acyl-CoA oxidase 1 activation [15]. Even overexpression of FAT/CD36, as well as a hypoxia-inducible factor (HIF)− 1α-dependent overexpression of FABP3 and FABP7, drive the progression of cancer through rapid uptake of long-chain fatty acids and cholesterol, that obtained from the adipocytes in the microenvironment [12,16].

These fatty acids are subsequently stored in cytoplasmic lipid droplets in cancer cells that sequester excess fatty acids in triacylglycerols and sterol esters [17]. The accumulated lipid droplets maintain lipid homeostasis, prevent lipotoxicity, and provide a vital source of ATP and NADPH during metabolic stress (Fig. 1) [17,18]. The stored lipids produce acetyl-CoA through β-oxidation, which subsequently enter the tricarboxylic acid (TCA) cycle to produce six times more ATP than oxidation of carbohydrates [19,20]. However, oxidation of acetyl-CoA-derived citrate by isocitrate dehydrogenase 1 is considered a significant source of cellular NADPH synthesis [21]. Henceforth, β-oxidation of lipid droplets produces sufficient ATP to fuel the metastatic cascade and provides NADPH for anabolic metabolism and detoxification of reactive oxygen species [22–25]. Obesity-associated adipose tissue induces persistent inflammation by secreting tumor necrosis factor α, interleukin (IL)− 6, IL-8, vascular endothelial growth factor, prostaglandins, and leukotrienes [26]. Adipocyte-mediated endocrine and paracrine signaling maintains the crosstalk between adiposity and cancer cell fatty acid metabolism [27]. Secreted adipokines induce cancer cells to secrete exosomes containing pro-lipolytic factors (e.g., miRNA-144, miRNA-126) to promote lipolysis in adjacent adipocytes through activation of AMPK signaling and induction of autophagy as well as the release of free fatty acids to shift the metabolic dependencies of migrating cancer cells towards exogenous lipid uptake and β-oxidation for energy supply [14,28,29]. Therefore, targeting the tumor microenvironment through inhibition of adipocyte lipolysis could be the potential therapy to reduce the availability of free lipids for cancer cells [30].

Cancer cells' uptake and scavenging of extracellular fatty acids during metabolic stress compensate for the diminished flux from glucose to acetyl-CoA. Even upregulated uptake of exogenous lysophospholipids (e.g., lysophosphatidylcholine, lysophosphatidylethanolamines, lysophosphatidylglycerols) and oxygen-consuming enzyme stearoyl-CoA desaturase-1 (SCD-1) dependent conversion of saturated fatty acids into monounsaturated fatty acids by cancer cells might support proliferation and survival [31]. This regulation of exogenous lipid uptake under hypoxia and oncogenic Ras activation under normoxic conditions mainly occurs through the HIF-dependent overexpression of lipid-binding proteins, e.g., FABP4 [31,32]. And citrate synthesis from reductive carboxylation and ultimate independence from SCD-1 to derive unsaturated fatty acids [31]. These results depict that microenvironmental conditions or oncogenic activation of signaling pathways resist SCD-1 inhibitors, which might open novel opportunities for therapy to rely on fatty acid uptake by cancer cells.

When fatty acids are formed from glucose and amino acid-derived carbon atoms, the process is known as de novo lipogenesis [33]. The process commonly occurs in hepatocytes and adipocytes, but tumor cells reactivate the process even in the presence of exogenous lipid sources [3,34]. Glucose or glutamine-derived carbons contribute to citrate biosynthesis [35,36]. Citrate or acetate-derived cytoplasmic acetyl-CoA is the basic substrate for de novo lipogenesis (Fig. 1) [3]. Metabolic stress, e.g., hypoxia or lipid depletion, induces acetyl-CoA synthetase 2 upregulation in cancer cells [37]. The irreversible carboxylation of acetyl-CoA into malonyl-CoA is known as the rate-limiting step of de novo lipogenesis and condensation of seven malonyl-CoA molecules and one molecule of acetyl-CoA by fatty acid synthase (FASN), ultimately produces palmitate (saturated 16-carbon fatty acid) [30,38]. Transcriptional modulation (e.g., sterol regulatory element-binding proteins (SREBPs) activation) contributes predominantly to de novo lipogenesis [39–41]. Sustained upregulated de novo lipogenesis followed by downstream elongation and desaturation pathways by cancer cells are flexible to shunt them into various biosynthetic pathways to synthesize a distinct cellular pool of lipid species with diverse functions from the required nutrients (e.g., glucose, glutamine, and acetate) [42].



Resistance to therapy

- ⇩Membrane fluidity, ⇧Membrane saturation →⇩Passive diffusion
- ⇧Signalling domains → ⇧Cell survival, ⇧Multi drug resistance drug-pump mediated drug efflux
- ⇩Endocytosis
- ⇩Reactive oxygen species
- ⇩Ferroptosis
- ⇩Apoptosis

Fig. 1. *Sources of Fatty acids by cancer cells and contribution to resistance to therapy.* Cancer cells obtain FAs from surrounding microenvironment as well as by de novo lipogenesis. Exogenous FA uptake is facilitated by specialized transporter, such as LDLR, CD36, FATPs and FABPpm. FAs and synthetic products are stored as lipid droplets and used for acetyl-CoA and NADPH production through β-oxidation. On the other hand, cancer cells depend on glucose, glutamine, and acetate for de novo lipogenesis. Palmitate is ultimately produced from citric acid and subsequently desaturated and elongated to form various group of lipid species. These changes result in decreased membrane fluidity, endocytosis, and passive diffusion of anticancer medicines, as well as decreased reactive oxygen species generation, ferroptosis, and apoptosis. Finally, it has enhanced signaling domains that promote cell survival and drug efflux via multidrug resistance drug pumps.

Subsequently, saturated palmitate synthesizes fatty acids (Fig. 1) [30,43,44]. As the prime product of de novo lipogenesis, palmitate can be elongated and desaturated through the activity of SCD-1, elongation of very long-chain fatty acids, and fatty acid desaturases (FADSs) to produce additional fatty acid species, including stearate and oleate to contribute to producing more complex lipids [45].

Considerably, oleate feeds into phosphatidic acid synthesis through the enzymatic activities of glycerol-3-phosphate acyltransferase one and acyl-CoA:LPA acyltransferase. Oleic acid,18:1n-9 (OA) is incorporated into triacylglycerides for storage in a glycerol-3-phosphate acyltransferase 1-dependent fashion [46–48]. Even phosphatidic acid has vital structural and signaling roles and is one of the main substrates for DAG and complex glycerolipids biosynthesis [49–53]. Several compensatory fatty acid metabolism pathways in cancer cells have been elucidated recently. SCD-1 enzymes are the most extensively studied, which regulate the cellular pool of unsaturated fatty acids as building blocks for phosphoglycerides, phosphoinositides, eicosanoids and sphingolipids. Albeit inhibitors targeting SCD-1 enzymes have shown modest effects that suggests possible alternative desaturation pathways e.g., fatty acid desaturase (FADS) 2 to generate functionally useful lipid species to support their membrane synthesis during proliferation [54–56].

3. Direct uptake of fatty acid

If glucose-based acetyl CoA synthesis is suppressed under hypoxia, cancer cells can boost the uptake of exogenous fatty acids [57]. Both *de novo* fatty acid synthesis and lipoprotein lipase (LPL) mediated extracellular lipolysis are found to be equipped by breast and liposarcoma tumors [58]. Cancer cells require more cholesterol than normal cells to obtain extra energy.

3.1. Low-density lipoprotein receptor

Low-density lipoprotein (LDL) carries and transfers cholesterol from the liver to the peripheral tissues through the LDL receptor (LDLR). LDLR has been found to be over-expressed in different cancers. Due to fulfilling the high cholesterol requirement to obtain more energy, cancer cells promote LDL uptake through endocytosis by the overexpressed level of LDLR [59].

3.2. CD36

Cluster of differentiation 36 (CD36) is a multiligand scavenger cell-surface receptor which binds to the long-chain fatty acids. The extracellular domains of CD36 contain multiple ligand binding sites. The extracellular region's CLESH (CD36 LIMP-II Emp sequence homology) motif interacts with thrombospondin-1/− 2 (TSP-1 and TSP-2). TSP-1 and CD36 interaction induces apoptosis and inhibits angiogenesis in tumor-associated endothelial cells [60]. TSP-1 expression is lost in various major cancer types 268 during malignant progression. ABT-510 (Abbott Laboratories, Abbot Park, IL) is a TSP-1 analog that exerts its biological effect via CD36 and inhibits tumor growth in vivo in different tumor models. Although ABT-510 could not show any significant activity in the phase II clinical trial, no significant toxicity was observed either by mono or combined therapy [61]. The extracellular region's hydrophobic fatty acid binding cavity mediates the uptake of oxidized low-density lipoproteins (OxLDL), advanced glycation end products (AGEs), and peptides by the interaction with the plasma membrane [62]. OxLDL was found to play an important role in inducing mutagenesis, which results in inflammation, promotion of tumor growth, and metastasis of cancer [59]. OxLDL deletion slowed cancer progression, and inhibition by monoclonal antibody reduced cancer severity in patients derived from preclinical models of prostate cancer [63]. Sulfo-N-hydroxy succinimidyl (NHS) ester of oleate (SSO) is an inhibitor that binds irreversibly to CD36 and inhibits OxLDL uptake by macrophages in Chinese hamster ovary cells and FA uptake in hepatocellular carcinoma cells [64,65]. Recently, an anti-inflammatory natural drug, Nobiletin (5,6,7,8,3,4′-hexamethoxyflavone) was found to inhibit CD36-dependent tumor angiogenesis, migration, invasion, and sphere formation through binding to the extracellular domain of CD36 [66]. Nobiletin has been suggested to be a potent inhibitor of cancer stem cells in multiple ways.

3.3. Fatty acid-binding proteins

The intracellular lipid carrier or fatty acid-binding proteins (FABPs) are required to transport fatty acids throughout various cellular compartments, including ER, lipid droplets, mitochondria, nucleus, and peroxisomes [67]. Alteration of FABP expression has been reported in various cancer types [68]. FABP1 was found to be upregulated in hepatocellular carcinoma and gastric cancer. FABP2 and FABP3 expression was reduced in breast cancer cells in in vitro studies [69]. In the case of FABP4, it has been suggested that exogenous FABP4 might promote prostate cancer cell progression [70]. From a cancer perspective, the role of FABP5 (alternative names epidermal-FABP or E-FABP) in pancreatic cancer has been mostly studied [69]. FABP5 enhances the transcriptional activity of the PPARβ/δ receptor by facilitating the delivery of fatty acids from the cytosol to the PPARβ/δ receptor. The enhanced activation of FABP5/PPARβ/δ pathway induces the expression of PPARβ/δ target genes and contributes to prostate cancer development [71]. Saturated long-chain fatty acids can inhibit the FABP5/PPARβ/δ pathway and suppress tumorigenic properties in gastric cancer [72]. FABP5 affects cancer invasiveness and fatty acid synthesis, while FABP4 promotes cancer cell invasion, angiogenesis, and inflammation [4]. These proteins have potential as diagnostic markers and therapeutic targets for obesity-associated cancers [4]. In breast cancer cells, considerable heterogeneity of FABP7 expression pattern has also been reported [73]. In the presence of chemotherapeutics Docetaxel or Cabazitaxel, two second-generation synthetic inhibitors -Stony Brook fatty acid-binding protein inhibitor 102 (SBFI-102) or SBFI-103 were able to reduce tumor growth in in vivo animal studies [74].

4. *De novo* fatty acid synthesis

Cancer cells require an increased number of fatty acids for rapid cell proliferation. One of the pathways that cancer cells choose to fulfill the requirement is increased *de novo* fatty acid synthesis. Targeting *de novo* fatty acid synthesis is one of the simplest ways to reduce fatty acid synthesis (Table 1). The FA metabolism consists of different enzymes. Among them, ATP citrate lyase (ACLY), acetyl-CoA carboxylase (ACC), FA synthase (FASN), and acyl-CoA synthetases (ACS) are required to produce bioactive FAs. Citrate acts as the key signaling metabolite that determines fatty acid metabolism. Citrate inside mitochondria is used in the TCA cycle, and outside mitochondria is used for fatty acid synthesis [75]. The citrate carrier (CIC) protein is important for tumor proliferation. To maintain electroneutrality across the mitochondrial membrane CIC exports tricarboxylate citrate with a proton outside mitochondria and imports dicarboxylate malate inside mitochondria. This transported dicarboxylate malate stimulates oxidative phosphorylation and maintains mitochondrial membrane potential [76]. One of the discovered inhibitors of CIC, benzene tricarboxylate (BTA), which is an analog of CIC exhibits an antitumor effect in various cancer cell lines as well as in tumor-prone animal models. Because a high concentration (5 mM) of BTA is required in vivo, new analogues 4-Chloro-3-[[(3-nitrophenyl) amino] sulfonyl]-benzoic acid (CNASB or CTPI-1) and 2-(4-Chloro-3-nitro-benzenesulfonylamino)-benzoic acid) or CTPI-2 have been identified. The 3rd generation citrate analog CTPI-2 inhibits tumor proliferation and shows twenty-fold greater binding activity in vivo than the 2nd generation citrate analog CTPI-1. CIC is not rate-limiting for lipid synthesis because other CIC-independent pathways can provide cytosolic citrate.

One of the plasma membrane citrate transporters (pmCIC), SLC13A5 is found to provide a mechanism that can compensate for citrate in the cytosol when CTPI-2 inhibits CIC in diet-induced non-alcoholic fatty liver disease (NAFLD)/non-alcoholic steatohepatitis (NASH) [77]. Similar experiments are not conducted on tumor-prone animal models, so it cannot be concluded if the same scenario is possible for tumor cells. Combinatorial therapy can be an effective way to stop both citrate uptake through pmCIC and inhibit CIC. Gluconate, a competitive and irreversible inhibitor of SLC13A5, stopped human tumor growth in immunodeficient mice. Sodium antimony gluconate (Stibogluconate) showed significant tumor regression in vivo. Labeled gluconate can differentiate between benign and metastatic lesions and shows an affinity for malignant cancers, although the attraction mechanism is still unknown. It is still unclear if gluconate acts solely as an inhibition because the positive antitumor effect is visible when it is combined with other putative anticancer agents. [78]. BI01383298, a newly identified and potent small molecule irreversible inhibitor of SLC13A5, shows time-dependent inhibition in the human liver cell line HepG2 [79]. Another inhibitor, dicarboxylate 2 (or PF-06649298) has been identified recently using a substrate-based design strategy. PF-06649298 is a competitive inhibitor that inhibits SLC13A5 in vitro in HEK-293-derived stable cell lines and blocks in vivo hepatic uptake of citrate in high-fat

Table 1
Summary table for inhibitors (natural and synthetic) against CIC, pmCIC, ACLY, and ACC.

Targets	Inhibitors	IC50	Ki	Cells used	Stage
CIC	BTA[77]	5–10 mM	-	tumor cell in vivo	Preclinical
	CTPI-1[77]	1–2 mM	-	tumor cell in vivo	Preclinical
	CTPI-2[77]	10–50 μM	-	tumor cell in vivo	Preclinical
pmCIC	Gluconate[78]	-	-	99mTc-labeled gluconate showed antitumor effect on different carcinogenic cells	-
	BI01383298[79]	~100 nM	-	HepG2 cells in vitro	Preclinical
	PF-06649298[80]	0.41 μM	-	(i) HEKNaCT cell line.	Preclinical
		4.5 μM	-	(ii) Mouse hepatocyte	Preclinical
ACLY	SB-201076[84]		1 μM	inhibits human and rat ACLY in enzymatic assay	Preclinical
	SB-204990[84]	10–30 μM	-	inhibits de novo fatty acid and cholesterol synthesis in HepG2 cells	Preclinical
	HCA[88,338]	-	300 μM	ACLY from human liver in enzymatic assay	Phase 4 clinical trial
	Cucurbitacin B[90]	~0.3 μM	-	(i)Human prostate cancer PC-3 and LNCaP cells in vitro (ii) Inhibits tumor growth in vivo	Preclinical
	Bis-brominated emodin[92]	2.9 μM	-	(i) ACLY from human liver in enzymatic assay (ii) Inhibit cancer cells proliferation and reduce cancer stemness in vitro	Preclinical
	Furan carboxylate derivative 1[93]	4.1 μM	-	(i) Human ACLY in ADP Glo ACL enzymatic assay (ii) Dose dependent decrease of cancer stem cell	Preclinical
	Furan carboxylate derivative 2[93]	11.9 μM	-	(i) Human ACLY in ADP Glo ACL enzymatic assay (ii) Dose dependent decrease of cancer stem cell	Preclinical
	Furan carboxylate derivative 3[93]	13.8 μM	-	(i) Human ACLY in ADP Glo ACL enzymatic assay (ii) Dose dependent decrease of cancer stem cell	Preclinical
	Sulfoximine and 3-hydroxy-β-lactam containing analogue of citric acid[94]	-	250 μM	ACLY from rat liver in enzymatic assay	Preclinical
	(+)− 2,2-difluorocitrate[95]	-	0.7 μM	ACLY from rat liver in enzymatic assay	Preclinical
	(-)− 2,2-difluorocitrate[95]	-	3.2 μM	ACLY from rat liver in enzymatic assay	Preclinical
	SC2193[96]	283 nM	-	ACLY from rat liver in enzymatic assay	Preclinical
	Epoxide[97]	-	18 μM	ACLY from rat liver in enzymatic assay	Preclinical
	Antimycins A2[98]	-	4.2 μM	ACLY from rat liver in enzymatic assay	Preclinical
	Antimycins A8[98]	-	4.0 μM	ACLY from rat liver in enzymatic assay	Preclinical
	Radicicol[99]	-	13 μM	ACLY from rat liver in enzymatic assay	Preclinical
	2-hydroxy-N-arylbenzenesulfonamide [100]	130 nM	-	Inhibit ACLY in hig fat diet mouse model	Preclinical
	NDI-091143[101,102]	2.1 ± 0.3 nM	-	Human ACLY in ADP Glo ACL enzymatic assay	Preclinical
		4.8 ± 0.05 nM	-	Human ACLY in coupled enzymatic assay	
		44.0 ± 3.0 nM	-	Malate dehydrogenase coupled-enzyme assay	
			7.0 ± 0.8 nM		
	Compund 1[102]	69.7 ± 9.6 nM	-	Malate dehydrogenase coupled-enzyme assay	Preclinical
	Leelamine[103]	-	-	Suppresses SREBP1-ACLY expression and inhibits fatty acid synthesis in prostate cancer cells	Preclinical
	DCV[104]	0.93 μM	-	ADP-Glo enzymatic assay	Preclinical
	ETC-1002-CoA[105]	-	0.2uM	Human ACLY in enzymatic assay	Preclinical
ACC	CP-640186[126]	53 nM	-	Inhibits rat liver ACC1	Preclinical
		61 nM	-	Inhibits rat skeletal muscle ACC2	
		0.62 μM	-	Inhibits fatty acid synthesis in HepG2 cell line	
	Compund 2[129]	101 nM	-	Inhibits recombinant human ACC1 in cell enzyme assay	Preclinical
		23 nM	-	Inhibits recombinant human ACC2 in cell enzyme assay	
		76 nM	-	Inhibits human ACC1/2 in enzyme assay	
		0.34 μM	-	Inhibits human ACC1/2 in HepG2 cell-based assay	
	Compound 3[130]	33 nM	-	Inhibits malonyl-CoA synthesis of human ACC1/2	Preclinica
		290 nM	-	Inhibits fatty acid synthesis in HepG2 cell-based assay	
	Compound 4[130]	9.7 nM	-	Inhibits malonyl-CoA synthesis of human ACC1/2	Preclinical
	Compound 5[130]	8.4 nM	-	Inhibits malonyl-CoA synthesis of human ACC1/2	Preclinical
	Compound 6[131]	192 nM	-	Inhibits rhACC1 in cell enzyme assay	Preclinical
		95 nM	-	Inhibits rhACC2 in cell enzyme assay	
		58 nM	-	Inhibits human ACC1/2 in enzyme assay	
		60 nM	-	Inhibits human ACC1/2 in HepG2 cell-based assay	
	Compound 8[132]	12 nM	-	Inhibits rACC1 in vitro	Preclinical
		20 nM	-	Inhibits human ACC2 in vitro	
	Compound 9[133]	27.0 ± 2.7	-	Inhibits human ACC1 in enzyme assay	Preclinical
		33.0 ± 4.1	-	Inhibits human ACC1 in enzyme assay	
	WZ66[134]	435.9 nM	-	Inhibits human ACC1 in ADP-Glo kinase assay	Preclinical
		141.3 nM	-	Inhibits human ACC2 in ADP-Glo kinase assay	
	MK-4074[138]	3 nM	-	Inhibits human ACC1/2 in vitro	Preclinical
	Compound 10[135]	0.30 μM	-	inhibited de novo lipogenesis in rat hepatocytes	Preclinical
	Compound 11[136]	10 ± 5 nM	-	Inhibits ACC1 in vitro	Preclinical
		4 ± 1 nM	-	Inhibits ACC2 in vitro	
	Compound 12[137]	0.527 μM	-	Inhibits ACC1 in vitro	Preclinical
		0.397 μM	-	Inhibits ACC2 in vitro	
	Compound 13[139]	0.58 nM	-	Inhibits human ACC1 in vitro	Preclinical
		100 μM	-	Inhibits human ACC2 in vitro	

(*continued on next page*)

Table 1 (*continued*)

Targets	Inhibitors	IC50	Ki	Cells used	Stage
	Compound 14[140]	1.5 μM	-	Inhibits human ACC1 in vitro	Preclinical
		140uM	-	Inhibits human ACC2 in vitro	
	ND-630[141,142,339]	2.1 nM	-	Inhibits human ACC1 in ADP-Glo kinase assay	Phase 2 clinical trial
		6.1 nM	-	Inhibits human ACC2 in ADP-Glo kinase assay	
		> 20uM	-	poor cytotoxicity in A549 cell viability assay	
	ND-646[142]	3.5 nM	-	Inhibits human ACC1 in ADP-Glo kinase assay	Preclinical
		16.2 ± 10.6 nM	-	Showed cytotoxicity against A549 cells in cell viability assay	
	ND-654[143]	3 nM	-	Inhibits human ACC1 in ADP-Glo kinase assay	Preclinical
		8 nM	-	Inhibits human ACC2 in ADP-Glo kinase assay	
	Soraphen A[145]	5 nM	-	Human ACC in HepG2 cell line in vitro	Preclinical
CPT1	Etomoxir[111,338]	5–20 nM	-	Inhibits CPT1 in rat liver	Preclinical
	Perhexiline[338]	77 μM	-	Inhibits CPT1 in rat heart	
		148 μM	-	Inhibits CPT1A	
CD36	ABT-510[61]	-	-	Inhibits tumor growth in vivo in both xenograft and syngeneic tumor model	Phase 2 clinical trial
	Nobiletin[66]	-	-	inhibits cancer stem cell growth	Preclinical
		-	-	inhibits CD36-mediated in vitro angiogenesis	
FABP	SBFI-102[74]	-	-	Tumor reduction in in vivo animal model	Preclinical
	SBFI-103[74]	-	-	Tumor reduction in in vivo animal model	
SCD1	A-939572[206,221]	-	-	*In vitro* and in vivo antitumor activity	Preclinical
		65, 50, 65, and 6 nM	-	Dose dependent decrease in proliferation of different carcinoma cells such as Caki1, A498, Caki2, and ACHN	
	MF-438[223]	2.3 nM	-	Inhibits proliferation of ATC cells *In vitro*	Preclinical
	XEN-103[224]	2 nM	-	Inhibits SCD1 in human HepG2 cells	Preclinical

* (-) refers that the data is unavailable.

diet-fed C57/B6 mice [80]. No experimental studies were recorded on the inhibition activity of BI01383298 or PF-06649298 against hepatocellular carcinoma in vitro or in vivo. Further experiments in vitro and using tumor-prone animal models can shed light on the activity of these potent inhibitors against cancer cells.

4.1. ATP citrate lyase

The homotetrameric enzyme ACLY catalyzes the ATP-dependent reaction between cytosolic citrate and coenzyme A. One of the products of the reaction is acetyl-coenzyme A, which is the precursor for the mevalonate pathway fatty acid synthesis pathway and is required for protein modification such as acetylation of histones. The next product is oxaloacetate, used in gluconeogenesis in the liver or reduced to malate. The malate can be converted to pyruvate in the cytosol or returned to the mitochondria to convert into citrate, depending on the system's demand.

Upregulation of *de novo* fatty acid synthesis is necessary for proliferation in cancer cells. To fulfill this requirement, glucose uptake increases, increasing lactate production to provide sufficient energy for cell proliferation [81]. It has been found that targeting ACLY is ineffective if the cell line is not highly glycolytic cells [82]. A cytosolic enzyme, acyl-CoA synthetase short-chain family member 2 (ACSS2), can convert exogenous acetate to acetyl-CoA. A recent study confirmed the upregulation of ACSS2 in ACLY-deficient cells. Still, the level of histone acetylation was low, and the cell proliferation rate was damaged, although the cells survived [83]. This proves the importance of ACLY in maintaining cell survival, proliferation rate, and histone acetylation.

Since the versatile ACLY enzyme initiates lipogenesis, inhibition of ACLY has been considered an effective way to stop FA synthesis. Increased expression of ACLY is found to be common in many tumor types. Inhibiting ACLY by genetic methods or an inhibitor SB-204990 (a γ-lactone prodrug of one of the (3 R*,5 S*)-ω-substituted-3-carboxy-3,5-dihydroxyalkanoic acids, SB-201076) was found to reduce the proliferation and survival of tumor cells in a xenograft tumor model. This made ACLY a potential target in anticancer therapy. When administered orally, SB-204990 could induce a hypotriglyceridemic and hypocholesterolemic response in rats and dogs [82,84,85].

Hydroxycitric acid (or (2 S,3 S)− 2-hydroxycitrate, HCA) was the first discovered ACLY inhibitor that showed hypolipidemic effects in animal models [86,87]. Extensive studies on HCA have confirmed its effect on the regulation of lipogenesis in vitro and in vivo [88]. Combining the standard anticancer drug cisplatin or methotrexate with HCA and α-lipoic acid reduced tumor growth in a tumor-prone animal model. The efficacy of the tested anticancer drug was potentiated in combined therapy [89].

Both HCA and SB-201076 had the same problem of poor cell permeability, which was improved in SB-204990. Compared to SB-204990, for an equivalent reduction of de novo lipid synthesis in HepG2 cells in vitro, a 10-fold greater concentration of HCA was required [85]. SB-204990 showed antiproliferative activity in A549, PC3, and SKOV3 cell lines in vitro and antitumor activity in xenograft tumor models in nude mice using A549 and PC3 cell lines [82]. This shows the high potency of SB-204990 as a hypolipidemic and antitumorigenic agent.

Another natural product inhibitor, Cucurbitacin B, inhibited proliferation in prostate cancer cells in vitro and inhibited PC-3 xenograft growth significantly in athymic mice [90]. Approximately 10% oral bioavailability of Cucurbitacin B was found, with a high volume of distribution to several organs in male Wister rats. This finding of poor bioavailability will be crucial in determining the appropriate dose in the future [91]. Bis-brominated emodin (1,3,8-Trihydroxy-2,4-dibromo-6--methyl-anthraquinone) inhibits human ACLY in enzymatic ADP Glo assays and reduces proliferation of A549 non-small cell lung cancer cell line [92]. With the help of in silico screening of chemical databases, 11 potential inhibitors containing furan carboxylate moiety have been identified. Three furoic acid derivatives among 11 virtual hits are found to be the most potent. Two inhibitors, which are 4-substituted-2-furoic acids with differently substituted 2-chromenone moieties, and one inhibitor, which is a 5-sulfonamido-naphtofuran-3-carboxylic acid, were found to inhibit human ACLY in ADP-Glo ACL enzymatic assay [93]. Both emodin and furoic acid derivatives were found to reduce cancer stemness in vitro dose-dependent manner [92,93]. There are other inhibitors, such as sulfoximine and 3-hydroxy-β-lactam containing analogs of citric acid, (+)− 2,2-difluorocitrate, (-)− 2,2-difluorocitrate, SC2193 (or 2-Chloro-1,3,8-trihydroxy-6-methylanthracen-9(10 H)-one), cis-epoxide, which is a citric acid analog, antimycin A2 and A8 that belong to the antimycin class of antibiotics, and radicicol, which were identified to inhibit ACLY from rat liver in enzymatic assays [94–99]. SC2193 inhibited human ACLY in an enzymatic assay with an IC_{50} of 283 nM

[96]. Further studies on the inhibitory action against human ACLY in enzymatic assays can disclose their potentiality, like SC2193. They can be taken to the next steps: in *vitro* and in vivo experimental studies for cytotoxicity and effectiveness for cancer study, followed by clinical trials.

A series of 2-hydroxy-N-arylbenzenesulfonamides was identified as a potent ACLY inhibitor, considering the cell permeation ability. The most potent one among 2-hydroxy-N-arylbenzenesulfonamides showed ACLY inhibition with IC_{50} of 130 nM in a high-fat diet mouse model but showed no cytotoxicity up to 50uM in HepG2 cells. However, it lowered plasma cholesterol, triglycerides, and glucose levels in mice fed on a high-fat diet [100]. Recently, a novel macrocyclic inhibitor NDI-091143 of ACLY has been synthesized with a structure similar to the previous compound. From the co-crystal structure of ACLY bound to ND-091143 by Cryo-EM, it has been found that extensive conformational changes in amino acid residues are required for ND-091143 to bind with the citrate domain of ACLY, which concludes ND-091143 as an allosteric inhibitor of human ACLY [101]. Recently, Y. Zang's group synthesized a novel macrocyclic ACLY inhibitor with a ring-closing strategy and a structure similar to ND-091143. In the malate dehydrogenase (MDH) coupled-enzyme assay, **compound 1** showed less potent inhibition with an IC_{50} of 69.7 ± 9.6 nM compared to the positive control ND-091143 with an IC_{50} of 44.0 ± 3.0 nM. The metabolic stability of **compound 1** ($T_{1/2}$= 531.22 min) significantly improved compared to Nd-091143 ($T_{1/2}$ = 3.36 min) in human liver microsomes. Further studies are being carried out on **compound 1** by the same group [102]. Another natural product inhibitor Leelamine is found to suppress transcriptional activity of androgen receptors. This lipogenesis inhibitor showed downregulation of protein and/or mRNA expression of ACLY, acetyl-CoA carboxylase 1 (ACC1), fatty acid synthase (FASN), which resulted in the inhibition of fatty acid synthesis in both in vitro and in vivo experimental studies. In 22Rv1 tumor xenografts of Leelamine treated mice, a significant decrease in ACLY expression was observed [103]. 10, 11-de-hydrocurvularin (DCV) is another natural product that is the first potent irreversible inhibitor of ACLY. DCV showed ACLY inhibition with an IC_{50} of 0.93uM in ADP-Glo enzymatic assay and cytotoxicity in Jurkat cells [104]. Bempedoic acid or ETC-1002, developed by Esperion Therapeutics, Inc. company, is an inhibitor that conjugates with very long-chain acyl-CoA synthetase-1 (ACSVL1) to get activated. The activated ETC-1002-CoA inhibits human ACLY in enzymatic assay [105]. Currently, ETC-1002 is in phase 3 clinical trials as a therapeutic agent to reduce low-density lipoprotein cholesterol (LDL-C). Still, no experimental studies have carried on in the context of cancer until now [106].

4.2. Acetyl CoA carboxylase

Acetyl CoA carboxylase (ACC) is a multidomain enzyme containing biotin carboxylase (BC) and carboxyltransferase (CT) active sites [107]. In yeast ACC, biotin is covalently attached to the biotin carboxyl carrier protein domain [108]. BC catalyzes ATP-dependent carboxylation of biotin with bicarbonate, followed by the formation of malonyl CoA through carboxyl transfer from biotin to acetyl CoA by CT [107,109]. In the human genome, two isoforms of ACC exist. The first one, ACC1, is found in lactating mammary gland, liver, and adipose tissue and produces malonyl-CoA, which synthesizes fatty acids.

On the contrary, ACC2 exists on the outer membrane of more oxidative tissues, such as the heart and skeletal muscle. It produces malonyl-CoA, which allosterically inhibits carnitine palmitoyltransferase I (CPT1) and prevents fatty acid degradation [107]. CPT1C -one of the three isotopes of CPT1, plays an important role in cancer cell lipotoxicity regulation and cell senescence [110]. Genetic knockdown of CPT1 decreases cancer cell proliferation [111]. Two inhibitors of CPT1, Etomoxir or Perhexiline showed antitumor potential against various cancer cells, including breast, bladder, glioma, and prostate cancer [112–115]. But, in some cancer cell lines, Etomoxir reduced fatty acid oxidation with no effect on cancer cell proliferation. It has been suggested that cancer cell proliferation might be independent of fatty acid oxidation [111]. AMP-dependent protein kinase (AMPK) becomes inactivated by ATP when the AMP level is low. Inactivated AMPK cannot inactivate ACC through phosphorylation. At that moment, dephosphorylation of ACC by protein phosphatase 2 A activates ACC. A natural compound Silibinin, can activate AMPK, thereby inhibiting sterol response element binding protein 1 (SREBP −1) [116]. SREBP-1c and carbohydrate response element binding protein (ChERBP) regulate ACC at the transcription level [107,117,118]. In the presence of abundant intracellular sterol levels, SREBP cleavage-activating protein (SCAP) binds to insulin-induced genes (INSIGs) for the retention of SREBP in the endoplasmic reticulum (ER) [119]. A natural compound inhibitor Betulin promotes the retention process, which reduces SREBP-mediated lipogenesis and decreases hepatocellular carcinoma development and progression [120]. In case of scarce intracellular sterol level, the SREBP-SCAP complex translocates to the nucleus through Golgi to activate the transcription of the target genes [119]. Fatostatin -an inhibitor of SCAP, blocks the translocation of the SREBP-SCAP complex and cell invasion in different cancer cells, including ER-positive breast cancer, prostate, and pancreatic cancer [121–124].

Harwood and co-researchers identified an isozyme nonselective inhibitor (CP-497485) of ACC by 96-well plate high throughput screening method [125]. The reversible ACC inhibitor CP-610431, the R-enantiomer of the prototype CP497485, inhibited both ACC isozymes with an IC_{50} of 50 nM. CP-640186, the metabolically stable analog of CP-610431, inhibited both ACC with an IC_{50} of 55 nM. CP-640186 inhibited fatty acid and triglyceride synthesis in HepG2 cell, CD1, and ob/ob mice with 2–3 times higher potency when administered orally than CP-610431 [126]. In yeast ACC, CP-640186 was found to bind tightly to the active site of CT domain [127]. CP-640186 showed antiproliferative activity against lung cancer cells (H460) in a cell proliferation assay [128]. Further in vitro and xenograft animal model studies must confirm its antitumor potency. A (4-piperidinyl)-piperazine derivative (compound 2) was identified in 2009 which binds similarly to the CT domain like CP-640186. Compound 2 was found to inhibit rat ACC1 (IC50 = 101 nM), rat ACC2 (IC50 = 23 nM), and human ACC1/2 (IC50 = 76 nM) more actively than CP-640186 (IC50 for rACC1 =456 nM, rACC2 =194 nM, and hACC1/2 =116 nM) in enzymatic assays. Compound 2 also inhibits FA synthesis in HepG2 cell assay (IC_{50} = 0.34uM/0.84uM), similarly with more activity than CP-640186. In inhibition and metabolic stability, compound 2 showed greater activity than CP-640286 in human liver microsomes (87/52) [129]. As compound 2 could act on multiple targets, further in vivo cytotoxicity studies are required to evaluate its potency against different cancer cells. Compound 3, compound 4, and compound 5 are indole derivatives of compound 2 that showed improved human ACC1/2 inhibition. Compound 3 also showed good hydrosolubility and cell permeability and could inhibit fatty acid synthesis in a dose-dependent manner in a HepG2 cell-based assay. Through structure-based analysis, it was found that compounds 4 and 5 show excellent potency as non-selective ACC1/2 inhibitors [130]. 1,1,1-trifluoro-2-methylpropan2-yl 4-{4-[(2-amino-6-methyl-1-benzothiophen-3-yl) carbonyl] piperazin-1 (Compound 6), another advanced analog of compound 2 inhibited human ACC1/2 in a similar range to compound 2 in enzyme assay but showed better fatty acid synthesis inhibition in a cell-based assay. A significant decrease in plasma and hepatic triglyceride levels was found in fructose-drinking SD rats when compound 6 was administered [131].

In 2010, cocrystal structure of yeast CT domain and a spirochromanone (compound 7) which was determined through screening of Pfizer compounds, resulting in several hits and improving the inhibition potency of the primary hit compound. Compound 7 binds to the CT domain similarly to CP-640186 but forms an additional hydrogen bond. Further optimization led to identifying a more potent analog, compound 8 (6-aza-5-alkoxyspirochromanones derivative), by improving the structure of compound 7 using SAR analysis for better

inhibitory action and ligand efficiency. Compound 8 inhibited rACC1 with an IC_{50} of 12 and hACC2 with an IC_{50} of 20, and it exhibitedreasonable pharmacokinetic properties in two species [132]. Another spirochromanone derivative, compound 9, was identified to inhibit hepatic DNL, hepatic malonyl-CoA and skeletal muscle malonyl-CoA in rats. Based on the satisfying preclinical studies (191), clinical studies have also been performed in type 2 diabetic patients [133]. However, no data have been recorded regarding the action of compound 9 on a tumor-prone animal model. Recently, a novel inhibitor of ACC isozymes, WZ66, was identified. It was designed based on spirochromanone. WZ66 reduced malonyl-CoA levels in AML12 mouse hepatocytes. The biodistribution of WZ66 is mostly liver-specific compared to other organs in mice. WZ66 also showed a reduction of hepatic steatosis in high fat fed mice. No information about the cytotoxic potentiality of WZ66 has been recorded yet [134].

A novel series of spirocyclic-diamine-based inhibitors was identified in 2015 which binds to the CT domain by mimicking the hydrogen bonding pattern and structural rigidity of spirochromanone. Among them, the most potent compound 10 (methyl-pyrrolidine–piperidine) showed moderate potency in inhibition of *de novo* lipogenesis in rat hepatocytes but marked unsuitable for further in vivo studies because compound 10 showed high lipophilicity which caused high clearance in vitro and *vivo* [135]. A spirocyclic salicylamide derivative was identified and the potentiality of inhibition was improved by using synthetic chemistry. The synthesized inhibitor compound 11 decreased *de novo* lipogenesis in acute rat PD studies and showed promising pharmacokinetic properties in rats. Although toxicological studies and preclinical development of compound 11 were ongoing for T2DM, no data was recorded regarding the anticancer potentiality of compound 11 [136]. In 2018, a series of spiropentacylamide derivatives were synthesized. Among all analogs, the most potent compound 12 was able to exhibit anti-proliferation activities against A549, Caco-2, H1975, HCT116, and SW620 tumor cell lines with IC50 values of 1.92 μM, 5.42 μM, 0.38 μM, 1.22 μM, and 2.05 μM respectively. Compound 12 is considered a lead compound for anti-cancer therapy according to the SAR studies and inhibitory action on ACC [137].

MK-4074 is another potent human ACC inhibitor developed by high throughput screening and medicinal chemistry efforts in 2017. MK-4074 inhibited both human ACC isozymes with an IC_{50} of 3 nM. MK-4074 significantly decreased DNL in male KKAy mice and inhibited fractional DNL by 91–96%, depending on the daily dose in healthy young males in the phase one clinical trial. The clinical studies also revealed that MK-4074 reduces hepatic steatosis with an unexpected increase in plasma triglycerides [138]. These results are promising for hepatic steatosis, but nothing has been reported yet regarding the cytotoxicity of MK-4074.

Takeda researchers optimized a series of 2-azetidyl-1,3-benzoxazole derivatives, and it was found that these derivatives show greater inhibition to ACC1 than ACC2. The most potent 2-phenyl-1,3-benzoxazole (compound 13), which is a monocyclic derivative of 2-azetidyl-1,3-benzoxazole, inhibited human ACC1 with an IC_{50} of 0.58 nM and human ACC2 with an IC_{50} of 100uM. The IC_{50} value shows a higher selectivity of compound 13 for human ACC1 than human ACC2 [139]. Recently, another inhibitor compound 14 has been identified by the same research group by developing the most potent bicyclic derivates of 2-azetidyl-1, 3-benzoxazole [139,140]. Compound 14 also showed greater inhibition to human ACC1 ($IC_{50} = 1.5$uM) than human ACC2 ($IC_{50} = 140$uM), but the difference in inhibition was similar to compound 13. *In vivo* studies of compounds 13 and 14 showed a significant reduction of malonyl-CoA concentration in HCT-116 xenograft tumors [139,140]. Compound 14 inhibited tumor growth in 786-O xenograft mice when administered orally [140]. Further pharmacological evaluation is required to count compound 13 and compound 14 as novel potential inhibitors of human ACC.

Another ACC1/2 inhibitor ND-630 was identified and reported by the Harriman group in 2016 by structure-based drug design. This isozyme is a nonselective and reversible inhibitor that inhibits dimerization by interacting within the subunit dimerization site of the BC domain and phosphopeptide acceptor of the ACC enzyme. ND-630 exhibited more potency compared Soraphen A, although the mechanism of inhibition is similar for both inhibitors. ND-630 reduced FA synthesis and induced FA oxidation in vitro and in vivo [141]. ND-630 was able to reduce hypertriglyceridemia, hypercholesterolemia in different animal models (chow-fed rats) and is currently in phase II clinical trial studies of nonalcoholic fat liver disease but also showed poor cytotoxicity against A549 cells [141,142]. ND-646 is the amide derivative of ND-630, which showed hACC1 inhibition with an IC_{50} value like that of ND-630 but showed cytotoxicity against A549 cells. The author has hypothesized that the specificity of ND-630 toward the liver could be the reason behind the poor cytotoxicity of ND-630 against A549 cells. Later, several ND-646 derivatives with a small structural change were synthesized; among them, the most potent compound 13 showed cytotoxicity with an IC_{50} less than ND-646 in A549 cells [142]. Another liver-specific inhibitor ND-654, was identified in 2019, which could suppress hepatic DNL development and hepatocellular carcinoma and improve survival in tumor-bearing rats alone or in combination with sorafenib, a multi-kinase inhibitor [143].

A natural product, Soraphen A is one of the allosteric inhibitors of ACC. In yeast ACC, soraphen A binds to the BC domain and interferes with the oligomerization of the BC domain [144]. Soraphen A also showed ACC inhibitory action on *de novo* lipogenesis in HepG2 and LnCap cell lines [145]. The proliferation of LnCap and PC-3 M cell lines was reduced by the inhibitory action of soraphen A against FA synthesis at a nanomolar concentration [146].

4.3. Fatty acid synthase

The key biosynthetic enzyme, fatty acid synthase (FAS), undergoes reductive synthesis of fatty acid (palmitate) using acetyl-CoA, malonyl-CoA, and nicotinamide adenine dinucleotide phosphate (NADPH) [147]. FAS plays a multifaceted role that supports anabolic metabolism and signaling in cancer cells [148]. Subsequent to the first exploration of FAS regulation in human breast cancer cells in 1980 [149], high level of FAS has been reported in different types of cancer cells such as colon [150], endometrium [151], ovary [152], prostate [153], thyroid [147], bladder [154], stomach [155], kidney [156], skin [157], pancreas [158], soft tissues [159] and head and neck [160]. Each of the two identical and multifunctional polypeptides of FASN contains seven catalytic domains [154]. Several inhibitors have been identified that bind to the active site of different domains.

Cerulenin [(2 R,3 S), 2–3-epoxy-4-oxo-7,10- trans, trans-dodecadienamide] is the first identified non-competitive and natural inhibitor of FAS [161]. Cerulenin forms a covalent bond with a cysteine residue of the active site of the fungal FAS ketoacyl synthase (KS) domain and changes the active site conformation significantly [162]. Cerulenin treatment delays disease progression in an ovarian cancer xenograft model [163], significantly decreases *de novo* synthesized FA levels in MCF-7 breast cancer cells [164], retarded growth of liver metastatic tumors of murine colorectal cancer cell lines [165], reduces tumor burden in neuroblastoma cell lines [166]. However, it may be possible that Cerulenin's highly reactive epoxy group interacts with other cellular processes such as palmitoylation [167], proteolysis [168]' and antigen processing [154]. To solve this problem C75 (trans-4--carboxy-5-octyl-3-methylenebutyrolactone), an analog of cerulenin, was synthesized by removing the epoxy group [169]. C75 is a competitive, reversible inhibitor of KS, enoyl reductase (ER), thioesterase (TE) domains of FAS [170]. C75 has been shown to reduce tumor growth in in vitro and in vivo studies on human breast [171], mesothelioma [154], ovarian [172], prostate [173,] and renal cancer cell lines [174]. While inhibiting FAS activity, C75 was found to trigger activation of FA oxidation through direct activation of carnitine palmitoyl-CoA transferase 1 (CPT1), which was expected to impact whole body energy

expenditure [175–177]. For this reason, as well as due to the suppression of food intake, C75 induces weight loss in mice [176,178]. Another Cerulenin derivative, C93 was designed to solve the side effects caused by using both Cerulenin and C75. C93 showed a significant antitumor effect on xenograft tumors from human non-small cell lung cancer (NSCLC) cell lines without causing anorexia and weight loss [179]. Plant-derived natural compounds epigallocatechin gallate (EGCG) and epicatechin gallate (ECG) were found to inhibit the β-ketoacyl reductase (KR) domain of FAS. They showed induction of selective apoptosis in carcinogenic prostate and human breast cells [180,181]. EGCG has no effect on weight loss induction or FA oxidation in experimental animals as C75 [182], but it shows low potency in FAS inhibition (IC_{50} = 52 μM). ECG and EGCG are competitive inhibitors to NADPH, and ECG shows similar potency (IC_{50} = 52 μM) as EGCG [183]. G28, a naphthalene derivative of EGCG, showed anticancer activity in combination with gefitinib or Osimertinib, which are epidermal growth factor receptor (EGFR) tyrosine kinases inhibitors (TKI). G28 showed greater cytotoxicity (IC_{50} = 12–18 μM) than EGCG (IC_{50} = 75–90 μM) in different NSCLC models [184]. The Structure-Activity Relationship (SAR) study of G28 against FAS is required to consider it as a selective inhibitor for further in vivo studies. There are other natural compounds, such as Cacalol, Diosgenin, Luteolin, Mollugin, Quercetin, Resveratrol, Osthole, and Ornidonin, showed inhibition of FAS and anticancer activity against multiple cancer cell lines. In the case of inhibition of proliferation of MIA PaCa-2 pancreatic cancer cells, Resveratrol (IC_{50} = 163 μM), and Quercetin (IC_{50} = 178 μM) showed less potency compared to C75 (IC_{50} = 65 μM) and Luteolin (IC_{50} = 75 μM) showed similar dose-dependent inhibition [185]. Many natural compounds could not pass the preclinical studies to become a selective inhibitor for phase I clinical trial [186].

Orlistat (tetrahydrolipstatin), a Food and Drug Administration (FDA) approved synthetic anti-obesity drug, inhibited the TE domain of FAS. Orlistat was able to halt tumor cell proliferation and promote tumor cell apoptosis in prostate cancer and melanoma cell lines and xenografts [187,188]. Orlistat inhibited metastasis in mouse metastatic melanoma cell line B16-F10[188] and showed antitumor effects on breast cancer cells in vitro [189]. However, low cell permeability, poor solubility, oral bioavailability, lack of selectivity, and poor metabolic stability are the limitations of Orlistat for which its potential in clinical application is limited [190,191]. Another inhibitor Triclosan, an FDA-approved antimicrobial agent, inhibits ER domain of FAS, and shows superior cytotoxicity compared to C75 or Orlistat in prostate cancer cell lines [192]. But Triclosan also enhances tumor progression in breast cancer cell lines and mouse xenograft model and tumor growth in Human BG-1 ovarian cancer cells via activation of estrogen signaling pathway [193,194]. Recently, some reversible imidazopyridine-based FASN inhibitors TVB-2640, and TVB-3166, were developed by 3-V-Biosciences and demonstrated antitumor activity both in vitro and in vivo [195]. TVB-3166 was found to bind to the KR domain of FAS. It inhibited tumor growth in multiple cancer cell lines and in vivo xenograft tumors as an orally available, potent, and selective inhibitor. TVB-3166 also showed well-tolerated in vivo toxicity compared to the high side effects of C75, Orlistat, and Cerulenin [196]. TVB-3166 also reduces cell viability and proliferation and promotes cell cycle arrest and cell death of oral squamous cell carcinoma (OSCC) cell lines SCC-9 and metastatic LN-1A.

Further preclinical studies are required to confirm the anticancer effect of TVB-3166 in the future, to make TVB-3166 a selective inhibitor of FAS in clinical trials [195]. TVB-2460 was the first FAS inhibitor used in the human-dose-escalation study to determine the maximum tolerated dose in phase I clinical trial and recommended phase II dose (RP2D). TVB-2460, in combination with a common chemotherapeutic drug Paclitaxel, showed a partial response (PR) of 11% and a disease control rate (DCR) of 70% in patients with breast, $KRAS^{MUT}$ lung, and ovarian cancer. The side effects of the combined dose are reversible skin and ocular effects due to decreased lipid production. Skin effects were seen to be improved with concomitant use of emollients.

Further investigation of TUV-2460 in patients with solid tumors could be promising [197]. A novel FAS inhibitor Triazolone GSK2194069 was identified by high throughput screening of GlaxoSmithKline (GSK) compound collection in an assay that measures NADPH consumption using full-length recombinant human FAS [198]. GSK2194069 binds to the KR domain of FAS and reduces the tumor volume and acetate uptake in prostate cancer xenograft [199]. α-Linolenic acid,18:3n-3 (ALA), an n-3 fatty acid, was found to reduce FAS expression and induce breast cancer cell apoptosis. ALA showed greater affinity towards FAS's TE domain than palmitic acid,16:0 (PA) [200]. The reduction of osteosarcoma cell proliferation, invasion, and arrest of the cell cycle in breast cancer cells by ALA makes it a promising candidate for further studies in vivo [200,201]. We have summarized the FAS inhibitors in Table 2.

Table 2
Summary table of the inhibitors targeting different domains of the FAS.

Inhibitors	FAS Domains	Effects
Cerulenin[165,166]	KS	Showed antitumor effects in murine colorectal and neuroblastoma cancer cell lines
C75[171–174]	KS, ER, TE	Antitumor effects in multiple cancer cell lines and xenografts
C93[179]	KS	Significant antitumor effects in NSCLC cell lines and xenografts
EGCG[182,183,340]	KR	Induced apoptosis in prostate and human breast cells. In phase 2 clinical trial
G28[184]	KR	Showed anticancer effect combined with gefitinib or Osimertinib
Resveratrol[185,341]	KR	Inhibition of proliferation of MIA PaCa-2 cells Destroyed breast cancer stem cell in xenograft animal model
Luteolin[185]	-	Inhibition of proliferation of MIA PaCa-2 cells
Quercetin[185]	MAT	Inhibition of proliferation of MIA PaCa-2 cells
Mollugin[342]	-	induced apoptosis in ovarian and breast cancer cells
Diosgenin[343] Osthole[344]	-	Induced apoptosis in HER2-overexpressing human breast adenocarcinoma cell lines
Cacalol[345]	-	Induced apoptosis in breast adenocarcinoma cell lines
Oridonin[346]	-	Showed anticancer activity in human colorectal cancer cell lines
Orlistat[187–189,347]	TE	Induced apoptosis in prostate cancer and melanoma cell lines and xenografts; In phase 3 clinical trial Inhibited metastasis and showed antitumor effect in melanoma and breast cancer cell lines
Triclosan[192–194]	ER	Showed cytotoxicity greater than C75 in prostate cancer cells Enhanced tumor growth and tumor progression in different cell lines and xenografts
TVB-3166[195,196]	-	Inhibited tumor growth and showed well tolerated cytotoxicity in multiple cancer cell lines and in vivo xenograft tumor Reduced tumor cell proliferation and induced cell cycle arrest in OSCC and metastatic LN-1A cell lines
TVB-2640[197,348]	-	First FAS inhibitor that was used in phase I clinical trial in patients with breast, KRASMUT lung and ovarian cancer; In phase 2a clinical trial
GSK2194069[199]	KR	Reduced the tumor volume in prostate cancer xenograft
α-Linolenic acid,18:3n-3 (ALA)[200,201]	TE	Induced apoptosis and reduced metastasis and invasion in breast cancer cell lines

* (-) refers that the data is unavailable.

4.4. Fatty acid desaturation

A substantial fraction of *de* novo synthesized fatty acids need to get desaturated by stearoyl-CoA desaturase (SCD) enzyme with the introduction of a double bond at the cis-delta-9 position of saturated fatty acyl-CoAs and converted to D9-mono-unsaturated fatty acids (D9-MUFAs). For instance, SCD1, which is one of the two human isomers of SCD, converts palmitate (16:0) and stearate (18:0) to palmitoleate (16:1n-7) and oleate (18:1n-9), respectively [202]. SCD1 is overexpressed in many tumors, including bladder cancer, hepatocellular carcinoma, and breast cancer, and is involved in cancer cell proliferation, migration, metastasis, and tumor growth [203–206]. It has also been reported that most cancer cells have MUFAs in higher proportion than normal tissues, excluding colorectal cancer cells, which are enriched in polyunsaturated fatty acids (PUFAs) [207–209]. A specific balance between saturated and unsaturated fatty acids is crucial for limiting lipotoxicity and ferroptosis and promoting cell survival [210]. It has been suggested that inhibition of SCD1 decreases an endogenous membrane antioxidant CoQ10, which has been linked to ferroptosis [211]. In the case of different cancer cells, including bone, bladder, colon, and kidney carcinoma, it has been reported that chemical inhibition or genetic knockdown of SCD1 could be a promising therapeutic strategy [211–218]. Although primary human liver and lung carcinoma cells could follow an alternative FA desaturation pathway to overcome cell death, targeting both desaturation pathways simultaneously could damage cancer cell proliferation [219]. A-939572, a pyridazine and piperazine-based second-generation inhibitor of SCD, was identified in 2005 [220]. A-939572 induced apoptosis and inhibited growth in tumor cells such as FaDu cells, clear cell renal cell carcinoma (ccRCC) in vitro [206,221]. Combined with temsirolimus, an FDA-approved mTOR inhibitor, synergistically inhibited tumor growth in A498 ccRCC xenografts [222]. Another SCD1 inhibitor MF-438, a thiadiazole–pyridazine derivative, was identified in 2010[223]. MF-438 showed better potency while inhibiting anaplastic thyroid carcinoma (ATC) cell proliferation in vitro than A-939572. Recently, a piperazin-1-ylpyridazine-based potent and selective SCD1 inhibitor XEN-103 has been identified as highly efficacious (ED 50 = 0.8 mg/kg) with a good oral bioavailability (F = 49%) [224]. XEN-103 showed inhibition of SCD1 in mouse liver microsomal (mSCD1), and HepG2 cell-based activity assay. The efficacy study was carried out on rats in the context of obesity and metabolic syndrome, but no studies have been recorded regarding cancer.

5. Fatty acids mediated lipid peroxidation to modulate ferroptosis

Fatty acid pool affects the ferroptosis sensitivity. n-6 LCPUFAs (ARA, adrenic acid,22:4n-6) synthesize from LA through the n-6 *de novo* PUFA synthesis pathway using elongation of very long-chain fatty acid protein

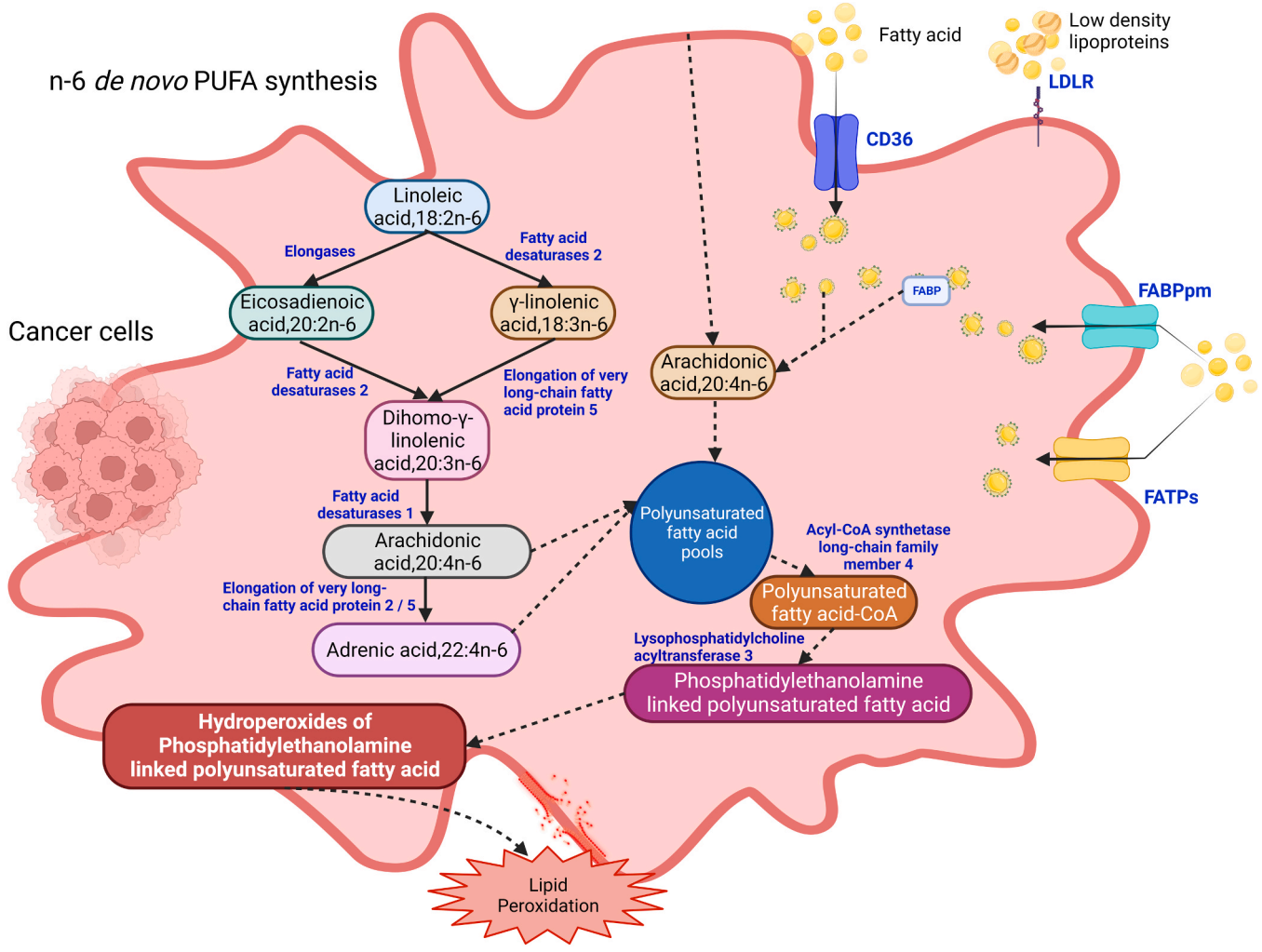


Fig. 2. : *PUFAs regulate ferroptosis.* PUFAs can accumulate in cells via the n-6 *de novo* PUFA synthesis route and fatty acid transport pathways comprised of CD36, FATP, and FABP. Imported LA is transformed into ARA and adrenic acid,22:4n-6 by ELOVL and FADS, which are then used to generate membrane phospholipids. The PUFA pools convert to PE-PUFA, which enhances ferroptosis in cancer cell through lipid peroxidation process.

2 (ELOVL2), ELOVL5, FADS1, and FADS2, which play crucial role in ferroptosis (Fig. 2) [56,225–227]. Due to hypermethylation in the promoter region, intestinal-type gastric cancer cells express extremely low levels of ELOVL5 and FADS1. They are resistant to ferroptosis, but mesenchymal-type gastric cancer cells are sensitive to ferroptosis at high ELOVL5 and FADS1 219 levels. Isotope-tracing studies show intestinal-type cells are defective in synthesizing ARA and adrenic acid, 22:4n-6 from LA. However, when supplemented with ARA, these cells become vulnerable to ferroptosis [225]. According to The Cancer Cell Line Encyclopedia, ELOVL5 and FADS1 are expressed in most cancer cells. Still, they are silenced in some cancer cells, including gastric and colorectal cancer cells, implying that these two enzymes could be used as prediction markers for ferroptosis-mediated cancer therapy [225]. Furthermore, FADS2 depletion or inhibition decreases (1 S,3 R)-RSL-3 (RSL3)-induced ferroptosis [56,225]. It's still a mystery how simply inhibiting PUFA production can prevent ferroptosis. According to transcriptome analysis, there were no significant changes in the levels of fatty acid transporters during this procedure. Interestingly, FATP2 levels in mesenchymal-type gastric cancer cells are very low, signaling that fatty acid import is somewhat limited in these cells; thus, these cells are dependent on PUFA production [225]. Although ARA is thought to be a key target for lipid peroxidation, ELOVL5-depleted gastric cancer cells still contain comparable levels of ARA and phosphatidylethanolamine-ARA, suggesting that ARA import is still active [225]. Instead, these cells have much lower amounts of adrenic acid,22:4n-6 and phosphatidylethanolamine (PE)-adrenic acid,22:4n-6 and are resistant to ferroptosis, implying that adrenic acid,22:4n-6 is important for lipid peroxidation and ferroptosis in gastric cancer [225]. Unlike PUFAs, which are required for ferroptosis, MUFAs such as OA can protect cells from ferroptosis [228,229]. According to lipidomic study, OA reduces the number of ferroptosis-related phospholipids, such as PC- or PE-linked ARA or adrenic acid,22:4n-6, without affecting free ARA and adrenic acid,22:4n-6 levels, implying that MUFAs compete with ARA and adrenic acid,22:4n-6 for incorporation into phospholipids [228]. ACSL3, which mediates MUFA phospholipid incorporation, is needed for MUFA-mediated ferroptosis inhibition [228]. Surprisingly, OA treatment causes a buildup of free OA but not phospholipid-containing OA, showing that more complex processes govern phospholipid composition and ferroptosis [228]. An intriguing finding was that the levels of OA and glutathione in lymph fluid were higher than those in blood plasma; iron levels in lymph fluid were lower than those in blood plasma; and these expression patterns may protect tumor cells from ferroptosis, leading to increased survival rates during metastasis [230]. These findings suggest that ferroptosis plays a major inhibitory function in tumor metastasis via blood, although tumor cells metastasizing via lymph are shielded from ferroptosis. Given that the levels of fatty acids, including MUFAs and PUFAs, in human serum are much higher than in classical culture medium supplemented with fetal bovine serum (FBS), information on how cells maintain free fatty acid pools and phospholipids in cells is much more important in determining whether cells ferroptose or survive [31,228]. PUFAs are liberated from membrane phospholipids via phospholipase A_2 (PLA_2)-catalyzed hydrolysis as membrane phospholipids undergo constant remodeling. ARA and EPA are preferentially produced by cytoplasmic PLA_2 ($cPLA_2$), whereas DHA is released by Ca^{2+}-independent PLA_2 ($iPLA_2$) [231]. Although no research has directly examined whether these parameters are linked to ferroptosis, multiple studies have shown a possible relationship between fatty acid transport and ferroptosis. According to recent research, chemoresistant tumors with high transforming growth factor-β (TGF-β) expression and epithelial-mesenchymal transition (EMT) gene profiles are more susceptible to ferroptosis [225,232,233]. Furthermore, most malignant tumors have abnormal lipid metabolism [234,235]. Furthermore, malignant tumors have enhanced CD36 expression, which permits greater fatty acid intake from outside the cell and supports the EMT process [25,236]. In prostate cancer, for example, fatty acids imported by CD36 are retained in cellular complexes such as phospholipids, DAG, and TAG rather than being oxidized [13]. This could aid in the ferroptosis of malignant tumors that express CD36. CD36, conversely, has been demonstrated to activate cPLA2, releasing ARA from phospholipids [237]. ARA is either exported from cells or transformed into PGE [237]. This implies that CD36 can also suppress ferroptosis by reducing ferroptosis-related phospholipids, such as PE/PC-linked ARA or adrenic acid,22:4n-6. Therefore, the role of CD36 in ferroptosis requires further investigation. Exogenous lipids, such as PUFAs and MUFAs, absorbed through CD36, as well as adiponectin cause metabolic and functional reprogramming of tumor-associated myeloid-derived suppressor cells [227,238]. CD36 also directly reduces the anti-tumor immunological function of $CD8^+$ tumor-infiltrating lymphocytes by increasing lipid peroxidation via the absorption of OxLDL [239]. Because glutathione peroxidase 4 (GPX4) overexpression can restore $CD8^+$ tumor cell activity, ferroptosis may be implicated in this process [239]. Because attempts to stimulate ferroptosis in cancer cells can also inhibit anti-tumor immunity, a method based on the differences in ferroptosis processes between cancer cells and immune cells is required. FATP2 has recently been found to play critical roles in lipid buildup in polymorphonuclear myeloid-derived suppressor cells [240]. FATP2 knock out cells, in particular, have considerably lower free ARA levels. ARA tracing research further demonstrated that FATP2 knock-out polymorphonuclear myeloid-derived suppressor cells lack ARA absorption, resulting in reduced levels of ARA-containing phospholipids and PGE_2. Given that PGE_2 mediates myeloid-derived suppressor cell tumor suppressive action, inhibiting FATP2 may reduce tumor growth via PGE_2 [240,241]. FATP2 deletion, on the other hand, is expected to result in ferroptosis resistance by limiting ARA absorption. While gastric cancer cells exhibit low levels of FATP2, cells appear to compensate for the ARA deficit by activating the de novo synthesis pathway, making them more susceptible to ferroptosis [225]. Two studies published recently found that iPLA2 plays a function in ferroptosis. First, the scientists concentrated on peroxiredoxin 6 (PRDX6), which has phospholipid hydroperoxide and iPLA2 activity [242]. PRDX6 depletion causes RSL3- or elastin-induced ferroptosis, as well as an increase in lipid peroxidation levels, implying that PRDX6 is a negative regulator of ferroptosis [242]. The authors argue that PRDX6 iPLA2 activity is responsible for ferroptosis suppression using MJ33, a selective PRDX6 phospholipase A2 (iPLA2) inhibitor [242]. The precise process by which iPLA2 remodels membrane phospholipids to reduce ferroptosis remains unknown. Another study looked specifically at the ability of PLA2G6 to hydrolyze Hp-PE molecules, which are the primary cause of ferroptosis [243]. The abundance of 15-HpETE-PE was increased in PLA2G6 knock-out cells relative to control cells in both normal and RSL3-treated conditions [243]. PLA2G6 KO mice are more sensitive to ferroptosis caused by RSL3 and ischemia/reperfusion during pregnancy than wild-type mice, increasing fetal death rates [243]. Glucose is the fundamental energy source for cells, and it generates ATP via glycolysis. Excess glucose can be turned into fatty acids and stored in triglycerides via the de novo lipogenesis. Cells in mammals synthesize saturated fatty acids like PA and MUFAs like OA from glucose, but they cannot produce PUFAs. Glucose shortage can cause metabolic stress by depleting ATP and causing cell death [244]. ATP depletion, on the other hand, can activate AMPK, alleviating energy stress by saving ATP and boosting cell survival [245]. Glucose deprivation reduces ferroptosis triggered by various triggers, including cysteine deficiency, GPX4 deletion, erastin, and RSL3 [246]. By suppressing the de novo lipogenesis pathway, AMPK-mediated acetyl-CoA carboxylase (ACC) phosphorylation suppresses ferroptosis [246]. Lipidomic studies show that AMPK activation downregulates free PA and free PUFAs such as dihomo-γ-linolenic acid (DGLA) and ARA [246]. Liver kinase 1 (LKB1, also known as STK11) acts as an upstream regulator, suppressing ferroptosis via the LBK1-AMPK-ACC-FAS axis [247]. Because PUFAs cannot be produced from PA, AMPK and PA may indirectly affect PUFA pools, suppressing ferroptosis. OA, which may be produced from PA via SCD1, on the other hand, suppresses ferroptosis, showing that AMPK may reduce ferroptosis

via a different route [31,229,230]. AMPK can also contribute to erastin-induced ferroptosis [248]. Erastin activates AMPK, which enhances the phosphorylation of beclin 1 [248]. Phosphorylated beclin 1 then inhibits system x_c^- by direct binding to SLC7A11, hastening ferroptosis [248]. Understanding how the de novo lipogenesis pathway collaborates with PUFA synthesis pathways to alter phospholipid metabolism under different situations may help us comprehend lipid peroxidation, ferroptosis, and other illnesses. Because cholesterol can undergo autoxidation and is abundant in cellular membranes and lipoproteins, it may be linked to ferroptosis [249–251]. The mevalonate process can be used to manufacture cholesterol from acetyl-CoA. Because isopentenyl pyrophosphate, an intermediary of the mevalonate system, is required for the isopentenylation of selenocysteine-tRNA, the mevalonate process is also required for the formation of selenoproteins, including GPX4 [252]. As a result, analysis of cancer cell line sensitivity data revealed that statins are selective inducers of ferroptosis in mesenchymal-type cancer cells, possibly by inactivating GPX4 [232]. Because statins can change tumor metabolism and reduce cell viability, it remains to be seen whether statins specifically trigger ferroptosis [253]. In addition to promoting GPX4 degradation, ferroptosis-inducing agent 56 (FIN56) activates squalene synthase (also known as farnesyl-diphosphate farnesyltransferase; FDFT1) in the mevalonate pathway, which makes squalene from farnesyl pyrophosphate [254]. Because coenzyme Q10 is generated from farnesyl pyrophosphate, activating squalene synthase with FIN56 depletes farnesyl pyrophosphate and coenzyme Q10, contributing to ferroptosis [254]. Some malignancies, such as ALK^+ anaplastic large cell lymphoma, lose the expression of squalene monooxygenase, which mediates cholesterol synthesis from squalene, indicating that these tumors rely on exogenous cholesterols [255]. Surprisingly, squalene accumulates in the membrane of these cells, suppressing ferroptosis through modifying membrane phospholipids [255]. Inhibiting squalene synthase, which prevents squalene formation, can make cells more susceptible to ferroptosis [255]. This study contradicts the findings involving FIN56-induced ferroptosis in HT-1080 cells, where suppression of squalene monooxygenase or squalene synthase reduces ferroptosis via farnesyl pyrophosphate and coenzyme Q10 accumulation [254]. Modulation of lipid metabolism could lead to new treatments for ferroptosis-related disorders. Because ferroptosis can kill cancer cells (Table 3) resistant to several anticancer medications, it is an emerging method for innovative cancer treatments. While certain ferroptosis-inducing compounds, such as RSL3 and erastin, are highly effective in vitro at killing cancer cells, their pharmacokinetic features, such as solubility and metabolic stability, make them unsuitable for in vivo application [256]. The most significant barrier to employing ferroptosis-inducing compounds for cancer treatment is that other tissues, such as the heart, liver, and kidney, are also susceptible to ferroptosis, which can result in unwanted side effects. Furthermore, ferroptosis can impair tumor-suppressing immune cells, decreasing anti-cancer immunity. To properly target this process, a cancer-specific ferroptosis induction method is required to treat cancer patients.

Table 3
Ferroptosis-inducing *compounds*.

Mechanism of Actions	Compound names
Glutamate-cystine antiporter (Systems x_c^-) inhibitors	Erastin[349] Sulfasalazine[349,350] Sorafenib[351,352] Diaryl-isoxazoles (Non-competitive inhibitor)[353]
γ-glutamylcysteine synthetase inhibitor	L-buthionine sulfoximine[256, 354,355]
GPX4 inhibitors	RSL3[256] ML162[256,356] ML210[256,356] Artemisinin derivatives [357–359]
GPX4 degradation inducer	FIN56[254]
GPX4 inhibitor and iron oxidation	$FINO_2$[360,361]
Synergistic effect on ferroptosis induction through an increase in intracellular iron concentration	Siramesine/Lapatinib[362]
Systemic depletion of L-cysteine	Engineered human cyst(e) inase[363]
Triggers GPX4 degradation and HO-1 upregulation	Withaferin[364]
Cargoes include polyunsaturated fatty acids, peroxides, and iron, as well as their mixtures, which cause iron overload and peroxide-mediated cancer cell death	Nanoparticle-based vehicles [365–368]

6. Convergence of fatty acid metabolic, molecular heterogeneity, and oncogenic signaling in cancer cells

Oncogenes and tumor suppressors maintain various metabolic processes in cancer cells. Oncogenic *KRAS* induces glucose metabolism by upregulating hexokinase 1 and hexokinase 2 and glutamine flux to malate to produce pyruvate [257,258]. Oncogenic *MYC* upregulates glutamine metabolism and anaplerosis (the metabolic pathway that replenishes the citric acid cycle intermediates) by transcriptionally activating mitochondrial glutaminase 1 and the SLC1A5 glutamine transporter [259,260]. Overactivity of phosphoinositide 3-kinase (PI3K) and AKT pathway also upregulates glutamine anaplerosis via activation of glutamate pyruvate transaminase 2, enhances glucose uptake through stabilization of glucose transporter 1 and remodeling of the cellular lipidome [261–263]. Therefore, the role of complex regulatory networks in fatty acid metabolism cannot be ignored.

Genes responsible for lipid metabolism are differently expressed in various cancer types and subtypes [5264]. For instance, receptor-positive breast cancers are associated with upregulated gene expression associated with de novo lipogenesis, fatty acid mobilization, and oxidation. In contrast, triple-negative breast cancers upregulate genes involved in exogenous lipid uptake and storage [265]. Interestingly overexpression of long-chain acyl-CoA synthetase 3 induces cholesterol synthesis and steroidogenesis in prostate cancer but is downregulated in triple-negative breast cancers [265,266]. Interestingly, α-methyl acyl-CoA racemase and carnitine palmitoyltransferase 1b are upregulated in the prostate, colorectal, and hepatic cancers, while carnitine palmitoyltransferase 1a is upregulated in breast cancer [266, 267]. So, it's obvious that various types of cancer may exhibit unique metabolic adaptations to remodel their lipidome. As gene expression analyses don't reflect enzyme activity or dependencies on specific metabolic pathways, studies have validated unique lipid-associated genetic signatures for therapeutic intervention [266,268]. For example, a genetic signature associated with fatty acid oxidation supports aggressiveness and poor clinical outcome of MYC-overexpressed triple--negative breast cancers [268]. Suppressing carnitine palmitoyltransferase 1 and fatty acid oxidation reduces the primary tumor growth of MYC-overexpressed breast cancers [268]. Therefore, it is crucial to understand the molecular subtype, tissue, and overall tumor microenvironment for better stratification methods and targeted application of lipid metabolism pathway inhibitors.

Oncogenic signaling pathways can modulate enzymes involved in lipid metabolism and shape the tumor lipidome. *PIK3CA* is one of the most mutated genes in cancer to promote growth, proliferation, and survival [269–271]. Constant upregulation of de novo lipogenesis in HER2-positive breast cancers is associated with hyperactivation of PI3K signaling [272,273]. Either blocking of downstream signaling of HER2 or de novo lipogenesis reduces oncogenic activity and induces apoptosis. Even AKT contributes to de novo lipogenesis by shuttling metabolic intermediates and synthesizing the cellular pool of NADPH [274–280].

As the main catalytic subunit of the mammalian target of rapamycin complex 1 (mTORC1) and mTORC2, the mammalian target of rapamycin (mTOR) mediated signaling is interlinked with PI3K and AKT activities [281]. Different metabolic processes such as Oxidative phosphorylation by inducing mitochondrial biosynthesis, de novo nucleotide synthesis and lipogenesis are known to be activated by

PI3K–AKT–mTORC1-dependent mechanisms [282–284]. Therefore, predominant key lipogenic enzymes, such as *FASN*, *ACC1* and *ACLY* are upregulated by mTORC1 [282,285,286]. Although mTORC1 phosphorylates and inactivates lipin-1 to sequestrate in the cytoplasm and modulate the lipid architecture in the nucleus and subsequently change nuclear lamina to directly affect SREBP activity in cancer cells (possibly dependent on lipid phosphatase activity of lipin-1 that specifically acts on phosphatidic acids) [285,287]. Various oncogenes e.g., Ras, KRAS, extracellular signal-regulated kinase 1/2 (ERK1/2) converge on mTORC1 to promote de novo lipogenesis [286,288–290].

Overactivation of PI3K induces mTORC2 to reprogram fatty acid metabolism in cancer cells by activating AKT, serum- and glucocorticoid-regulated (SGKs), and protein kinase Cs (PKCs) [291–293]. mTORC2 induces de novo synthesis of sphingolipids, glycerophospholipids, and cardiolipins to upregulate mitochondrial respiration [294]. Interestingly, blocking mTORC2, but not mTORC1, reduces overall lipid content, suggesting that mTORC1 activation alone is insufficient to induce lipid synthesis without functional AKT [294,295]. Although facilitating glucose uptake and glycolysis (Warburg effect) is supported by PI3K–AKT pathway signaling, dysregulated fatty acid metabolic processes in cancer through PI3K signaling are still obscured [296]. In addition, AKT contributes to the uncoupling of glycolysis and mitochondrial oxidative phosphorylation [297]. It should re-investigate how upregulated aerobic glycolysis impairs oxidative phosphorylation. However, glucose-6-phosphate (produced during glycolysis) shunts the pentose phosphate pathway to generate NADPH to sustain anabolic processes and detoxification of ROS [280,298]. AKT facilitates NADPH biosynthesis, while PI3K supports phosphorylation through PGC-1α-dependent mitochondrial biosynthesis and cardiolipins to increase respiration and improve mitochondrial activity [279,294,299]. So, overstimulated PI3Ksignalling induces the synthesis of metabolic intermediates required for anabolic metabolism and supports respiration to produce citrate from acetyl-CoA for de novo lipogenesis. Despite having complex homeostasis between oxidation of fatty acids and glucose, PI3K/AKT signaling supports lipid synthesis and inhibits lipolysis and β-oxidation [300].

Given that the obesity and insulin resistance are closely associated with cancer, it is convincing that PI3K signaling might play a crucial role in lipid synthesis by inducing mTORC1-p70S6K and subsequent blocking of insulin receptor substrate 1 [300–303]. As raised lipolysis in adipose-rich microenvironments supports cancer cells, and β-oxidation induces ATP and NADPH synthesis, therefore PI3K-mediated lipid metabolism and tumorigenesis supporting enhanced de novo lipogenesis are paradoxical [12,15,20]. Whole-body metabolism and obesity-related factors that support definite metabolic pathways during tumorigenesis might need to consider reuniting the anomalous regulatory pathways linking PI3K signaling and lipid metabolism. It is convincible that de novo lipogenesis and enzymatic networks reciprocally regulate oncogenic signaling throughout malignant transformation. For example, *FASN* and estrogen receptor α signaling or *HER2* crosstalk bidirectionally in breast cancers [304,305].

Besides pro-tumorigenic signaling, fatty acid metabolism affects cancer epigenome to regulate gene expression and cellular differentiation [306]. ACLY and ACSS2 serve not only as the main sources of acetyl-CoA, but also as the essential cofactors for several histone-modifying enzymes to promote the transcription of pro-proliferative and growth genes in cancer cells under nutrient-deplete conditions [307–310]. Acetyl-CoA also regulates cell differentiation and stemness of a tumor cell [311]. As an obligate cofactor for CREB-binding protein (CBP)/p300, acetyl-CoA induces expression of *Oct4*, *Sox2*, *Klf4*, and *CSF1R* genes [312]. Acetyl-CoA serves as the basic substrate for cholesterol and steroid synthesis along with the induction of epigenetic remodeling mediated pro-survival and metastatic genes upregulation [313,314]. Overall, induction of lipogenic enzymes such as FASN, ACLY, and ACSS2 regulate hyperactive oncogenic signaling reciprocally and produce metabolic end products.

7. Cancer progression regulation by fatty acids

It is well known that fatty acids support cancer cells by providing an energy source during metabolic stress and sustaining membrane biosynthesis during proliferation. Therefore, upregulated de novo lipogenesis in cancer cells contributes to the production of saturated and unsaturated fatty acids to reduce the susceptivity of chemotherapy-induced oxidative stress or cytotoxicity [315]. Interestingly, endogenously synthesized cholesterol is known to decrease membrane fluidity to reduce cellular migration and ultimate metastatic dissemination and develop multi-drug resistance [316,317]. However, the role of cholesterol metabolism in tumorigenesis is still controversial [318]. Low cholesterol levels support metastatic dissemination during cancer progression, while primary tumor is highly dependent on membrane cholesterol concentrations by forming lipid rafts [319]. Hence, targeting cholesterol metabolism or blocking cholesterol synthesis could be more effective at inhibiting cancer initiation and proliferation [316,319].

Phosphatidylinositols (containing fatty acid chains connected to an inositol ring and glycerol backbone) act as secondary messengers to synthesize bioactive lipids for supporting cell survival and proliferation [269]. Hydroxyl groups of the inositol ring are phosphorylated into several species, including triphosphorylated PI (3−5) P3 (also known as PIP_3) [269]. PIP_3 supports the localization of AKT to the cell membrane to activate phosphoinositide-dependent kinase 1 (PDK1) and mTORC2 downstream of hyperactive PI3K signaling. AKT facilitates de novo lipogenesis, promotes cell survival, and inhibits apoptosis [263,278,279,320]. Lipid phosphatases e.g., PTEN and inositol polyphosphate-4-phosphatase type II may also regulate pro-oncogenic signaling [270,321,322]. As phosphoinositides are derived from phosphatidylinositols and regulated by phosphatidylinositols transfer proteins, phosphatidylinositols transfer proteins are prime for several cellular processes and are associated with normal fatty acid metabolism [323]. Phosphatidylinositols transfer protein-α has a higher affinity for phosphatidylinositols to contribute to localized PIP_3 generation and EGFR activation [324–326]. Phosphatidylinositols transfer protein-α contributes to cancer metastasis to distant tissues via linking PIP_2 and inositol 1,4,5-triphosphate (IP_3), signaling [327]. Therefore, it's obvious that aberrant fatty acid metabolism has significant effects on the spatial production of secondary messengers that ultimately impact on cell-signaling pathways. Rapid PI3K–AKT signaling induction catalyzes the conversion of membrane-localized pools of phosphatidylinositols into pro-tumorigenic phosphoinositides by supporting the scaffold protein IQGAP1 [328]. 100-fold higher expression of PIP2 than PIP3 at the plasma membrane and phosphatidylinositols at sites of activated RTKs act as the rate-limiting step in the efficient production of secondary messenger [327,328]. In addition to phosphatidylinositols, phosphatidic acids also serve as potent signaling molecules to bind and stabilize mTOR to increase the activity of mTORC1 and mTORC2 to coordinate cellular growth and proliferation [329–333]. Bioactive lipids e.g., lysophosphatidic acids, can stimulate cell proliferation by activating G-protein-coupled receptors [334]. Dysregulated lipid metabolism-regulated lysophosphatidic acids are produced either by cleavage of existing phospholipids at the sn-2 position by phospholipases to release a lysophospholipid and a fatty acid or by lysophospholipase D activity of autotaxin to convert lysophosphatidylcholine into lysophosphatidic acids extracellularly [335,336]. Lysophosphatidic acids bind with lysophosphatidic acid receptors to exert the pro-tumorigenic effects by serving as important intermediaries between tumor cells and the surrounding microenvironment [334,337].

8. Conclusion and future perspectives

In recent years, there has been a growing appreciation of the substantial influence of fatty acid metabolism on tumor growth, its role in ATP generation through beta-oxidation, and its contribution to glycerophospholipid synthesis. This encompasses maintaining fatty acid

homeostasis in response to redox stress, averting ferroptosis, and regulating membrane fluidity and permeability to facilitate cell motility and metastasis. Moreover, these alterations in fatty acid metabolism have been associated with the development of treatment resistance, particularly in cases related to obesity, shedding light on the shifts in cancer cell behavior observed in obese individuals. Significantly, recent discoveries regarding the potential of targeting fatty acid metabolism to overcome treatment resistance suggest that co-targeting strategies hold promise as a practical future approach, with particular relevance in the context of obesity and metabolic dysfunction.

However, it is imperative to acknowledge that translating these findings into clinical practice will depend on developing pharmacological compounds capable of circumventing the known limitations and off-target effects associated with existing experimental and clinical inhibitors. Moreover, for co-targeting approaches to be effectively applied in the clinical setting, more intricate three-dimensional models and patient-derived specimens should be employed in future research studies. Finally, we believe there is considerable potential in integrating tumor genetic classification with environmental factors such as dietary habits and systemic metabolism to enhance patient prognosis and establish more comprehensive precision medicine methodologies.

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Declaration of Competing Interest

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Data Availability

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References

[1] P. Fagone, S. Jackowski, Membrane phospholipid synthesis and endoplasmic reticulum function, J. Lipid Res. vol. 50 (2009), https://doi.org/10.1194/jlr.R800049-JLR200.
[2] S. Beloribi-Djefaflia, S. Vasseur, F. Guillaumond, Lipid metabolic reprogramming in cancer cells, Oncogenesis 5 (2016).
[3] F. Röhrig, A. Schulze, The multifaceted roles of fatty acid synthesis in cancer, Nat. Rev. Cancer vol. 16 (2016), https://doi.org/10.1038/nrc.2016.89.
[4] R. Mallick, S. Basak, A.K. Duttaroy, Fatty acids and evolving roles of their proteins in neurological, cardiovascular disorders and cancers, Prog. Lipid Res. vol. 83 (2021), https://doi.org/10.1016/j.plipres.2021.101116.
[5] M.E. Monaco, Fatty acid metabolism in breast cancer subtypes, Oncotarget vol. 8 (2017), https://doi.org/10.18632/oncotarget.15494.
[6] R. Mallick, A.K. Duttaroy, Modulation of endothelium function by fatty acids, Mol. Cell. Biochem. vol. 477 (2022), https://doi.org/10.1007/s11010-021-04260-9.
[7] A.K. Duttaroy, Transport of fatty acids across the human placenta: A review, Prog. Lipid Res. vol. 48 (2009), https://doi.org/10.1016/j.plipres.2008.11.001.
[8] R. Mallick, S. Basak, A.K. Duttaroy, Docosahexaenoic acid,22:6n-3: Its roles in the structure and function of the brain, Int. J. Dev. Neurosci. 79 (2019).
[9] S. Basak, R. Mallick, A. Banerjee, S. Pathak, A.K. Duttaroy, Maternal supply of both arachidonic and docosahexaenoic acids is required for optimal neurodevelopment, Nutrients vol. 13 (2021), https://doi.org/10.3390/nu13062061.
[10] X. Su, N.A. Abumrad, Cellular fatty acid uptake: a pathway under construction, Trends Endocrinol. Metab. vol. 20 (2009), https://doi.org/10.1016/j.tem.2008.11.001.
[11] D. Calvo, D. Gómez-Coronado, Y. Suárez, M.A. Lasunción, M.A. Vega, Human CD36 is a high affinity receptor for the native lipoproteins HDL, LDL, and VLDL, J. Lipid Res 39 (1998).
[12] A. Ladanyi, et al., Adipocyte-induced CD36 expression drives ovarian cancer progression and metastasis, Oncogene 37 (2018).
[13] M.J. Watt, et al., Suppressing fatty acid uptake has therapeutic effects in preclinical models of prostate cancer, Sci. Transl. Med 11 (2019).
[14] E. Lengyel, L. Makowski, J. DiGiovanni, M.G. Kolonin, Cancer as a Matter of Fat: The Crosstalk between Adipose Tissue and Tumors, Trends Cancer vol. 4 (2018), https://doi.org/10.1016/j.trecan.2018.03.004.
[15] K.M. Nieman, et al., Adipocytes promote ovarian cancer metastasis and provide energy for rapid tumor growth, Nat. Med 17 (2011).
[16] K. Bensaad, et al., Fatty Acid Uptake and Lipid Storage Induced by HIF-1α Contribute to Cell Growth and Survival after Hypoxia-Reoxygenation, Cell Rep. 9 (2014) 349–365.
[17] J.A. Olzmann, P. Carvalho, Dynamics and functions of lipid droplets, Nat. Rev. Mol. Cell Biol. vol. 20 (2019), https://doi.org/10.1038/s41580-018-0085-z.
[18] T. Petan, E. Jarc, M. Jusović, Lipid droplets in cancer: Guardians of fat in a stressful world, Molecules vol. 23 (2018), https://doi.org/10.3390/molecules23081941.
[19] I.B. Fritz, B. McEwen, Effects of carnitine on fatty-acid oxidation by muscle, Science 129 (1959) 1979.
[20] A. Carracedo, L.C. Cantley, P.P. Pandolfi, Cancer metabolism: fatty acid oxidation in the limelight, Nat. Rev. Cancer 13 (2013).
[21] D.R. Wahl, et al., Glioblastoma therapy can be augmented by targeting IDH1-mediated NADPH biosynthesis, Cancer Res 77 (2017).
[22] Y. Mitsuishi, et al., Nrf2 redirects glucose and glutamine into anabolic pathways in metabolic reprogramming, Cancer Cell 22 (2012).
[23] S.C. Lu, Regulation of glutathione synthesis, Mol. Asp. Med. vol. 30 (2009), https://doi.org/10.1016/j.mam.2008.05.005.
[24] D. Samovski, et al., Regulation of AMPK activation by CD36 links fatty acid uptake to β-oxidation, Diabetes 64 (2015).
[25] G. Pascual, et al., Targeting metastasis-initiating cells through the fatty acid receptor CD36, Nature 541 (2017).
[26] A.R. Johnson, J. Justin Milner, L. Makowski, The inflammation highway: Metabolism accelerates inflammatory traffic in obesity, Immunol. Rev. 249 (2012).
[27] J. Huang, et al., Adipocyte p62/SQSTM1 suppresses tumorigenesis through opposite regulations of metabolism in adipose tissue and tumor, Cancer Cell 33 (2018).
[28] S. Sun, et al., Exosomes from the tumour-adipocyte interplay stimulate beige/brown differentiation and reprogram metabolism in stromal adipocytes to promote tumour progression, J. Exp. Clin. Cancer Res. 38 (2019).
[29] S. Balaban, et al., Adipocyte lipolysis links obesity to breast cancer growth: adipocyte-derived fatty acids drive breast cancer cell proliferation and migration, Cancer Metab. 5 (2017).
[30] E. Currie, A. Schulze, R. Zechner, T.C. Walther, R. v Farese, Cellular fatty acid metabolism and cancer, Cell Metab. vol. 18 (2013), https://doi.org/10.1016/j.cmet.2013.05.017.
[31] J.J. Kamphorst, et al., Hypoxic and Ras-transformed cells support growth by scavenging unsaturated fatty acids from lysophospholipids, Proc. Natl. Acad. Sci. USA 110 (2013).
[32] K.M. Gharpure, et al., FABP4 as a key determinant of metastatic potential of ovarian cancer, Nat. Commun. 9 (2018).
[33] F. Baenke, B. Peck, H. Miess, A. Schulze, Hooked on fat: The role of lipid synthesis in cancer metabolism and tumour development, DMM Dis. Models Mech. vol. 6 (2013), https://doi.org/10.1242/dmm.011338.
[34] G. Medes, A. Thomas, S. Weinhouse, Metabolism of neoplastic tissue. IV. A study of lipid synthesis in neoplastic tissue slices in vitro, Cancer Res 13 (1953).
[35] C.M. Metallo, et al., Reductive glutamine metabolism by IDH1 mediates lipogenesis under hypoxia, Nature 481 (2012).
[36] I. Guillet-Deniau, et al., Glucose induces de novo lipogenesis in rat muscle satellite cells through a sterol-regulatory-element-binding-protein-1c-dependent pathway, J. Cell Sci. 117 (2004).
[37] Z.T. Schug, et al., Acetyl-CoA synthetase 2 promotes acetate utilization and maintains cancer cell growth under metabolic stress, Cancer Cell 27 (2015).
[38] F.P. Kuhajda, et al., Fatty acid synthesis: A potential selective target for antineoplastic therapy, Proc. Natl. Acad. Sci. USA 91 (1994).
[39] L.P. Sun, L. Li, J.L. Goldstein, M.S. Brown, Insig required for sterol-mediated inhibition of Scap/SREBP binding to COPII proteins in vitro, J. Biol. Chem. 280 (2005).
[40] C.M. Adams, et al., Cholesterol and 25-hydroxycholesterol inhibit activation of SREBPs by different mechanisms, both involving SCAP and insigs, J. Biol. Chem. 279 (2004).
[41] D. Eberlé, B. Hegarty, P. Bossard, P. Ferré, F. Foufelle, SREBP transcription factors: master regulators of lipid homeostasis, Biochimie vol. 86 (2004), https://doi.org/10.1016/j.biochi.2004.09.018.
[42] J.M. Collins, et al., De novo lipogenesis in the differentiating human adipocyte can provide all fatty acids necessary for maturation, J. Lipid Res 52 (2011).
[43] J.M. Ntambi, M. Miyazaki, Regulation of stearoyl-CoA desaturases and role in metabolism, Prog. Lipid Res. vol. 43 (2004), https://doi.org/10.1016/S0163-7827(03)00039-0.
[44] T. Matsuzaka, et al., Crucial role of a long-chain fatty acid elongase, Elovl6, in obesity-induced insulin resistance, Nat. Med 13 (2007).

[45] J.M. Collins, M.J. Neville, M.B. Hoppa, K.N. Frayn, De novo lipogenesis and stearoyl-CoA desaturase are coordinately regulated in the human adipocyte and protect against palmitate-induced cell injury, J. Biol. Chem. 285 (2010).

[46] N. Marr, J. Foglia, M. Terebiznik, K. Athenstaedt, V. Zaremberg, Controlling lipid fluxes at glycerol-3-phosphate acyltransferase step in yeast: Unique contribution of Gat1p to oleic acid-induced lipid particle formation, J. Biol. Chem. 287 (2012).

[47] A.A. Wendel, T.M. Lewin, R.A. Coleman, Glycerol-3-phosphate acyltransferases: rate limiting enzymes of triacylglycerol biosynthesis (Preprint at), Biochim. Et. Biophys. Acta - Mol. Cell Biol. Lipids vol. 1791 (2009), https://doi.org/10.1016/j.bbalip.2008.10.010.

[48] T.M. Lewin, N.M.J. Schwerbrock, D.P. Lee, R.A. Coleman, Identification of a new glycerol-3-phosphate acyltransferase isoenzyme, mtGPAT2, in mitochondria, J. Biol. Chem. 279 (2004).

[49] H. Ren, et al., A phosphatidic acid binding/nuclear localization motif determines lipin1 function in lipid metabolism and adipogenesis, Mol. Biol. Cell 21 (2010).

[50] K. Takeuchi, K. Reue, Biochemistry, physiology, and genetics of GPAT, AGPAT, and lipin enzymes in triglyceride synthesis, Am. J. Physiol. - Endocrinol. Metab. vol. 296 (2009), https://doi.org/10.1152/ajpendo.90958.2008.

[51] X. Liu, Y. Yin, J. Wu, Z. Liu, Structure and mechanism of an intramembrane liponucleotide synthetase central for phospholipid biosynthesis, Nat. Commun. 5 (2014).

[52] C.P. Sparrow, C.R.H. Raetz, Purification and properties of the membrane-bound CDP-diglyceride synthetase from Escherichia coli, J. Biol. Chem. 260 (1985).

[53] J.R. Carter, E.P. Kennedy, Enzymatic synthesis of cytidine diphosphate diglyceride, J. Lipid Res 7 (1966).

[54] B. Peck, A. Schulze, Lipid desaturation – the next step in targeting lipogenesis in cancer? FEBS J. (2016) https://doi.org/10.1111/febs.13681.

[55] B. Peck, et al., Inhibition of fatty acid desaturation is detrimental to cancer cell survival in metabolically compromised environments, Cancer Metab. 4 (2016).

[56] K. Vriens, et al., Evidence for an alternative fatty acid desaturation pathway increasing cancer plasticity, Nature 566 (2019).

[57] R. Munir, J. Lisec, J. v Swinnen, N. Zaidi, Lipid metabolism in cancer cells under metabolic stress, Br. J. Cancer vol. 120 (2019) 1090–1098, https://doi.org/10.1038/s41416-019-0451-4.

[58] N. Zaidi, et al., Lipogenesis and lipolysis: The pathways exploited by the cancer cells to acquire fatty acids, Prog. Lipid Res. vol. 52 (2013) 585–589, https://doi.org/10.1016/j.plipres.2013.08.005.

[59] C.F. Deng, et al., Involvement of LDL and ox-LDL in cancer development and its therapeutical potential, Front. Oncol. vol. 12 (2022), https://doi.org/10.3389/fonc.2022.803473.

[60] L.Y. Chu, D.P. Ramakrishnan, R.L. Silverstein, Thrombospondin-1 modulates VEGF signaling via CD36 by recruiting SHP-1 to VEGFR2 complex in microvascular endothelial cells, Blood 122 (2013) 1822–1832.

[61] S.N. Markovic, et al., A phase II study of ABT-510 (thrombospondin-1 analog) for the treatment of metastatic melanoma, Am. J. Clin. Oncol.: Cancer Clin. Trials 30 (2007) 303–309.

[62] S. Collot-Teixeira, J. Martin, C. McDermott-Roe, R. Poston, J.L. McGregor, CD36 and macrophages in atherosclerosis, Cardiovasc. Res. vol. 75 (2007) 468–477, https://doi.org/10.1016/j.cardiores.2007.03.010.

[63] M.J. Watt, et al., Suppressing fatty acid uptake has therapeutic effects in preclinical models of prostate cancer, Sci. Transl. Med vol. 11 (2019). ⟨http://stm.sciencemag.org/⟩.

[64] A. Nath, I. Li, L.R. Roberts, C. Chan, Elevated free fatty acid uptake via CD36 promotes epithelial-mesenchymal transition in hepatocellular carcinoma, Sci. Rep. 5 (2015).

[65] O. Kuda, et al., Sulfo-N-succinimidyl oleate (SSO) inhibits fatty acid uptake and signaling for intracellular calcium via binding CD36 lysine 164: SSO also inhibits oxidized low density lipoprotein uptake by macrophages, J. Biol. Chem. 288 (2013) 15547–15555.

[66] N. Sp, et al., Nobiletin inhibits CD36-dependent tumor angiogenesis, migration, invasion, and sphere formation through the Cd36/Stat3/Nf-Kb signaling axis, Nutrients 10 (2018).

[67] Smathers, R.L. & Petersen, D.R. The human fatty acid-binding protein family: Evolutionary divergences and functions. www.ncbi.nlm.nih.gov/.

[68] L.M. Butler, et al., Lipids and cancer: Emerging roles in pathogenesis, diagnosis and therapeutic intervention, Adv. Drug Deliv. Rev. vol. 159 (2020) 245–293, https://doi.org/10.1016/j.addr.2020.07.013.

[69] I.H. McKillop, C.A. Girardi, K.J. Thompson, Role of fatty acid binding proteins (FABPs) in cancer development and progression, Cell. Signal. vol. 62 (2019), https://doi.org/10.1016/j.cellsig.2019.06.001.

[70] H. Uehara, T. Takahashi, M. Oha, H. Ogawa, K. Izumi, Exogenous fatty acid binding protein 4 promotes human prostate cancer cell progression, Int J. Cancer 135 (2014) 2558–2568.

[71] N. Noy, E. Morgan, P. Kannan-Thulasiraman, Involvement of fatty acid binding protein 5 and PPAR β/δ in prostate cancer cell growth, PPAR Res. (2010), https://doi.org/10.1155/2010/234629.

[72] L. Levi, Z. Wang, M.K. Doud, S.L. Hazen, N. Noy, Saturated fatty acids regulate retinoic acid signalling and suppress tumorigenesis by targeting fatty acid-binding protein 5, Nat. Commun. 6 (2015).

[73] A.T. Alshareeda, E.A. Rakha, C.C. Nolan, I.O. Ellis, A.R. Green, Fatty acid binding protein 7 expression and its sub-cellular localization in breast cancer, Breast Cancer Res Treat. 134 (2012) 519–529.

[74] G. Carbonetti, et al., Docetaxel/cabazitaxel and fatty acid binding protein 5 inhibitors produce synergistic inhibition of prostate cancer growth, Prostate 80 (2020) 88–98.

[75] E. Currie, A. Schulze, R. Zechner, T.C. Walther, R. v Farese, Cellular fatty acid metabolism and cancer, Cell Metab. vol. 18 (2013) 153–161, https://doi.org/10.1016/j.cmet.2013.05.017.

[76] O. Catalina-Rodriguez, et al., The mitochondrial citrate transporter, CIC, is essential for mitochondrial homeostasis, Oncotarget vol. 3 (2012). ⟨www.impactjournals.com/oncotargetwww.impactjournals.com/oncotarget/⟩.

[77] R. Mosaoa, A. Kasprzyk-Pawelec, H.R. Fernandez, M.L. Avantaggiati, The mitochondrial citrate carrier slc25a1/cic and the fundamental role of citrate in cancer, inflammation and beyond, Biomolecules vol. 11 (2021) 1–17, https://doi.org/10.3390/biom11020141.

[78] M.E. Mycielska, et al., Potential use of gluconate in cancer therapy, Front Oncol. 9 (2019).

[79] K. Higuchi, et al., Functional analysis of a species-specific inhibitor selective for human Na+coupled citrate transporter (NaCT/SLC13A5/mINDY), Biochem. J. 477 (2020) 4149–4165.

[80] K. Huard, et al., Discovery and characterization of novel inhibitors of the sodium-coupled citrate transporter (NaCT or SLC13A5), Sci. Rep. 5 (2015).

[81] C. Granchi, ATP citrate lyase (ACLY) inhibitors: an anti-cancer strategy at the crossroads of glucose and lipid metabolism, Eur. J. Med. Chem. vol. 157 (2018) 1276–1291, https://doi.org/10.1016/j.ejmech.2018.09.001.

[82] G. Hatzivassiliou, et al., ATP citrate lyase inhibition can suppress tumor cell growth, Cancer Cell 8 (2005) 311–321.

[83] S. Zhao, et al., ATP-citrate lyase controls a glucose-to-acetate metabolic switch, Cell Rep. 17 (2016) 1037–1052.

[84] N.J. Pearce, et al., The role of ATP citrate-lyase in the metabolic regulation of plasma lipids Hypolipidaemic effects of SB-204990, a lactone prodrug of the potent ATP citrate-lyase inhibitor SB-201076, Biochem. J. vol. 334 (1998).

[85] Gribble, A.D. et al. ATP-Citrate Lyase as a Target for Hypolipidemic Intervention. 2. Synthesis and Evaluation of (3R*,5S*)-ω-Substituted-3-carboxy-3,5-dihydroxyalkanoic Acids and Their γ-Lactone Prodrugs as Inhibitors of the Enzyme in Vitro and in Vivo. https://pubs.acs.org/sharingguidelines (1998).

[86] A.C. Sullivan, M. Singh, P.A. Srere, J.P. Glusker, Reactivity and inhibitor potential of hydroxycitrate isomers with citrate synthase, citrate lyase, and ATP citrate lyase*, J. Biol. Chem. vol. 252 (1977).

[87] Hamilton, J.G., Sullivan, A.C., Kritchevsky, D., Triscari, J. & Ontko, J.A. SYMPOSIUM" HYPERLIPIDEMIA Presented at the AOCS 67th Annual Spring Meeting New Orleans, Louisiana Hypolipidemic Activity of (-)-Hydroxycitrate.

[88] B.S. Jena, G.K. Jayaprakasha, R.P. Singh, K.K. Sakariah, Chemistry and biochemistry of (-)-hydroxycitric acid from Garcinia, J. Agric. Food Chem. vol. 50 (2002) 10–22, https://doi.org/10.1021/jf010753k.

[89] L. Schwartz, et al., A combination of alpha lipoic acid and calcium hydroxycitrate is efficient against mouse cancer models: preliminary results, Oncol. Rep. 23 (2010) 1407–1416.

[90] Y. Gao, M.S. Islam, J. Tian, V.W.Y. Lui, D. Xiao, Inactivation of ATP citrate lyase by cucurbitacin B: a bioactive compound from cucumber, inhibits prostate cancer growth, Cancer Lett. 349 (2014) 15–25.

[91] N. Hunsakunachai, N. Nuengchamnong, W. Jiratchariyakul, T. Kummalue, P. Khemawoot, Pharmacokinetics of cucurbitacin B from Trichosanthes cucumerina L. in rats, BMC Complement Alter. Med 19 (2019).

[92] S.K. Koerner, et al., Design and synthesis of emodin derivatives as novel inhibitors of ATP-citrate lyase, Eur. J. Med Chem. 126 (2017) 920–928.

[93] F.E. Jernigan, J. ichi Hanai, V.P. Sukhatme, L. Sun, Discovery of furan carboxylate derivatives as novel inhibitors of ATP-citrate lyase via virtual high-throughput screening, Bioorg. Med Chem. Lett. 27 (2017) 929–935.

[94] R.E. Dolle, et al., The lipid research clinics coronary primary prevention trial results ii. the relationship of reduction in incidence of coronary heart disease to cholesterol lowering, Ross., R. Mech. Atheroscler. -A Rev. Adv. Nephrol. vol. 35 (1992). ⟨https://pubs.acs.org/sharingguidelines⟩.

[95] B.A. Saxty, et al., Synthesis and evaluation of (+) and (-)-2,2-difluorocitrate as inhibitors of rat-liver ATP-citrate lyase and porcine-heart aconitase, Eur. J. Niochem vol. 202 (1992).

[96] J.J. Oleynek, et al., Anthrones, Nat. Occur. Compét. Inhib. Aden ne-Tr. i Phosphate-Ci t rate Lyase (1995).

[97] R.E. Dolle, et al., v Present address: glaxo institute for molecular biology, J. Med. Chem. vol. 38 (1995). ⟨https://pubs.acs.org/sharingguidelines⟩.

[98] Barrow, C.J. et al. THE JOURNAL OF ANTIBIOTICS Antimycins, Inhibitors of ATP-Citrate Lyase, from a Streptomyces sp.

[99] S.W. Ki, et al., Radicicol binds and inhibits mammalian ATP citrate lyase, J. Biol. Chem. 275 (2000) 39231–39236.

[100] J.J. Li, et al., 2-Hydroxy-N-arylbenzenesulfonamides as ATP-citrate lyase inhibitors, Bioorg. Med Chem. Lett. 17 (2007) 3208–3211.

[101] J. Wei, et al., An allosteric mechanism for potent inhibition of human ATP-citrate lyase, Nature 568 (2019) 566–570.

[102] Y. Zang, et al., Discovery of a Novel Macrocyclic ATP Citrate Lyase Inhibitor, J. Chem. Inf. Model 62 (2022) 3123–3132.

[103] K.B. Singh, E.R. Hahm, S.K. Pore, S. v Singh, Leelamine is a novel lipogenesis inhibitor in prostate cancer cells in vitro and in vivo, Mol. Cancer Ther. 18 (2019) 1800–1810.

[104] Z. Deng, et al., Dehydrocurvularin is a potent antineoplastic agent irreversibly blocking ATP-citrate lyase: evidence from chemoproteomics, Chem. Commun. 55 (2019) 4194–4197.

[105] J.P. Samsoondar, et al., Prevention of diet-induced metabolic dysregulation, inflammation, and atherosclerosis in Ldlr-/- mice by treatment with the ATP-citrate lyase inhibitor bempedoic acid, Arterioscler. Thromb. Vasc. Biol. 37 (2017) 647–656.

[106] O. Bilen, C.M. Ballantyne, Bempedoic Acid (ETC-1002): an investigational inhibitor of ATP citrate lyase, Curr. Atheroscler. Rep. vol. 18 (2016), https://doi.org/10.1007/s11883-016-0611-4.

[107] C. Wang, et al., The acetyl-CoA carboxylase enzyme: a target for cancer therapy? Expert Rev. Anticancer Ther. vol. 15 (2015) 667–676, https://doi.org/10.1586/14737140.2015.1038246.

[108] J. Wei, L. Tong, Crystal structure of the 500-kDa yeast acetyl-CoA carboxylase holoenzyme dimer, Nature 526 (2015) 723–727.

[109] L. Abu-Elheiga, D.B. Almarza-Ortega, A. Baldini, S.J. Wakil, Human acetyl-CoA carboxylase 2. Molecular cloning, characterization, chromosomal mapping, and evidence for two isoforms, J. Biol. Chem. 272 (1997) 10669–10677.

[110] H. Zhang, et al., Lipidomics reveals carnitine palmitoyltransferase 1C protects cancer cells from lipotoxicity and senescence, J. Pharm. Anal. 11 (2021) 340–350.

[111] C.H. Yao, et al., Identifying off-target effects of etomoxir reveals that carnitine palmitoyltransferase i is essential for cancer cell proliferation independent of β-oxidation, PLoS Biol. 16 (2018).

[112] X.R. Ren, et al., Perhexiline promotes HER3 ablation through receptor internalization and inhibits tumor growth, Breast Cancer Res. 17 (2015).

[113] S. Cheng, et al., Fatty acid oxidation inhibitor etomoxir suppresses tumor progression and induces cell cycle arrest via PPARγ-mediated pathway in bladder cancer, Clin. Sci. 133 (2019) 1745–1758.

[114] H. Lin, et al., Fatty acid oxidation is required for the respiration and proliferation of malignant glioma cells, Neuro Oncol. 19 (2017) 43–54.

[115] Itkonen, H.M. et al. Oncotarget 38264 www.impactjournals.com/oncotarget Lipid degradation promotes prostate cancer cell survival. Oncotarget vol. 8 www.impactjournals.com/oncotarget/ (2017).

[116] D.K. Nambiar, G. Deep, R.P. Singh, C. Agarwal, R. Agarwal, Silibinin inhibits aberrant lipid metabolism, proliferation and emergence of androgen-independence in prostate cancer cells via primarily targeting the sterol response element binding protein 1, Oncotarget vol. 5 (2014). ⟨www.impactjournals.com/oncotarget/⟩.

[117] N. Yahagi, et al., Co-ordinate activation of lipogenic enzymes in hepatocellular carcinoma, Eur. J. Cancer 41 (2005) 1316–1322.

[118] C. Postic, R. Dentin, P.D. Denechaud, J. Girard, ChREBP, a transcriptional regulator of glucose and lipid metabolism (Preprint at), Annu. Rev. Nutr. vol. 27 (2007) 179–192, https://doi.org/10.1146/annurev.nutr.27.061406.093618.

[119] J.M. Ellis, J.L. Frahm, L.O. Li, R.A. Coleman, Acyl-Coenzyme A Synth. Metab. Control (2010).

[120] N. Li, et al., Inhibition of the sterol regulatory element-binding protein pathway suppresses hepatocellular carcinoma by repressing inflammation in mice, Hepatology 65 (2017).

[121] V.T.M. Nguyen, et al., Differential epigenetic reprogramming in response to specific endocrine therapies promotes cholesterol biosynthesis and cellular invasion, Nat. Commun. 6 (2015).

[122] X. Li, Y.T. Chen, P. Hu, W.C. Huang, Fatostatin displays high antitumor activity in prostate cancer by blocking SREBP-regulated metabolic pathways and androgen receptor signaling, Mol. Cancer Ther. 13 (2014) 855–866.

[123] V. Brovkovych, et al., Fatostatin induces pro- and anti-apoptotic lipid accumulation in breast cancer, Oncogenesis 7 (2018).

[124] S. Sekar, V. Gopalakrishnan, C. Taghibiglou, Sterol regulatory element-binding protein 1 inhibitors decrease pancreatic cancer cell viability and proliferation, Biochem Biophys. Res Commun. 488 (2017) 136–140.

[125] H.J. Harwood, et al., Isozyme-nonselective N-substituted bipiperidylcarboxamide acetyl-CoA carboxylase inhibitors reduce tissue malonyl-CoA concentrations, inhibit fatty acid synthesis, and increase fatty acid oxidation in cultured cells and in experimental animals, J. Biol. Chem. 278 (2003).

[126] H.J. Harwood, et al., Isozyme-nonselective N-substituted bipiperidylcarboxamide acetyl-CoA carboxylase inhibitors reduce tissue malonyl-CoA concentrations, inhibit fatty acid synthesis, and increase fatty acid oxidation in cultured cells and in experimental animals, J. Biol. Chem. 278 (2003) 37099–37111.

[127] H. Zhang, B. Tweel, J. Li, L. Tong, Crystal structure of the carboxyltransferase domain of acetyl-coenzyme A carboxylase in complex with CP-640186, Structure 12 (2004) 1683–1691.

[128] D. Hess, J.W. Chisholm, R.A. Igal, Inhibition of stearoylCoA desaturase activity blocks cell cycle progression and induces programmed cell death in lung cancer cells, PLoS One 5 (2010).

[129] T. Chonan, et al., 4-Piperidinyl)-piperazine: a new platform for acetyl-CoA carboxylase inhibitors, Bioorg. Med Chem. Lett. 19 (2009) 6645–6648.

[130] T. Chonan, et al., Design and synthesis of disubstituted (4-piperidinyl)-piperazine derivatives as potent acetyl-CoA carboxylase inhibitors, Bioorg. Med Chem. Lett. 20 (2010) 3965–3968.

[131] T. Chonan, et al., Discovery of novel (4-piperidinyl)-piperazines as potent and orally active acetyl-CoA carboxylase 1/2 non-selective inhibitors: F-Boc and triF-Boc groups are acid-stable bioisosteres for the Boc group, Bioorg. Med Chem. 19 (2011) 1580–1593.

[132] J.W. Corbett, et al., Discovery of small molecule isozyme non-specific inhibitors of mammalian acetyl-CoA carboxylase 1 and 2, Bioorg. Med Chem. Lett. 20 (2010) 2383–2388.

[133] D.A. Griffith, et al., Decreasing the rate of metabolic ketone reduction in the discovery of a clinical acetyl-CoA carboxylase inhibitor for the treatment of diabetes, J. Med Chem. 57 (2014) 10512–10526.

[134] Y. sheng Gao, et al., WZ66, a novel acetyl-CoA carboxylase inhibitor, alleviates nonalcoholic steatohepatitis (NASH) in mice, Acta Pharm. Sin. 41 (2020) 336–347.

[135] D.W. Kung, et al., Discovery of spirocyclic-diamine inhibitors of mammalian acetyl CoA-carboxylase, Bioorg. Med Chem. Lett. 25 (2015) 5352–5356.

[136] D.A. Griffith, et al., Spirolactam-based acetyl-CoA carboxylase inhibitors: toward improved metabolic stability of a chromanone lead structure, J. Med Chem. 56 (2013) 7110–7119.

[137] Q. Wei, et al., Design, synthesis and biological evaluation of novel spiro-pentacylamides as acetyl-CoA carboxylase inhibitors, Bioorg. Med Chem. 26 (2018) 3866–3874.

[138] C.W. Kim, et al., Acetyl CoA carboxylase inhibition reduces hepatic steatosis but elevates plasma triglycerides in mice and humans: a bedside to bench investigation, Cell Metab. 26 (2017) 394–406.e6.

[139] R. Mizojiri, et al., Discovery of novel selective acetyl-coa carboxylase (ACC) 1 inhibitors, J. Med Chem. 61 (2018) 1098–1117.

[140] R. Mizojiri, et al., The identification and pharmacological evaluation of potent, selective and orally available ACC1 inhibitor, Bioorg. Med Chem. Lett. 29 (2019).

[141] G. Harriman, et al., Acetyl-CoA carboxylase inhibition by ND-630 reduces hepatic steatosis, improves insulin sensitivity, and modulates dyslipidemia in rats, Proc. Natl. Acad. Sci. USA 113 (2016) E1796–E1805.

[142] E.Q. Li, et al., Synthesis and anti-cancer activity of ND-646 and its derivatives as acetyl-CoA carboxylase 1 inhibitors, Eur. J. Pharm. Sci. 137 (2019).

[143] J.S.V. Lally, et al., Inhibition of acetyl-CoA carboxylase by phosphorylation or the inhibitor ND-654 suppresses lipogenesis and hepatocellular carcinoma, Cell Metab. 29 (2019) 174–182.e5.

[144] Y. Shen, S.L. Volrath, S.C. Weatherly, T.D. Elich, L. Tong, A mechanism for the potent inhibition of eukaryotic acetyl-coenzyme A carboxylase by soraphen A, a macrocyclic polyketide natural product, Mol. Cell 16 (2004) 881–891.

[145] D.B. Jump, M. Torres-Gonzalez, L.K. Olson, Soraphen A, an inhibitor of acetyl CoA carboxylase activity, interferes with fatty acid elongation, Biochem Pharm. 81 (2011) 649–660.

[146] A. Beckers, et al., Chemical inhibition of acetyl-CoA carboxylase induces growth arrest and cytotoxicity selectively in cancer cells, Cancer Res 67 (2007) 8180–8187.

[147] Kuhajda, F.P. Fatty-Acid Synthase and Human Cancer: New Perspectives on Its Role in Tumor Biology.

[148] F. Röhrig, A. Schulze, The multifaceted roles of fatty acid synthesis in cancer (Preprint at), Nat. Rev. Cancer vol. 16 (2016) 732–749, https://doi.org/10.1038/nrc.2016.89.

[149] D. Chalbos, M. Chambon, G. Ailhaud, H. Rochefort, Fatty acid synthetase and its mRNA are induced by progestins in breast cancer cells, J. Biol. Chem. 262 (1987) 9923–9926.

[150] A. Rashid, et al., Elevated expression of fatty acid synthase and fatty acid synthetic activity in colorectal neoplasia, Am. J. ofPathology vol. 150 (1997).

[151] E.S. Pizer, et al., Fat. Acid. Synthase Expr. Endometrial Carcinoma Correl. Cell Prolif. Horm. Recept. (1998).

[152] Hardman Iii, W. & Schaffel, S. Increased Expression of Fatty Acid Synthase (OA-519) in Ovarian Neoplasms Predicts Shorter Survival. (1997).

[153] J. Of Medicine, City, Immunohistochem. Detect. a Fat. Acid. Synthase (OA-519) a Predict. Progress. Prostate Cancer (1996).

[154] Biochemistry , molecular biology, and pharmacology of fatty acid synthase, an emerging therapeutic target and diagnosis or prognosis marker.

[155] Kusakabe, T., Nashimoto, A., Honma, K. Suzuki, & T. Fatty acid synthase is highly expressed in carcinoma, adenoma and in regenerative epithelium and intestinal metaplasia of the stomach.

[156] F.D. Camassei, et al., Expression of the lipogenic enzyme fatty acid synthase (FAS) as a predictor of poor outcome in nephroblastoma: an interinstitutional study, Med Pedia Oncol. 40 (2003) 302–308.

[157] B.M. Printed, I. Denmark, Fatty acid synthase expression in melanoma, J. Cutan. Pathol. 30 (2003) 23–28.

[158] Role of fatty acid synthase in gemcitabine and radiation resistance of pancreatic cancer. www.ijbmb.org.

[159] Takahiro, T., Shinichi, K. & Toshimitsu, S. Expression of Fatty Acid Synthase as a Prognostic Indicator in Soft Tissue Sarcomas 1. http://aacrjournals.org/clincancerres/article-pdf/9/6/2204/2088005/df0603002204.pdf.

[160] S.D. Silva, et al., Expression of fatty acid synthase, ErbB2 and Ki-67 in head and neck squamous cell carcinoma. A clinicopathological study, Oral. Oncol. 40 (2004) 688–696.

[161] D. Vance, I. Goldberg, K. Bloch, S. bmura, S. Nomura, BIOCHEMICAL BIOPHYSICAL Res. Commun. INHIBITION Fat. ACID SYNTHETASES ANTIBIOTIC CERULENIN vol. 48 (1972).

[162] Johansson, P. et al. Inhibition of the fungal fatty acid synthase type I multienzyme complex. www.pnas.org/cgi/content/full/ (2008).

[163] Pizer, E.S. et al. Inhibition of Fatty Acid Synthesis Delays Disease Progression in a Xenograft Model of Ovarian Cancer1. http://aacrjournals.org/cancerres/article-pdf/56/6/1189/2462910/cr0560061189.pdf.

[164] J. Ross, et al., Fatty acid synthase inhibition results in a magnetic resonance-detectable drop in phosphocholine, Mol. Cancer Ther. 7 (2008) 2556–2565.

[165] S. Murata, et al., Fatty acid synthase inhibitor cerulenin suppresses liver metastasis of colon cancer in mice, Cancer Sci. 101 (2010) 1861–1865.

[166] M.V. Ruiz-Pérez, et al., Inhibition of fatty acid synthesis induces differentiation and reduces tumor burden in childhood neuroblastoma, iScience 24 (2021).

[167] D.S. Lawrence, J.T. Zilfou, C.D. Smith, Structure-activity studies of cerulenin analogues as protein palmitoylation inhibitors, J. Med Chem. 42 (1999) 4932–4941.

[168] K. Ikuta, J. Coward, R.B. Luftig, The effect of cerulenin on the synthesis of the precursor gag polyprotein in defective murine leukemia and sarcoma virus producing cell lines, VIROLOGY vol. 154 (1986).

[169] Kuhajda, F.P. et al. Synthesis and antitumor activity of an inhibitor of fatty acid synthase. www.pnas.orgcgidoi10.1073pnas.050582897 (1999).

[170] A.R. Rendina, D. Cheng, Characterization of the inactivation of rat fatty acid synthase by C75: inhibition of partial reactions and protection by substrates, Biochem. J. vol. 388 (2005).
[171] E.S. Pizer, et al., Malonyl-coenzyme-A is a potential mediator of cytotoxicity induced by fatty-acid synthase inhibition in human breast cancer cells and xenografts 1, CANCER Res. vol. 60 (2000). ⟨http://aacrjournals.org/cancerres/article-pdf/60/2/213/2480202/ch020000213.pdf⟩.
[172] H.Q. Wang, et al., Positive feedback regulation between AKT activation and fatty acid synthase expression in ovarian carcinoma cells, Oncogene 24 (2005) 3574–3582.
[173] E.S. Pizer, et al., Increased fatty acid synthase as atherapeutic target in androgen-independent prostate cancer progression, Prostate vol. 47 (2001).
[174] A. Horiguchi, et al., Pharmacological inhibitor of fatty acid synthase suppresses growth and invasiveness of renal cancer cells, J. Urol. 180 (2008) 729–736.
[175] C. Nicot, et al., C75 activates malonyl-CoA sensitive and insensitive components of the CPT system, Biochem Biophys. Res Commun. 325 (2004) 660–664.
[176] Cha, S.H., Hu, Z., Chohnan, S. & Daniel Lane, M. Inhibition of hypothalamic fatty acid synthase triggers rapid activation of fatty acid oxidation in skeletal muscle. www.pnas.orgcgidoi10.1073pnas.0507300102 (2005).
[177] N. Yang, et al., C75 [4-methylene-2-octyl-5-oxo-tetrahydro-furan-3-carboxylic acid] activates carnitine palmitoyltransferase-1 in isolated mitochondria and intact cells without displacement of bound malonyl CoA, J. Pharmacol. Exp. Ther. 312 (2005) 127–133.
[178] S. Dridi, et al., FAS Inhib. cerulenin reduces Food intake melanocortin Recept. gene Expr. Modul. Other orexigenic Neuropept. Chick. (2006), https://doi.org/10.1152/ajpregu.00899.2005.-Cerulenin.
[179] H. Orita, et al., Selective inhibition of fatty acid synthase for lung cancer treatment, Clin. Cancer Res. 13 (2007) 7139–7145.
[180] D. Vergote, et al., −)-Epigallocatechin (EGC) of green tea induces apoptosis of human breast cancer cells but not of their normal counterparts, Breast Cancer Res. Treat. vol. 76 (2002).
[181] K. Brusselmans, E. de Schrijver, W. Heyns, G. Verhoeven, J. v Swinnen, Epigallocatechin-3-gallate is a potent natural inhibitor of fatty acid synthase in intact cells and selectively induces apoptosis in prostate cancer cells, Int J. Cancer 106 (2003) 856–862.
[182] T. Puig, et al., Fatty acid metabolism in breast cancer cells: differential inhibitory effects of epigallocatechin gallate (EGCG) and C75, Breast Cancer Res Treat. 109 (2008) 471–479.
[183] W.-X. Tian, Inhibition of fatty acid synthase by polyphenols, Curr. Med. Chem. vol. 13 (2006).
[184] E. Polonio-alcalá, et al., Fatty acid synthase inhibitor g28 shows anticancer activity in egfr tyrosine kinase inhibitor resistant lung adenocarcinoma models, Cancers 12 (2020).
[185] D.M. Harris, et al., Diverse mechanisms of growth inhibition by luteolin, resveratrol, and quercetin in MIA PaCa-2 cells: a comparative glucose tracer study with the fatty acid synthase inhibitor C75, Metabolomics 8 (2012) 201–210.
[186] L.S.S. Pulla, S. Begum Ahil, Review on target domains and natural compound-based inhibitors of fatty acid synthase for anticancer drug discovery (Preprint at), Chem. Biol. Drug Des. vol. 98 (2021) 869–884, https://doi.org/10.1111/cbdd.13942.
[187] Kridel, S.J., Axelrod, F., Rozenkrantz, N., Smith, J.W. Orlistat Is a Novel Inhibitor of Fatty Acid Synthase with Antitumor Activity. CANCER RESEARCH vol. 64 http://aacrjournals.org/cancerres/article-pdf/64/6/2070/2523704/zch00604002070.pdf (2070).
[188] M.A. Carvalho, et al., Fatty acid synthase inhibition with Orlistat promotes apoptosis and reduces cell growth and lymph node metastasis in a mouse melanoma model, Int J. Cancer 123 (2008) 2557–2565.
[189] J.A. Menendez, L. Vellon, R. Lupu, Antitumoral actions of the anti-obesity drug orlistat (Xenical™) in breast cancer cells: Blockade of cell cycle progression, promotion of apoptotic cell death and PEA3-mediated transcriptional repression of Her2/neu (erbB-2) oncogene, Ann. Oncol. 16 (2005) 1253–1267.
[190] H.S. Hoover, J.L. Blankman, S. Niessen, B.F. Cravatt, Selectivity of inhibitors of endocannabinoid biosynthesis evaluated by activity-based protein profiling, Bioorg. Med Chem. Lett. 18 (2008) 5838–5841.
[191] J. Zhi, et al., Metabolic profiles of minimally absorbed orlistat in obese/overweight volunteers, J. Clin. Pharm. 36 (1996) 1006–1011.
[192] Sadowski, M.C. et al. The fatty acid synthase inhibitor triclosan: repurposing an anti-microbial agent for targeting prostate cancer. vol. 5 www.impactjournals.com/oncotarget.
[193] J.Y. Kim, et al., Methoxychlor and triclosan stimulates ovarian cancer growth by regulating cell cycle- and apoptosis-related genes via an estrogen receptor-dependent pathway, Environ. Toxicol. Pharm. 37 (2014) 1264–1274.
[194] H.R. Lee, K.A. Hwang, K.H. Nam, H.C. Kim, K.C. Choi, Progression of breast cancer cells was enhanced by endocrine-disrupting chemicals, triclosan and octylphenol, via an estrogen receptor-dependent signaling pathway in cellular and mouse xenograft models, Chem. Res Toxicol. 27 (2014) 834–842.
[195] I.G. de Aquino, et al., Anticancer properties of the fatty acid synthase inhibitor TVB-3166 on oral squamous cell carcinoma cell lines, Arch. Oral. Biol. 113 (2020).
[196] R. Ventura, et al., Inhibition of de novo palmitate synthesis by fatty acid synthase induces apoptosis in tumor cells by remodeling cell membranes, inhibiting signaling pathways, and reprogramming gene expression, EBioMedicine 2 (2015) 808–824.
[197] G. Falchook, et al., First-in-human study of the safety, pharmacokinetics, and pharmacodynamics of first-in-class fatty acid synthase inhibitor TVB-2640 alone and with a taxane in advanced tumors, EClinicalMedicine 34 (2021).
[198] M.A. Hardwicke, et al., A human fatty acid synthase inhibitor binds β-ketoacyl reductase in the keto-substrate site, Nat. Chem. Biol. 10 (2014) 774–779.
[199] G. Shaw, et al., Therapeutic fatty acid synthase inhibition in prostate cancer and the use of 11c-acetate to monitor therapeutic effects, J. Urol. 189 (2013).
[200] W. Huang, et al., α-Linolenic acid induces apoptosis, inhibits the invasion and metastasis, and arrests cell cycle in human breast cancer cells by inhibiting fatty acid synthase, J. Funct. Foods 92 (2022).
[201] H. Fan, W. Huang, Y. Guo, X. Ma, J. Yang, α-Linolenic acid suppresses proliferation and invasion in osteosarcoma cells via inhibiting fatty acid synthase, Molecules 27 (2022).
[202] L.M. Butler, et al., Lipids and cancer: Emerging roles in pathogenesis, diagnosis and therapeutic intervention, Adv. Drug Deliv. Rev. vol. 159 (2020) 245–293, https://doi.org/10.1016/j.addr.2020.07.013.
[203] M. Presler, et al., Increased expression of the gene encoding stearoyl-CoA desaturase 1 in human bladder cancer, Mol. Cell Biochem 447 (2018) 217–224.
[204] M. Wang, et al., Dysregulated fatty acid metabolism in hepatocellular carcinoma, Hepat. Oncol. 3 (2016) 241–251.
[205] A.M. Holder, et al., High stearoyl-CoA desaturase 1 expression is associated with shorter survival in breast cancer patients, Breast Cancer Res Treat. 137 (2013) 319–327.
[206] U. v Roongta, et al., Cancer cell dependence on unsaturated fatty acids implicates stearoyl-CoA desaturase as a target for cancer therapy, Mol. Cancer Res. 9 (2011) 1551–1561.
[207] Guo, D., Hlavin Bell, E., Mischel, P., Chakravarti, A. Targeting SREBP-1-driven lipid metabolism to treat cancer.
[208] M. Notarnicola, et al., Differential tissue fatty acids profiling between colorectal cancer patients with and without synchronous metastasis, Int J. Mol. Sci. 19 (2018).
[209] A. Mika, et al., Preferential uptake of polyunsaturated fatty acids by colorectal cancer cells, Sci. Rep. 10 (2020).
[210] A.J. Hoy, S.R. Nagarajan, L.M. Butler, Tumour fatty acid metabolism in the context of therapy resistance and obesity, Nat. Rev. Cancer vol. 21 (2021) 753–766, https://doi.org/10.1038/s41568-021-00388-4.
[211] L. Tesfay, et al., Stearoyl-CoA desaturase 1 protects ovarian cancer cells from ferroptotic cell death, Cancer Res 79 (2019) 5355–5366.
[212] C. Piao, et al., Inhibition of stearoyl CoA desaturase-1 activity suppresses tumour progression and improves prognosis in human bladder cancer, J. Cell Mol. Med 23 (2019) 2064–2076.
[213] M.E. Pisanu, et al., Inhibition of Stearoyl-CoA desaturase 1 reverts BRAF and MEK inhibition-induced selection of cancer stem cells in BRAF-mutated melanoma, J. Exp. Clin. Cancer Res. 37 (2018).
[214] K. Imamura, et al., Discovery of novel and potent stearoyl coenzyme a desaturase 1 (SCD1) inhibitors as anticancer agents, Bioorg. Med Chem. 25 (2017) 3768–3779.
[215] M. Minville-Walz, et al., Inhibition of stearoyl-CoA desaturase 1 expression Induces CHOP-dependent cell death in human cancer cells, PLoS One 5 (2010).
[216] D. Hess, J.W. Chisholm, R.A. Igal, Inhibition of stearoylCoA desaturase activity blocks cell cycle progression and induces programmed cell death in lung cancer cells, PLoS One 5 (2010).
[217] C.A. von Roemeling, et al., Oncotarget 3 www.impactjournals.com/oncotarget accelerated bottom-up drug design platform enables the discovery of novel stearoyl-CoA desaturase 1 inhibitors for cancer therapy, Oncotarget vol. 9 (2018). ⟨www.impactjournals.com/oncotarget/⟩.
[218] P.C. Theodoropoulos, et al., Discovery of tumor-specific irreversible inhibitors of stearoyl CoA desaturase, Nat. Chem. Biol. 12 (2016) 218–225.
[219] K. Vriens, et al., Evidence for an alternative fatty acid desaturation pathway increasing cancer plasticity, Nature 566 (2019) 403–406.
[220] D.O. Koltun, J. Zablocki, Enzymatic targets in the triglyceride synthesis pathway, Annu. Rep. Med. Chem. vol. 45 (2010).
[221] C.A. Von Roemeling, et al., Stearoyl-CoA desaturase 1 is a novel molecular therapeutic target for clear cell renal cell carcinoma, Clin. Cancer Res. 19 (2013) 2368–2380.
[222] B.I. Rini, Temsirolimus, an inhibitor of mammalian target of rapamycin, Clin. Cancer Res. vol. 14 (2008) 1286–1290, https://doi.org/10.1158/1078-0432.CCR-07-4719.
[223] S. Léger, et al., Synthesis and biological activity of a potent and orally bioavailable SCD inhibitor (MF-438), Bioorg. Med Chem. Lett. 20 (2010) 499–502.
[224] Z. Zhang, et al., Discovery of piperazin-1-ylpyridazine-based potent and selective stearoyl-CoA Desaturase-1 inhibitors for the treatment of obesity and metabolic syndrome, J. Med Chem. 56 (2013) 568–583.
[225] J.Y. Lee, et al., Polyunsaturated fatty acid biosynthesis pathway determines ferroptosis sensitivity in gastric cancer, Proc. Natl. Acad. Sci. USA 117 (2020).
[226] D. Penzo, C. Tagliapietra, R. Colonna, V. Petronilli, P. Bernardi, Effects of fatty acids on mitochondria: implications for cell death, Biochim Biophys. Acta Bioenerg. 1555 (2002).
[227] D.V. Pham, P.H. Park, Adiponectin triggers breast cancer cell death via fatty acid metabolic reprogramming, J. Exp. Clin. Cancer Res. 41 (2022).
[228] L. Magtanong, et al., Exogenous monounsaturated fatty acids promote a ferroptosis-resistant cell state, Cell Chem. Biol. 26 (2019).
[229] W.S. Yang, et al., Peroxidation of polyunsaturated fatty acids by lipoxygenases drives ferroptosis, Proc. Natl. Acad. Sci. USA 113 (2016).
[230] J.M. Ubellacker, et al., Lymph protects metastasizing melanoma cells from ferroptosis, Nature 585 (2020).

[231] S.C. Dyall, A.T. Michael-Titus, Neurological benefits of omega-3 fatty acids, NeuroMolecular Med. vol. 10 (2008), https://doi.org/10.1007/s12017-008-8036-z.

[232] V.S. Viswanathan, et al., Dependency of a therapy-resistant state of cancer cells on a lipid peroxidase pathway, Nature 547 (2017).

[233] M.J. Hangauer, et al., Drug-tolerant persister cancer cells are vulnerable to GPX4 inhibition, Nature 551 (2017).

[234] D. Li, Y. Li, The interaction between ferroptosis and lipid metabolism in cancer, Signal Transduct. Target. Ther. vol. 5 (2020), https://doi.org/10.1038/s41392-020-00216-5.

[235] L.P. Fernández, M. Gómez de Cedrón, A. Ramírez de Molina, Alterations of lipid metabolism in cancer: implications in prognosis and treatment, Front. Oncol. vol. 10 (2020), https://doi.org/10.3389/fonc.2020.577420.

[236] A. Nath, I. Li, L.R. Roberts, C. Chan, Elevated free fatty acid uptake via CD36 promotes epithelial-mesenchymal transition in hepatocellular carcinoma, Sci. Rep. 5 (2015).

[237] O. Kuda, et al., CD36 protein is involved in store-operated calcium flux, phospholipase A2 activation, and production of prostaglandin E2, J. Biol. Chem. 286 (2011).

[238] A.A. Al-Khami, et al., Exogenous lipid uptake induces metabolic and functional reprogramming of tumor-associated myeloid-derived suppressor cells, Oncoimmunology 6 (2017).

[239] S. Xu, et al., Oxidized Lipids And CD36-mediated lipid peroxidation in CD8 T cells suppress anti-tumor immune responses. bioRxiv, 2020.

[240] F. Veglia, et al., Fatty acid transport protein 2 reprograms neutrophils in cancer, Nature 569 (2019).

[241] P.C. Rodriguez, et al., Arginase I in myeloid suppressor cells is induced by COX-2 in lung carcinoma, J. Exp. Med. 202 (2005).

[242] B. Lu, et al., Identification of PRDX6 as a regulator of ferroptosis, Acta Pharm. Sin. 40 (2019).

[243] O. Beharier, et al., PLA2G6 guards placental trophoblasts against ferroptotic injury, Proc. Natl. Acad. Sci. USA 117 (2020).

[244] D.R. Green, L. Galluzzi, G. Kroemer, Metabolic control of cell death, Science vol. 345 (2014), https://doi.org/10.1126/science.1250256.

[245] D.G. Hardie, F.A. Ross, S.A. Hawley, AMPK: A nutrient and energy sensor that maintains energy homeostasis, Nat. Rev. Mol. Cell Biol. vol. 13 (2012), https://doi.org/10.1038/nrm3311.

[246] H. Lee, et al., Energy-stress-mediated AMPK activation inhibits ferroptosis, Nat. Cell Biol. 22 (2020).

[247] C. Li, et al., LKB1-AMPK axis negatively regulates ferroptosis by inhibiting fatty acid synthesis, Signal Transduct. Target. Ther. vol. 5 (2020), https://doi.org/10.1038/s41392-020-00297-2.

[248] X. Song, et al., AMPK-Mediated BECN1 phosphorylation promotes ferroptosis by directly blocking system xc– activity, Curr. Biol. 28 (2018).

[249] J.P. Thomas, P.G. Geiger, M. Maiorino, F. Ursini, A.W. Girotti, Enzymatic reduction of phospholipid and cholesterol hydroperoxides in artificial bilayers and lipoproteins, Biochim. Et. Biophys. Acta (BBA)/Lipids Lipid Metab. 1045 (1990).

[250] Z.A.M. Zielinski, D.A. Pratt, Cholesterol autoxidation revisited: debunking the dogma associated with the most vilified of lipids, J. Am. Chem. Soc. 138 (2016).

[251] G.C. Forcina, S.J. Dixon, GPX4 at the crossroads of lipid homeostasis and ferroptosis, Proteomics vol. 19 (2019), https://doi.org/10.1002/pmic.201800311.

[252] G.J. Warner, et al., Inhibition of selenoprotein synthesis by selenocysteine tRNA ([Ser]Sec) lacking isopentenyladenosine, J. Biol. Chem. 275 (2000).

[253] J.W. Clendening, L.Z. Penn, Targeting tumor cell metabolism with statins, Oncogene vol. 31 (2012), https://doi.org/10.1038/onc.2012.6.

[254] K. Shimada, et al., Global survey of cell death mechanisms reveals metabolic regulation of ferroptosis, Nat. Chem. Biol. 12 (2016).

[255] J. Garcia-Bermudez, et al., Squalene accumulation in cholesterol auxotrophic lymphomas prevents oxidative cell death, Nature 567 (2019).

[256] W.S. Yang, et al., Regulation of ferroptotic cancer cell death by GPX4, Cell 156 (2014).

[257] C.A. Lyssiotis, J. Son, L.C. Cantley, A.C. Kimmelman, Pancreatic cancers rely on a novel glutamine metabolism pathway to maintain redox balance (Preprint at), Cell Cycle vol. 12 (2013), https://doi.org/10.4161/cc.25307.

[258] H. Ying, et al., Oncogenic kras maintains pancreatic tumors through regulation of anabolic glucose metabolism, Cell 149 (2012).

[259] P. Gao, et al., C-Myc suppression of miR-23a/b enhances mitochondrial glutaminase expression and glutamine metabolism, Nature 458 (2009).

[260] M. Yuneva, N. Zamboni, P. Oefner, R. Sachidanandam, Y. Lazebnik, Deficiency in glutamine but not glucose induces MYC-dependent apoptosis in human cells, J. Cell Biol. 178 (2007).

[261] E.C. Lien, et al., Glutathione biosynthesis is a metabolic vulnerability in PI(3)K/Akt-driven breast cancer, Nat. Cell Biol. 18 (2016).

[262] Y. Hao, et al., Oncogenic PIK3CA mutations reprogram glutamine metabolism in colorectal cancer, Nat. Commun. 7 (2016).

[263] A.N. Waldhart, et al., Phosphorylation of TXNIP by AKT mediates acute influx of glucose in response to insulin, Cell Rep. 19 (2017).

[264] J.A. Menendez, R. Lupu, Fatty acid synthase and the lipogenic phenotype in cancer pathogenesis, Nat. Rev. Cancer vol. 7 (2007), https://doi.org/10.1038/nrc2222.

[265] T. Migita, et al., ACSL3 promotes intratumoral steroidogenesis in prostate cancer cells, Cancer Sci. 108 (2017).

[266] H.J. Wright, et al., CDCP1 drives triple-negative breast cancer metastasis through reduction of lipid-droplet abundance and stimulation of fatty acid oxidation, Proc. Natl. Acad. Sci. USA 114 (2017).

[267] L.M. Butler, M.M. Centenera, J. v Swinnen, Androgen control of lipid metabolism in prostate cancer: novel insights and future applications (Preprint at), Endocr. -Relat. Cancer vol. 23 (2016), https://doi.org/10.1530/ERC-15-0556.

[268] R. Camarda, et al., Inhibition of fatty acid oxidation as a therapy for MYC-overexpressing triple-negative breast cancer, Nat. Med 22 (2016).

[269] D.A. Fruman, et al., The PI3K Pathway in Human Disease, Cell vol. 170 (2017), https://doi.org/10.1016/j.cell.2017.07.029.

[270] P. Liu, H. Cheng, T.M. Roberts, J.J. Zhao, Targeting the phosphoinositide 3-kinase pathway in cancer, Nat. Rev. Drug Discov. vol. 8 (2009), https://doi.org/10.1038/nrd2926.

[271] I.G. Campbell, et al., Mutation of the PIK3CA gene in ovarian and breast cancer, Cancer Res 64 (2004).

[272] D.T. Kruger, et al., Hierarchical clustering of activated proteins in the PI3K and MAPK pathways in ER-positive, HER2-negative breast cancer with potential therapeutic consequences, Br. J. Cancer 119 (2018).

[273] J.A. Menendez, Fine-tuning the lipogenic/lipolytic balance to optimize the metabolic requirements of cancer cell growth: Molecular mechanisms and therapeutic perspectives, Biochim. Et. Biophys. Acta - Mol. Cell Biol. Lipids vol. 1801 (2010), https://doi.org/10.1016/j.bbalip.2009.09.005.

[274] P.S. Ward, C.B. Thompson, Signaling in control of cell growth and metabolism, Cold Spring Harb. Perspect. Biol. 4 (2012).

[275] P.J. Fernandez-Marcos, S. Nóbrega-Pereira, NADPH: New oxygen for the ROS theory of aging, Oncotarget vol. 7 (2016), https://doi.org/10.18632/oncotarget.10744.

[276] H.K. Bryan, A. Olayanju, C.E. Goldring, B.K. Park, The Nrf2 cell defence pathway: Keap1-dependent and -independent mechanisms of regulation, Biochem. Pharmacol. vol. 85 (2013), https://doi.org/10.1016/j.bcp.2012.11.016.

[277] Y. Cui, et al., NADPH accumulation is responsible for apoptosis in breast cancer cells induced by fatty acid synthase inhibition, Oncotarget 8 (2017).

[278] D.C. Berwick, I. Hers, K.J. Heesom, S. Kelly Moule, J.M. Tavaré, The identification of ATP-citrate lyase as a protein kinase B (Akt) substrate in primary adipocytes, J. Biol. Chem. 277 (2002).

[279] G. Hoxhaj, et al., Direct stimulation of NADP + synthesis through Akt-mediated phosphorylation of NAD kinase, Science 363 (2019) *1979*.

[280] P. Jiang, W. Du, M. Wu, Regulation of the pentose phosphate pathway in cancer, Protein Cell 5 (2014).

[281] R.A. Saxton, D.M. Sabatini, mTOR signaling in growth, metabolism, and disease, Cell vol. 168 (2017), https://doi.org/10.1016/j.cell.2017.02.004.

[282] T. Porstmann, et al., SREBP activity is regulated by mTORC1 and contributes to Akt-dependent cell growth, Cell Metab. 8 (2008).

[283] I. Ben-Sahra, G. Hoxhaj, S.J.H. Ricoult, J.M. Asara, B.D. Manning, mTORC1 induces purine synthesis through control of the mitochondrial tetrahydrofolate cycle, Science 351 (2016) *1979*.

[284] J.T. Cunningham, et al., mTOR controls mitochondrial oxidative function through a YY1–PGC-1α transcriptional complex, Nature 450 (2007) 736–740.

[285] T.R. Peterson, et al., MTOR complex 1 regulates lipin 1 localization to control the srebp pathway, Cell 146 (2011).

[286] S.J.H. Ricoult, J.L. Yecies, I. Ben-Sahra, B.D. Manning, Oncogenic PI3K and K-Ras stimulate de novo lipid synthesis through mTORC1 and SREBP, Oncogene 35 (2016).

[287] G. Lee, et al., Post-transcriptional Regulation of De Novo Lipogenesis by mTORC1-S6K1-SRPK2 Signaling, Cell 171 (2017).

[288] A.M. Gouw, et al., Oncogene KRAS activates fatty acid synthase, resulting in specific ERK and lipid signatures associated with lung adenocarcinoma, Proc. Natl. Acad. Sci. USA 114 (2017).

[289] L. Ma, Z. Chen, H. Erdjument-Bromage, P. Tempst, P.P. Pandolfi, Phosphorylation and functional inactivation of TSC2 by Erk: Implications for tuberous sclerosis and cancer pathogenesis, Cell 121 (2005).

[290] J. Downward, Targeting RAS signalling pathways in cancer therapy, Nat. Rev. Cancer vol. 3 (2003), https://doi.org/10.1038/nrc969.

[291] B.D. Manning, A. Toker, AKT/PKB Signaling: Navigating the Network, Cell vol. 169 (2017), https://doi.org/10.1016/j.cell.2017.04.001.

[292] A. Hagiwara, et al., Hepatic mTORC2 activates glycolysis and lipogenesis through Akt, glucokinase, and SREBP1c, Cell Metab. 15 (2012).

[293] S.J. Humphrey, et al., Dynamic adipocyte phosphoproteome reveals that akt directly regulates mTORC2, Cell Metab. 17 (2013).

[294] Y. Guri, et al., mTORC2 promotes tumorigenesis via lipid synthesis, Cancer Cell 32 (2017) 807–823.e12.

[295] J.L. Yecies, et al., Akt stimulates hepatic SREBP1c and lipogenesis through parallel mTORC1-dependent and independent pathways, Cell Metab. 14 (2011).

[296] H. Makinoshima, et al., Signaling through the phosphatidylinositol 3-kinase (PI3K)/mammalian target of rapamycin (mTOR) axis is responsible for aerobic glycolysis mediated by glucose transporter in epidermal growth factor receptor (EGFR)-mutated lung adenocarcinoma, J. Biol. Chem. 290 (2015).

[297] G.L. Semenza, HIF-1 mediates the Warburg effect in clear cell renal carcinoma, J. Bioenerg. Biomembr. vol. 39 (2007), https://doi.org/10.1007/s10863-007-9081-2.

[298] N. Ghanem, et al., The pentose phosphate pathway in cancer: regulation and therapeutic opportunities, Chemotherapy vol. 66 (2021), https://doi.org/10.1159/000519784.

[299] J.T. Cunningham, et al., mTOR controls mitochondrial oxidative function through a YY1–PGC-1α transcriptional complex, Nature 450 (2007) 736–740.

[300] X. Huang, G. Liu, J. Guo, Z.Q. Su, The PI3K/AKT pathway in obesity and type 2 diabetes, Int. J. Biol. Sci. vol. 14 (2018), https://doi.org/10.7150/ijbs.27173.
[301] A. Tzatsos, Raptor binds the SAIN (Shc and IRS-1 NPXY binding) domain of insulin receptor substrate-1 (IRS-1) and regulates thephosphorylation of IRS-1 at Ser-636/639 by mTOR, J. Biol. Chem. 284 (2009).
[302] O.J. Shah, T. Hunter, Turnover of the Active Fraction of IRS1 Involves Raptor-mTOR- and S6K1-dependent serine phosphorylation in cell culture models of tuberous sclerosis, Mol. Cell Biol. 26 (2006).
[303] D.B. Savage, K.F. Petersen, G.I. Shulman, Mechanisms of insulin resistance in humans and possible links with inflammation (Preprint at), Hypertension vol. 45 (2005), https://doi.org/10.1161/01.HYP.0000163475.04421.e4.
[304] J.A. Menendez, R. Lupu, Fatty acid synthase regulates estrogen receptor-α signaling in breast cancer cells. Oncogenesis 6 (2017).
[305] J.A. Menendez, R. Lupu, Oncogenic properties of the endogenous fatty acid metabolism: molecular pathology of fatty acid synthase in cancer cells (Preprint at), Curr. Opin. Clin. Nutr. Metab. Care vol. 9 (2006), https://doi.org/10.1097/01.mco.0000232893.21050.15.
[306] C. Ye, B.P. Tu, Sink into the epigenome: histones as repositories that influence cellular metabolism, Trends Endocrinol. Metab. vol. 29 (2018), https://doi.org/10.1016/j.tem.2018.06.002.
[307] A. Kinnaird, S. Zhao, K.E. Wellen, E.D. Michelakis, Metabolic control of epigenetics in cancer, Nat. Rev. Cancer vol. 16 (2016), https://doi.org/10.1038/nrc.2016.82.
[308] K.E. Wellen, et al., ATP-citrate lyase links cellular metabolism to histone acetylation, Science 324 (2009) *1979*.
[309] X. Li, X. Qian, Z. Lu, Local histone acetylation by ACSS2 promotes gene transcription for lysosomal biogenesis and autophagy, Autophagy vol. 13 (2017), https://doi.org/10.1080/15548627.2017.1349581.
[310] J. v Lee, et al., Akt-dependent metabolic reprogramming regulates tumor cell Histone acetylation, Cell Metab. 20 (2014).
[311] T.B. Toh, J.J. Lim, E.K.H. Chow, Epigenetics in cancer stem cells, Mol. Cancer vol. 16 (2017), https://doi.org/10.1186/s12943-017-0596-9.
[312] N. Liu, S. Li, N. Wu, K.S. Cho, Acetylation and deacetylation in cancer stem-like cells, Oncotarget vol. 8 (2017), https://doi.org/10.18632/oncotarget.19167.
[313] A. Carrer, et al., Acetyl-CoA metabolism supports multistep pancreatic tumorigenesis, Cancer Discov. 9 (2019).
[314] J.S. Roe, et al., Enhancer reprogramming promotes pancreatic cancer metastasis, Cell 170 (2017).
[315] E. Rysman, et al., De novo lipogenesis protects cancer cells from free radicals and chemotherapeutics by promoting membrane lipid saturation, Cancer Res 70 (2010).
[316] W. Zhao, et al., Candidate antimetastasis drugs suppress the metastatic capacity of breast cancer cells by reducing membrane fluidity, Cancer Res 76 (2016).
[317] D. Heilos, et al., Altered membrane rigidity via enhanced endogenous cholesterol synthesis drives cancer cell resistance to destruxins, Oncotarget 9 (2018).
[318] O.F. Kuzu, M.A. Noory, G.P. Robertson, The role of cholesterol in cancer, Cancer Res. vol. 76 (2016), https://doi.org/10.1158/0008-5472.CAN-15-2613.
[319] Y.C. Li, M.J. Park, S.K. Ye, C.W. Kim, Y.N. Kim, Elevated levels of cholesterol-rich lipid rafts in cancer cells are correlated with apoptosis sensitivity induced by cholesterol-depleting agents, Am. J. Pathol. 168 (2006).
[320] H. Zhou, X.M. Li, J. Meinkoth, R.N. Pittman, Akt regulates cell survival and apoptosis at a postmitochondrial level, J. Cell Biol. 151 (2000).
[321] J.A. Gasser, et al., SGK3 mediates INPP4B-dependent PI3K signaling in breast cancer, Mol. Cell 56 (2014).
[322] K.M. Vasudevan, et al., AKT-independent signaling downstream of oncogenic PIK3CA mutations in human cancer, Cancer Cell 16 (2009).
[323] A. Grabon, D. Khan, V.A. Bankaitis, Phosphatidylinositol transfer proteins and instructive regulation of lipid kinase biology, Biochim. Et. Biophys. Acta - Mol. Cell Biol. Lipids vol. 1851 (2015), https://doi.org/10.1016/j.bbalip.2014.12.011.
[324] A.H. Nile, V.A. Bankaitis, A. Grabon, Mammalian diseases of phosphatidylinositol transfer proteins and their homologs, Clin. Lipidol. vol. 5 (2010), https://doi.org/10.2217/clp.10.67.
[325] K.E. Cosker, et al., Regulation of PI3K signalling by the phosphatidylinositol transfer protein PITPα during axonal extension in hippocampal neurons, J. Cell Sci. 121 (2008) 796–803.
[326] A. Kauffmann-Zeh, et al., Requirement for phosphatidylinositol transfer protein in epidermal growth factor signaling, Science 268 (1995) *1979*.
[327] L. Zhao, et al., Phosphatidylinositol transfer protein-α in platelets is inconsequential for thrombosis yet is utilized for tumor metastasis, Nat. Commun. 8 (2017), 1216.
[328] S. Choi, et al., Agonist-stimulated phosphatidylinositol-3,4,5-trisphosphate generation by scaffolded phosphoinositide kinases, Nat. Cell Biol. 18 (2016).
[329] A. Toschi, et al., Regulation of mTORC1 and mTORC2 complex assembly by phosphatidic acid: competition with rapamycin, Mol. Cell Biol. 29 (2009).
[330] J. Gomez-Cambronero, Phosphatidic acid, phospholipase D and tumorigenesis, Adv. Biol. Regul. vol. 54 (2014), https://doi.org/10.1016/j.jbior.2013.08.006.
[331] M.S. Yoon, Y. Sun, E. Arauz, Y. Jiang, J. Chen, Phosphatidic acid activates mammalian target of rapamycin complex 1 (mTORC1) kinase by displacing FK506 binding protein 38 (FKBP38) and exerting an allosteric effect, J. Biol. Chem. 286 (2011).
[332] L. Chantranupong, et al., The CASTOR proteins are arginine sensors for the mTORC1 pathway, Cell 165 (2016).
[333] R.L. Wolfson, et al., Sestrin2 is a leucine sensor for the mTORC1 pathway, Science 351 (2016) *1979*.
[334] G.B. Mills, W.H. Moolenaar, The emerging role of lysophosphatidic acid in cancer, Nat. Rev. Cancer vol. 3 (2003), https://doi.org/10.1038/nrc1143.
[335] X. Sheng, Y.C. Yung, A. Chen, J. Chun, Lysophosphatidic acid signalling in development, Development 142 (2015).
[336] J.H. Cho, J.S. Han, Phospholipase D and its essential role in cancer, Mol. Cells vol. 40 (2017), https://doi.org/10.14348/molcells.2017.0241.
[337] F.R. Auciello, et al., A stromal lysolipid–autotaxin signaling axis promotes pancreatic tumor progression, Cancer Discov. 9 (2019).
[338] K. Liang, J.Y. Dai, Progress of potential drugs targeted in lipid metabolism research, Front. Pharmacol. vol. 13 (2022), https://doi.org/10.3389/fphar.2022.1067652.
[339] N. Alkhouri, E. Lawitz, M. Noureddin, R. DeFronzo, G.I. Shulman, GS-0976 (Firsocostat): an investigational liver-directed acetyl-CoA carboxylase (ACC) inhibitor for the treatment of non-alcoholic steatohepatitis (NASH), Expert Opin. Invest. Drugs 29 (2020) 135–141.
[340] N. Khan, F. Afaq, M. Saleem, N. Ahmad, H. Mukhtar, Targeting multiple signaling pathways by green tea polyphenol (-)-epigallocatechin-3-gallate (Preprint at), Cancer Res. vol. 66 (2006) 2500–2505, https://doi.org/10.1158/0008-5472.CAN-05-3636.
[341] P.R. Pandey, et al., Resveratrol suppresses growth of cancer stem-like cells by inhibiting fatty acid synthase, Breast Cancer Res Treat. 130 (2011) 387–398.
[342] M.T. Do, Y.P. Hwang, H.G. Kim, M. Na, H.G. Jeong, Mollugin inhibits proliferation and induces apoptosis by suppressing fatty acid synthase in HER2-overexpressing cancer cells, J. Cell Physiol. 228 (2013) 1087–1097.
[343] C. Chiang, T. te, Way, S.J. der, Tsai, J.K. Lin, Diosgenin, a naturally occurring steroid, suppresses fatty acid synthase expression in HER2-overexpressing breast cancer cells through modulating Akt, mTOR and JNK phosphorylation, FEBS Lett. 581 (2007) 5735–5742.
[344] V.C.H. Lin, et al., Osthole suppresses fatty acid synthase expression in HER2-overexpressing breast cancer cells through modulating Akt/mTOR pathway, J. Agric. Food Chem. 58 (2010) 4786–4793.
[345] W. Liu, et al., Cacalol, a natural sesquiterpene, induces apoptosis in breast cancer cells by modulating Akt-SREBP-FAS signaling pathway, Breast Cancer Res Treat. 128 (2011) 57–68.
[346] H.Y. Kwan, et al., The anticancer effect of oridonin is mediated by fatty acid synthase suppression in human colorectal cancer cells, J. Gastroenterol. 48 (2013) 182–192.
[347] C.W. Pemble IV, L.C. Johnson, S.J. Kridel, W.T. Lowther, Crystal structure of the thioesterase domain of human fatty acid synthase inhibited by Orlistat, Nat. Struct. Mol. Biol. 14 (2007) 704–709.
[348] R. Loomba, et al., TVB-2640 (FASN inhibitor) for the treatment of nonalcoholic steatohepatitis: FASCINATE-1, a randomized, placebo-controlled phase 2a trial, Gastroenterology 161 (2021) 1475–1486.
[349] S.J. Dixon, et al., Ferroptosis: An iron-dependent form of nonapoptotic cell death, Cell 149 (2012).
[350] P.W. Gout, A.R. Buckley, C.R. Simms, N. Bruchovsky, Sulfasalazine, a potent suppressor of lymphoma growth by inhibition of the x-c cystine transporter: A new action for an old drug, Leukemia 15 (2001).
[351] S.J. Dixon, et al., Pharmacological inhibition of cystine-glutamate exchange induces endoplasmic reticulum stress and ferroptosis, Elife 2014 (2014).
[352] C. Louandre, et al., Iron-dependent cell death of hepatocellular carcinoma cells exposed to sorafenib, Int J. Cancer 133 (2013).
[353] J.L. Newell, et al., Novel di-aryl-substituted isoxazoles act as noncompetitive inhibitors of the system xc- cystine/glutamate exchanger, Neurochem Int 73 (2014).
[354] J.P. Friedmann Angeli, et al., Inactivation of the ferroptosis regulator Gpx4 triggers acute renal failure in mice, Nat. Cell Biol. 16 (2014).
[355] A. Seiler, et al., Glutathione peroxidase 4 senses and translates oxidative stress into 12/15-lipoxygenase dependent- and aif-mediated cell death, Cell Metab. 8 (2008).
[356] M. Weïwer, et al., Development of small-molecule probes that selectively kill cells induced to express mutant RAS, Bioorg. Med Chem. Lett. 22 (2012).
[357] E. Ooko, et al., Artemisinin derivatives induce iron-dependent cell death (ferroptosis) in tumor cells, Phytomedicine 22 (2015).
[358] N. Eling, L. Reuter, J. Hazin, A. Hamacher-Brady, N.R. Brady, Identification of artesunate as a specific activator of ferroptosis in pancreatic cancer cells, Oncoscience 2 (2015).
[359] R. Lin, et al., Dihydroartemisinin (DHA) induces ferroptosis and causes cell cycle arrest in head and neck carcinoma cells, Cancer Lett. 381 (2016).

[360] M.M. Gaschler, et al., FINO2 initiates ferroptosis through GPX4 inactivation and iron oxidation, Nat. Chem. Biol. 14 (2018).
[361] R.P. Abrams, W.L. Carroll, K.A. Woerpel, Five-membered ring peroxide selectively initiates ferroptosis in cancer cells, ACS Chem. Biol. 11 (2016).
[362] S. Ma, E.S. Henson, Y. Chen, S.B. Gibson, Ferroptosis is induced following siramesine and lapatinib treatment of breast cancer cells, Cell Death Dis. 7 (2016).
[363] S.L. Cramer, et al., Systemic depletion of L-cyst(e)ine with cyst(e)inase increases reactive oxygen species and suppresses tumor growth, Nat. Med 23 (2017).
[364] B. Hassannia, et al., Nano-targeted induction of dual ferroptotic mechanisms eradicates high-risk neuroblastoma, J. Clin. Investig. 128 (2018).
[365] D.W. Zheng, et al., Switching apoptosis to ferroptosis: metal-organic network for high-efficiency anticancer therapy, Nano Lett. 17 (2017).
[366] W.P. Li, C.H. Su, Y.C. Chang, Y.J. Lin, C.S. Yeh, Ultrasound-induced reactive oxygen species mediated therapy and imaging using a fenton reaction activable polymersome, ACS Nano 10 (2016).
[367] Z. Zhou, et al., Activatable singlet oxygen generation from lipid hydroperoxide nanoparticles for cancer therapy, Angew. Chem. - Int. Ed. 56 (2017).
[368] S.E. Kim, et al., Ultrasmall nanoparticles induce ferroptosis in nutrient-deprived cancer cells and suppress tumour growth, Nat. Nanotechnol. 11 (2016).