

Review

Targeting the Key Enzymes of Abnormal Fatty Acid β -oxidation as a Potential Strategy for Tumor Therapy

Hongdan Chen¹, Zeyu Yang¹, Yiceng Sun¹, Supeng Yin¹, Mi Tang^{1,*},[†], Fan Zhang^{1,*},[†]¹Department of Breast and Thyroid Surgery, Chongqing General Hospital, University of Chinese Academy of Sciences, 401147 Chongqing, China*Correspondence: zhangfancgh@163.com (Fan Zhang); iris-tm@126.com (Mi Tang)[†]These authors contributed equally.

Academic Editor: Graham Pawelec

Submitted: 5 December 2021 Revised: 13 February 2022 Accepted: 17 February 2022 Published: 9 March 2022

Abstract

Fatty acid metabolism has attracted extensive attention for its key role in the occurrence and development of tumors. Fatty acids not only participate in the biosynthesis of phospholipids in the membrane to overcome the demand for rapidly proliferating membrane lipids but also provide ATP, signaling molecules, and NADPH through β -oxidation to maintain tumor survival and growth. However, the specific role of fatty acid β -oxidation in tumors and the description of multiple potential targets in this process are not comprehensive and systematic. Therefore, this review summarizes the function of fatty acid β -oxidation in tumors and studies of key enzymes that catalyze related reactions in various stages to improve the overall understanding of fatty acid β -oxidation and search for novel tumor treatment strategies and ideas.

Keywords: fatty acid β -oxidation; tumor; ATP; NADPH; review

1. Introduction

Tumor tissue is characterized by a microenvironment of hypoxia and low nutrients. Tumor cells undergo metabolic reprogramming to adapt to severe living conditions. “Metabolic reprogramming” has been recognized as one of the 10 markers of cancer [1]. In the last century, Otto Warburg, a German biologist, first described that compared with nonproliferating normal cells, tumor cells tend to choose to rapidly produce ATP by enhancing the conversion of glucose to pyruvate even when oxygen is sufficient [2]. Although the Warburg effect has been widely accepted as a common feature of metabolic reprogramming, increasing evidence has shown that tumor metabolic reprogramming is reflected not only in aerobic glycolysis, in which fatty acid metabolic reprogramming targeting tumor cells has gradually become the focus of tumor research. However, clinical research on tumor metabolism, especially fatty acid metabolism, failed to keep pace with the progress of basic research [3].

According to the length of the carbon chain, fatty acids (FAs) were divided into short-chain, medium-chain, and long-chain fatty acids. FAs play an important role in all stages of tumors [4,5]. Generally, rapidly proliferating cells need a large number of fatty acids to promote membrane synthesis and form phospholipids to support replication. Simultaneously, fatty acids act as substrates for mitochondrial ATP synthesis [6], to regulate post-translational lipid modification and the function of signaling proteins [7,8]. In conclusion, fatty acids show an important effect in tumors, and interfering with fatty acid metabolism may become a potential strategy for tumor treatment. Targeting fatty acid

metabolism reprogramming of tumor cells has gradually become the focus of research [9]. Most of the current studies have focused on the therapeutic targets of de novo fatty acid synthesis and on FAs uptake to limit its use as a source of energy and cell membrane phospholipids [10,11]. However, some studies have found that fatty acid β -oxidation (FAO) is the ultimate fate in the FAs energy generation cycle [12,13]. It is worth noting that fatty acids are an important energy source of tumors in nutritional deficiency and even for some types of malignant tumors. ATP, NADPH, and intermediates produced by β -oxidation are vital for cell survival and the maintenance of a malignant phenotype. Therefore, clarifying the key role of FAO reprogramming in the tumor process may help to find potential targets for tumor therapy, which is of great research significance and clinical value. Herein, we summarize the important role of key enzymes and important metabolites involved in the process of FAO in promoting tumor progression and further explore the value and potential of targeted FAO in tumor therapy.

2. Fatty Acid β -oxidation Provides Favorable Conditions for Tumor Progression

Although mitochondrial FAO is the main source of bioenergy, it is not generally considered a part of the cancer metabolic blueprint. However, in the past few years, people’s views on the relationship between FAO and tumors have changed. The proliferation, survival, stemness, drug resistance, and metastasis of cancer cells depend on FAO. FAO is also reprogrammed in cancer-related immune cells and other stromal cells, which may contribute to the



immunosuppressive tumor microenvironment. FAO is the transformation of long-chain fatty acids into acetyl-CoA through the process of fatty acid activation, fatty acid transport and fatty acid oxidation under the action of a series of enzymes. The whole process produces a large number of reducing agents and ATP, which is more efficient than the tricarboxylic acid cycle. Recently, studies have provided vital evidence that cancer has a “Lipolytic phenotype” [14]. Similar to glycolysis or fatty acid synthesis in tumors, FAO shows abnormalities in a variety of tumors [15–17].

Some studies demonstrated that the expression of β -oxidation-related proteins in the mitochondria of liver cancer cells is higher than that of normal stem cells, and the oxidation rate of free fatty acids and other NAD-linked substrates by the mitochondria of liver cancer cells is faster, up to 6.6 times [18]. The expression of FAO-related enzymes (CPT1 and CD36) was significantly upregulated in the EMT model of breast cancer [19]. Lee CK *et al.* [20] proposed that FAO is an emerging factor for tumor lymph node metastasis. In lymph nodes, a lipid-rich microenvironment, tumor cells may preferentially use FAs as an energy source to enhance their metastatic potential [20,21]. The above studies suggested that the survival, proliferation, stemness, drug resistance, and metastasis of tumor cells depend on FAO [22–25]. Moreover, in addition to affecting tumor cells, FAO also plays a decisive role in the differentiation and function of stromal cells and immune cells. For example, the abnormal activity of FAO promoted the M2 differentiation of macrophages [26,27], and FAO contributed to the proliferation of Treg cells *in vitro* [28,29].

In addition, FAO produces a large amount of ATP, which provides the possibility for rapid tumor proliferation, invasion, and metastasis. Simultaneously, as one of the main sources of NADPH, the role of balancing ROS, maintaining redox balance, and promoting tumor cell survival cannot be ignored [30]. Moreover, a variety of intermediates are produced in the process of FAO as signal molecules or raw materials for the synthesis of other important substances, providing potential conditions for tumor progression [31]. FAO affects various aspects of cancer, including proliferation, metastasis, stemness, and the immune microenvironment (Fig. 1). The exploration of targeted FAO in tumor treatment is full of great potential and possibility.

3. The Key Enzymes of Fatty Acid β -oxidation May be Potential Targets for Tumor Therapy

In the presence of ATP, CoA-SH and Mg^{2+} , FAs are catalyzed by fatty acyl-CoA synthase to produce fatty acyl-CoA, which is then transported to mitochondria with the assistance of carnitine lipoacyltransferase. Based on the catalysis of a series of β -oxidases, long-chain fatty acids are gradually oxidized into multiple acetyl-CoAs, and different enzymes play a role in different links in the whole process

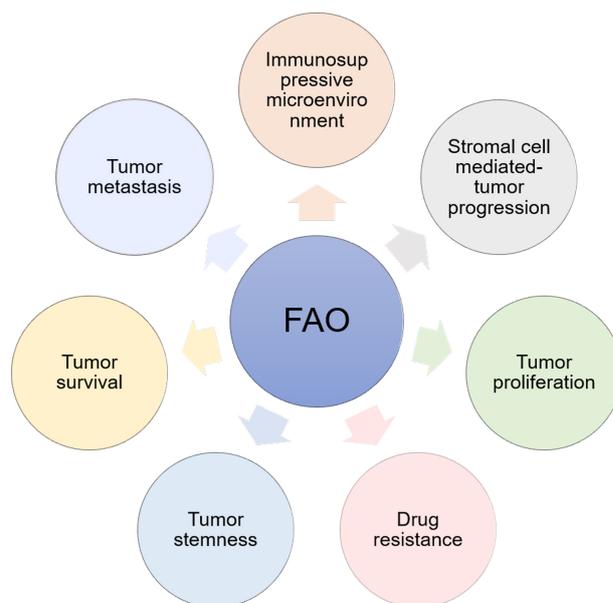


Fig. 1. Fatty acid β -oxidation plays a vital role in tumors. FAO affects all aspects of tumors, including not only the proliferation, metastasis, stemness, and drug resistance of tumors but also provides beneficial conditions for tumor progression by interfering with the function of immune cells and other stromal cells.

[32]. Some studies have shown that abnormal expression of genes involved in FAO is associated with malignant phenotypes, including therapeutic resistance, metastatic potential, and recurrence [33–35]. Therefore, several key enzymes in the FAO process may be used as therapeutic targets with tumor therapeutic potential (Fig. 2).

3.1 Fatty Acid Activation-Fatty acyl-CoA Synthetase

Long-chain fatty acyl-CoA synthetases (ACSLs) are a group of rate-limiting enzymes in fatty acid metabolism that catalyze the biotransformation of exogenous or de novo FAs to fatty acyl-CoA. The mammalian ACSLs family contains five members, including ACSL1, ACSL3, ACSL4, ACSL5, and ACSL6. Studies have suggested that abnormally active ACSLs are conducive to the proliferation, migration, and invasion of tumor cells [36]. Studies have shown that protein 1 containing the CUB structure, as a driving factor for a variety of tumor migrations and invasions, interacts with ACSLs family members to reduce lipid droplet abundance, stimulate FAO and provide power for driving tumor metastasis [37]. Some studies demonstrated that knockdown of ACSL1 inhibited the proliferation, migration, and cell cycle of prostate cancer cells and showed a tumor inhibitory effect *in vivo* [38]. Inhibition of ACSL1 could significantly interfere with LPS-mediated downstream pathways, including P38-MAPK-MEK1/2, ERK, JNK, and $NK-\kappa B$ [39]. In prostate cancer, targeting the signal transduction of androgen receptor (AR) led to a surge in ACSL4 levels, which increased the biosynthesis of fatty acyl-CoA, and the results suggested that AR

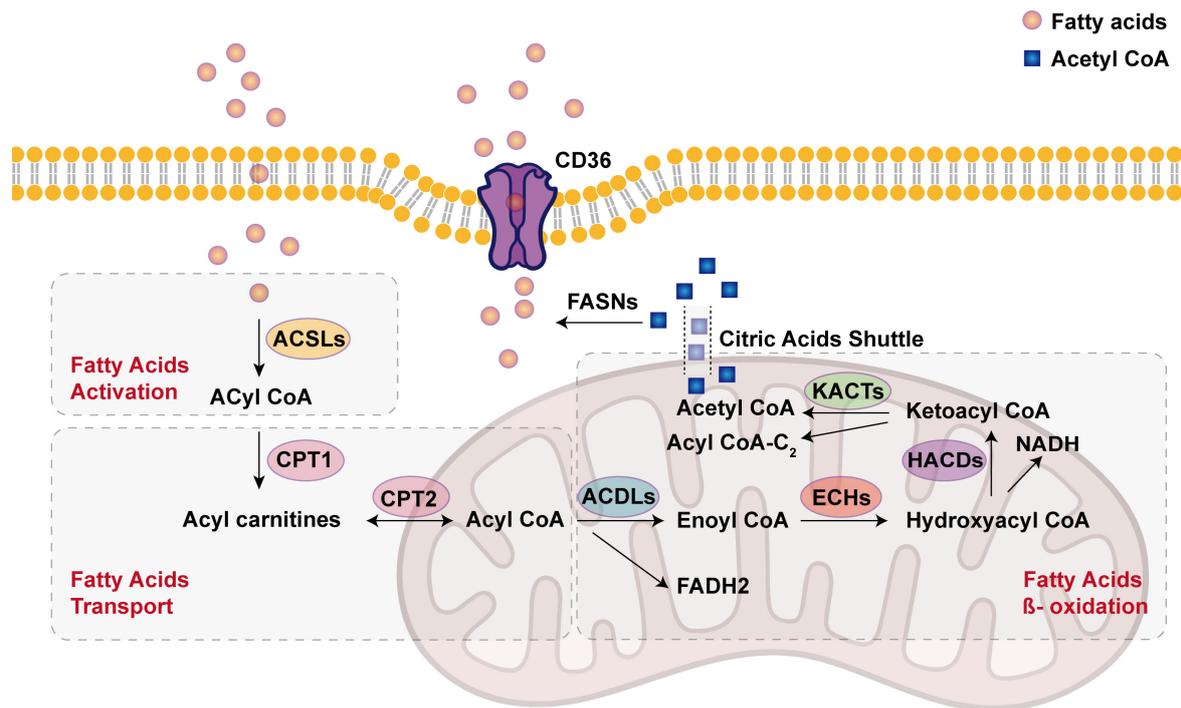


Fig. 2. Fatty acid β -oxidation process and various related key enzymes. ACSLs, acyl-CoA synthetases; CPT1, carnitine acyltransferases 1; CPT2, carnitine lipoxytransferases 2; ACDLs, lipoacyl-CoA dehydrogenases; FADH₂, flavin adenine dinucleotide transmitter; ECHs, enoyl-CoA hydratases; NADH, nicotinamide adenine dinucleotide; HACDs, hydroxyacyl-CoA dehydrogenases; KACTs, ketoacyl-CoA thiolases; FASNs, fatty acid synthetases; CD36, CD36 molecule.

coordinates the expression of ACSL3 and ACSL4 so that prostate tumors with independent AR pathways become dependent on ACSL4-mediated fatty acid metabolism [40]. The study pointed out that the overexpression of ACSL3 was associated with poor prognosis in patients with high-grade non-small-cell lung cancer. The authors revealed that patients with high expression of ACSL3 showed the clinical benefits of statins [41]. ACSL4 overexpression in triple-negative breast cancer was related to tumor aggressiveness, and there was a negative correlation with ER expression [42]. It has even been identified as a new marker and oncogene of alpha fetoprotein high subtype liver cancer [43]. ACSL5 has been shown to act as a modifier of Wnt signaling activity in addition to its proapoptotic effect [44]. Its abnormal expression may cause the downregulation of caspase-3 and E-cadherin and the upregulation of survivin and CD44 [45,46]. The above results suggest that ACSLs have the potential to become targets for tumor treatment.

3.2 Fatty Acid Transfer-Carnitine Palmitoyl Transferase

Carnitine palmitoyl transferase1 (CPT1), which is located in the outer mitochondrial membrane, is the FAO rate-limiting enzyme. It catalyzes acyl-CoA into acylcarnitine to transport fatty acids to mitochondria for further oxidation [47]. The CPT1 family consists of three subtypes: CPT1A, CPT1B, and CPT1C. CPT1C is mainly ex-

pressed in the brain [48], and an atypical isomer of CPT1. Some studies have proposed that CPTC may be a potential oncogene. The author found that the abnormal expression of CPT1C in cancer cells can promote the FAO process, promote ATP production, rescue cells from metabolic pressure, and produce resistance to mTORC1 inhibitors [49–51]. CPT1A and CPT1B are widely distributed in human organs. Compared with CPT1B, CPT1A is the key enzyme that determines the rate of FAO [52], which is more critical. CPT1A has been found to be associated with the development of a variety of tumors, such as prostate cancer, lymphocytic leukemia, and breast cancer [53,54]. The expression of CPT1A is enhanced in recurrent breast cancer. The use of FAO inhibitors or knockout of CPT1A to block the FAO process can inhibit radiation-induced ERK activation and the invasive growth and radioresistance of radiation-resistant breast cancer cells. Other studies have shown that excessive CPT1A plays a key role in stress adaptation and antioxidant defense in prostate cancer cells [55].

In colorectal cancer cells, CPT1A-mediated elimination of reactive oxygen species (ROS) is essential for cell survival. Colorectal cancer cells with CPT1A knockdown cannot maintain the NADPH/NADP⁺ ratio and GSH/GSSG ratio, as well as higher intracellular ROS levels. Studies have pointed out that CPT1A-mediated FAO removal of excessive ROS from tumor cells is essential for cell sur-

vival [56]. Research on drugs regulating CPT1 has been conducted for decades but have mainly focused on type 2 diabetes, obesity, cardiovascular disease, etc. [57,58]. In recent years, researchers have gradually realized the correlation between CPT1 and tumor progression. CPT1/2 inhibitors, as fatty acid metabolism regulators, have gradually developed into a new class of drugs, mainly malonyl-CoA analogs, glycidyl acid derivatives, and substrate inhibitors, providing new possibilities for tumor treatment [59]. With the development of research, the important role of CPT1B in cancer has been gradually recognized. Data from human breast cancer sources indicate that the STAT3-CPT1B-FAO pathway can promote the dry and chemical resistance of cancer cells. Blocking CPT1B expression will sensitize tumor cells to chemotherapy and inhibit tumor stem cells in mouse mammary tumors [60]. At present, fundamental research and clinical studies are targeting CPT1, providing powerful evidence to demonstrate the great potential of CPT1 in tumor therapy.

3.3 Fatty Acid β -oxidation-Fatty Acid β -oxidase System

The first step of FAO is catalyzed by acyl-CoA dehydrogenase (ACAD), which is a family of mitochondrial enzymes with different substrate specificities, including very-long-chain (VLCAD) and long-chain (LCAD), medium-chain (MCAD) and short-chain (SCAD) CoA dehydrogenase. Studies have shown that HIF-1 α can reduce ROS levels by inhibiting MCAD and LCAD and increase tumor cell proliferation. Further blocking LCAD inactivated PTEN expression and significantly affected tumor growth *in vivo* [61]. Downregulation of the expression of enoyl-CoA hydratase short-chain 1 (ECHS1) and peroxidase 3 (PRDX3) induced tumor cell apoptosis in human breast cancer MCF-7 cells [62].

FAO auxiliary enzyme, 2,4-dienoyl CoA reductase 1 (DECR1) is the rate-limiting enzyme for the oxidation of polyunsaturated fatty acids (PUFAs). Studies have shown that it is overexpressed in a variety of tumor tissues and has a certain relationship with the survival and prognosis of patients [3]. Knockdown of DECR1 blocked the β -oxidation of PUFAs in a mouse prostate cancer-transplanted tumor model. At the same time, the malignant phenotype of tumor cells was inhibited, accompanied by low DECR1 expression. It is speculated that targeting DECR1 may lead to the accumulation of PUFAs in cells and cause mitochondrial oxidative stress and lipid peroxidation. *In vivo* studies also show that DECR1 deletion could damage lipid metabolism [63].

4. NADPH Produced by Fatty Acid β -oxidation Maintains the Redox Homeostasis of Tumor Cells

Changes in tumor cell metabolic patterns inevitably affect cell redox homeostasis [64]. In most cases, the growth and survival potential of tumor cells is limited by the

level of NADPH in cells. On the one hand, it provides redox ability to counteract oxidative stress; on the other hand, it is a coenzyme of anabolic enzymes to maintain cell growth and proliferation. During the occurrence and development of tumors, the level of intracellular ROS increases significantly [65]. Reduced glutathione is an important antioxidant in cells that counteracts the oxidative pressure brought by ROS. In tumor cells with elevated ROS levels, reduced glutathione could be oxidized to oxidized glutathione, followed by glutathione reductase and reduced NADPH. It is reduced again under the action of to maintain the redox balance in tumor cells [66,67].

In addition to providing energy, FAO is also an important source of NADPH [68]. Numerous studies have shown that NADPH derived from FAO in tumor cells is a key factor in counteracting oxidative stress [14,69,70]. Acetyl-CoA produced by FAO entered tricarboxylic acid (TCA) cycle and generated citric acids with oxaloacetic acid. Citric acids were shuttled to the cytoplasm to generate NADPH [69] (Fig. 3). Previous studies have pointed out that the main purpose of FAO in rapidly proliferating endothelial cells is to carry out *de novo* dNTP synthesis. Compared with resting endothelial cells, the upregulation of FAO was three times or more higher than that of proliferating endothelial cells. Its main purpose is to maintain the tricarboxylic acid cycle through NADPH regeneration to maintain redox homeostasis [71]. Considering the adverse effects of a large number of ROS, cancer stem cell-like cells maintain ROS levels by coupling FOXM1-dependent PRX3 expression and fatty acid oxidation [30]. FAO was inhibited in glioma cells and showed a significant decrease in NADPH levels, resulting in an increase in ROS levels and cell death [70]. Nissim Hay *et al.* [72] also demonstrated the correlation between FAO and NADPH homeostasis. Nrf2, a transcription factor that regulates cellular redox status, has been shown to promote FAO and increase NADPH regeneration, thereby guiding metabolic reprogramming during stress [73]. FAO is an important component of metabolic reprogramming by providing ATP and maintaining redox balance to promote tumor progression.

5. Effects of Fatty Acid β -oxidation on Other Cells

A variety of cells constitute a complex tumor microenvironment, including immune cells and stromal cells. Therefore, we should take the tumor as a whole into consideration. In addition to tumor cells, the existence, phenotype and function of other cells affect the progression of tumors, and the functional phenotype of these cells is closely related to their metabolic mode [74,75]. Studies have shown that effector CD4⁺ T cells rely on glycolysis to provide energy and substances for biosynthesis. However, immunosuppressive T cells (Tregs) suggest a higher level of FAO [76]. Tregs combine glycolysis, fatty acid synthesis, oxidation, and other metabolic modes to defeat T

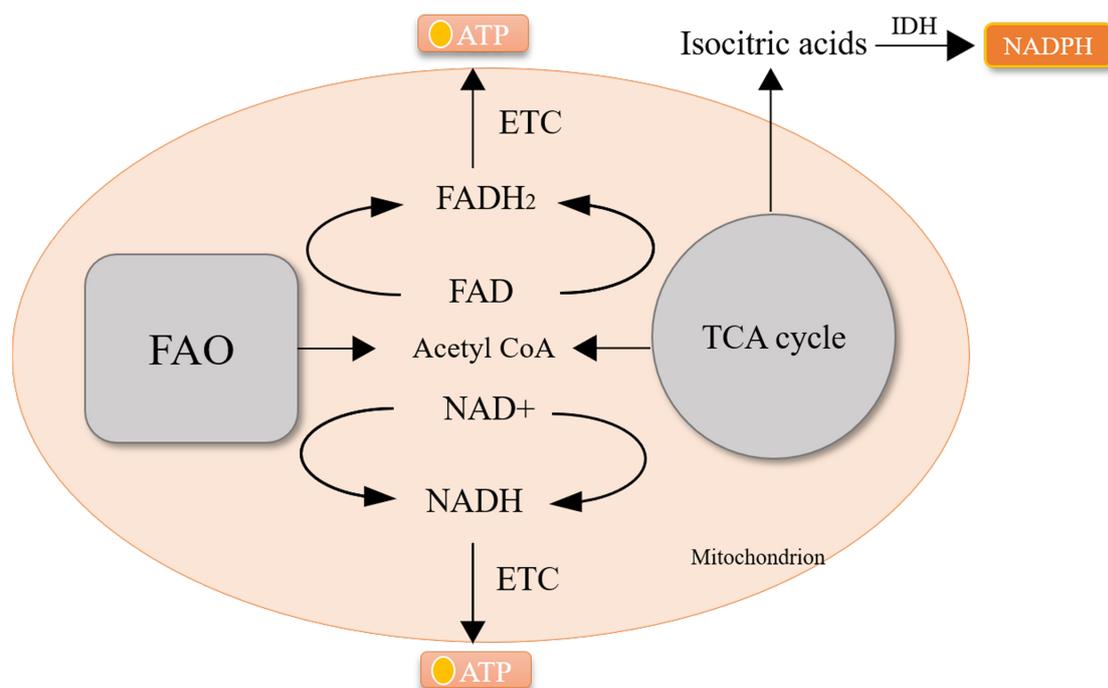


Fig. 3. FAO provides ATP and NADPH to promote tumor progression. On the one hand, NADH and FADH₂ produced in the process of FAO could generate ATP through the electron transport chain (ETC). On the other hand, its metabolite acetyl-CoA enters the tricarboxylic acid (TCA) cycle to synthesize citric acid with oxaloacetic acid. Citric acid enters the cytoplasm through the citric acid shuttle to generate isocitrate. Under the action of isocitrate dehydrogenase (IDH), cytoplasmic NADPH is generated.

cells that mainly rely on glycolysis to meet energy and material needs [77]. Several research groups have reported that M2 macrophages use FAO to promote mitochondrial oxidative phosphorylation, providing a survival advantage over M0 and M1 macrophages [78,79]. Inhibition of FAO could prevent macrophages from polarizing to the M2 type [80]. Early studies have shown abnormal lipid accumulation in tumor-associated dendritic cells with a tolerance phenotype [81]. We investigated and summarized the role of FAO in different immune cells in the early stage and found that active FAO can cause a variety of immune cells, such as macrophages, dendritic cells, and NK cells, to change into an immune tolerance phenotype and contribute to the immunosuppressive microenvironment [82].

The dynamic crosstalk between stromal cells and tumor cells is also one of the potential mechanisms of malignant tumor progression. Adipocytes are an important component of the tumor microenvironment. Adipocytes in the tumor microenvironment secrete a large number of exosomes. These exosomes are absorbed by tumor cells, which lead to increased migration and invasion. Interestingly, it was found that the vesicles secreted by these adipocytes were rich in FAO-related proteins, which was one of their highly specific characteristics [83]. Further studies showed that in the presence of these exosomes, FAO in melanoma cells was also mobilized and became more active [83]. In addition to the abnormal FAO of adipocytes in the tumor microenvironment, studies have found that cancer related-

fibroblasts actively oxidized FA and conducted minimal glycolysis by upregulating CPT1A to promote the proliferation, migration, and invasion of colon cancer cells [84]. Etomoxir directly blocks CPT1A-mediated FAO in fibroblasts, which could inhibit migration and invasion *in vitro* and reduce tumor growth and peritoneal metastasis *in vivo* [84].

6. Various Oncogenes and Tumor Suppressor Genes Involved in the Regulation of FAO

Abnormally active FAO is one of the characteristics of carcinoma, which is a prerequisite for some tumors. Some studies have shown that FAO is the driving force of β -catenin induced hepatocellular carcinoma (HCC), and inhibiting FAO would prevent the progress of HCC [85]. Other studies have also pointed out that mutant KRAS promotes fatty acid uptake, accumulation and β -oxidation in lung cancer with an ACSL3-dependent manner. Therefore, ACSL3-mediated FAO is necessary for the occurrence of KRAS mutant lung cancer [86].

FAO was also regulated by multiple oncogenes or tumor suppressor genes (Table 1) [43,61,85–98]. c-Myc upregulated the main FAs production regulator sterol regulatory element binding protein 1 (SREBP1) in tumor cells and promoted the production of fatty acids and the process of FAO [43]. Meanwhile, c-Myc has also been shown to regulate FAO by inhibiting the expression of ACC2, and ACC2

Table 1. FAO was regulated by oncogenes and tumor suppressor genes.

Type	Key Genes	Specific functions
oncogenes	β -catenin	β -catenin \uparrow →FAO \uparrow →the process of HCC
	KRAS	Mutant KRAS→FAO in lung cancer with ACSL3-dependent manner \uparrow
	c-Myc	c-Myc \uparrow →SREBP1 \uparrow →FA accumulation \uparrow ; c-Myc \uparrow →ACC2 \downarrow →CPT1A \uparrow
	PPAR α	PPAR α \downarrow →the expression of FAO related genes \uparrow , such as CPT1
	CD147	CD147 \uparrow →Akt/mTOR \uparrow →SREBP1 \uparrow and PPAR α /CPT1A pathway \downarrow
	CCAT1	CCAT1 \uparrow →FABP5 translocation→FA metabolism \uparrow →Malignant phenotype \uparrow
	Cyclin D1	Cyclin D1 \uparrow →PPAR α /CPT1c pathway \downarrow
	SIK	SIK/GNAS/PKA pathway \uparrow →FAO \uparrow
	PLA2	PLA2 mobilizes free fatty acids to maintain FAO
	HIF-1 α	HIF-1 α \uparrow →MCAD and LCAD \downarrow →FAO \downarrow
AMPK	AMPK/PGC-1 α \uparrow →FAO \uparrow	
Tumor suppressor genes	P53	Mutant p53→FAO \uparrow
	NDRG2	NDRG2 \uparrow →AMPK/ACC pathway and FAO activation \downarrow
	RARRES1	RARRES1 \downarrow →FAO \uparrow
	REDD1	REDD1 \downarrow →reprogrammes lipid metabolism→RAS mutant cancer \uparrow

PPAR α , peroxisome proliferator-activated receptor alpha; CCAT1, colon cancer associated transcript 1; SIK, salt-inducible kinase; PLA2, phospholipase A2; MCAD, medium-chain acyl-CoA dehydrogenase; LCAD, long-chain acyl-CoA dehydrogenase; HIF-1 α , hypoxia inducible factor 1 subunit alpha; AMPK, protein kinase AMP-activated catalytic subunit alpha 1; NDRG2, NDRG family member 2; RARRES1, retinoic acid receptor responder 1; REDD1, DNA-damage-inducible transcript 4.

suppressed the effect of CPT1A through targeting malonyl-CoA [87]. Significantly, Cyclin D1 is a cyclin, which is abnormally expressed in tumors as an oncogene. Studies have evaluated that it not only play a key role in the process of cell cycle, but also inhibit the activity of PPAR α and block CPT1 expression to regulate FAO [88,91]. CD147 is a key regulator of fatty acid metabolism and is overexpressed in a variety of cancers. At present, a drug named Licartin developed with CD147 antibody labeled with I¹³¹ has been approved by National Medical Products Administration (NMPA) for the treatment of HCC [89]. Previous studies have indicated that CD147 could not only upregulate SREBP1 by activating Akt/mTOR signaling pathway, and then activate FASN and ACC1 to promote fatty acids accumulation, but also inhibit PPAR α and CPT1A with activating p38/MAPK to disturb FAO [89]. FAO has showed protective factor in a variety of tumors [99,100], so that cancer cells survived with facing severe challenges. Partial oncogenes could controll the fate of tumor cells by regulating the activity of FAO. And the deletion of some tumor suppressor genes caused fatty acid reprogramming to maintain the malignant phenotype of tumor cells.

7. The Promising Drugs Targeting FAO in Cancer

At present, FAO and related regulatory genes as targets have been gradually recognized and tried as potential candidates for cancer therapy. The promising drugs (and related targets) targeting FAO in cancer mainly fo-

cused on CPT [101], we organized the main targeted drugs (Table 2 and Fig. 4). Among them, etomoxir plays an important role in the treatment of various tumors by targeting FAO. Etomoxir irreversibly inhibited CPT1A and CPT1B [102]. Etomoxir significantly reduced liver and lung metastatic nodules of colorectal cancer cells by promoting anoikis [56]. However, etomoxir has serious side effects. Long-term use of etomoxir could lead to cardiac hypertrophy by promoting oxidative stress and NF- κ B pathway [103]. The selective CPT1A inhibitor ST1326 (Teglicar) is safer than etomoxir, it does not cause cardiac hypertrophy, but still has some hepatotoxicity [104,105]. This novel CPT1A inhibitor has antitumor activity in hematological malignancies such as acute myeloid leukemia and Burkitt lymphoma [53]. ST1326 combined with Bcl2 inhibitor ABT199 showed strong synergistic inhibitory effects on acute myeloid leukemia (AML) [106]. At present, ST1326 is still in the preclinical experimental research stage. In addition to inhibiting CPT1A, perhexiline can also inhibit CPT2, showing a similar but stronger anti-tumor effect than etomoxir [107]. As a partial β -oxidation inhibitor, ranolazine has showed anticancer effects in leukemia and breast cancer [108,109]. Ranolazine increased the antitumor effect of prostate cancer cells by changing the activation status of the neighboring T-cells. 6-gingerol is known to have a potential anticancer agent by inducing apoptosis in cancer cells. Its apoptotic effect is to inhibit CPT1 by accumulating pathologically high concentrations of malonyl-CoA.

Table 2. The promising drugs targeting FAO.

Agent	Target	Tumor type and mechanism	Risks
Etomoxir	CPT1A and CPT1B	Colorectal cancer: CPT1↓-anoikis↑/anchorage-independent growth↓ Leukemia: FAO↓-Bcl-2↓ Nasopharyngeal: PGC1 α +CEBPB-CPT1A↑-FAO↑ Glioblastoma: NADPH↓-ROS↑ Breast cancer: JAK/STAT3↓-CPT1B↓-FAO↓ Ovarian cancer: CPT1↓-FAO/OXPHOS↓ Prostate cancer: CPT↓-cell cycle arrest and apoptosis↑	High liver transaminase level, cardiac hypertrophy
ST1326	CPT1A	Leukemia: CPT1A↓-Mcl-1↓ Breast cancer: JAK/STAT3↓-CPT1B↓-FAO↓ Ovarian cancer: CPT1A↓-CPT2↓-FAO/OXPHOS↓ Leukemia: CPT↓-cardiolipin↓ HCC: CPT↓-PPAR α ↓/ROS↑ Prostate cancer: CPT↓-cell cycle arrest and apoptosis↑	Hepatotoxicity
Perhexiline	CPT1 and CPT2	Breast cancer: FAO↓-tumor growth and cell proliferation↓/ apoptosis↑ Prostate cancer: FAO↓-CD8+ T-cells Tim3 content↓/macrophages↑ Colorectal cancer: FASN↓-PI3K/AKT/mTOR↓ FASN-overproduction of malonyl-CoA↓-CPT1↓-ROS↑	Transient effects: Predominantly are dizziness, headache, and nausea Long term side effects: Hepatotoxicity and neurotoxicity
Ranolazine	FAO/3-KAT	Breast cancer: FAO↓-tumor growth and cell proliferation↓/ apoptosis↑ Prostate cancer: FAO↓-CD8+ T-cells Tim3 content↓/macrophages↑	Excessive product can cause dizziness, nausea, vomiting, diplopia, paresthesia, confusion and loss of delayed consciousness
6-gingerol	CPT-1/FASN	Colorectal cancer: FASN↓-PI3K/AKT/mTOR↓ FASN-overproduction of malonyl-CoA↓-CPT1↓-ROS↑	nausea, stomachache

CPT1A, carnitine acyltransferases 1A; CPT1B, carnitine acyltransferases 1B; CPT1, carnitine acyltransferases 1; CPT2, carnitine acyltransferases 2; 3-KAT, 3-ketoacyl CoA thiolase; FASN, fatty acid synthetase; PGC1 α , PPAR coactivator-1 α ; CEBPB, CCAAT/enhancer binding protein β ; ROS, reactive oxygen species; JAK/STAT3, Janus kinase (JAK)/Signal transducer and activator of transcription 3 (STAT3); OXPHOS, oxidative phosphorylation; PPAR α , peroxisome proliferator-activated receptor alpha.

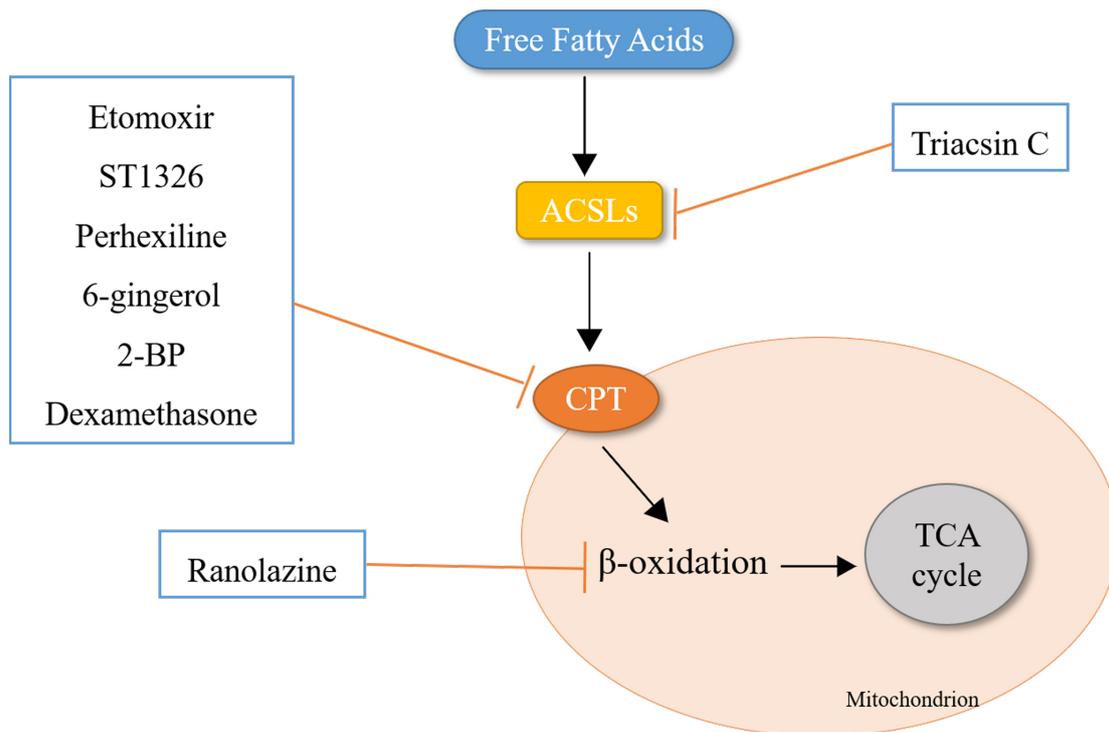


Fig. 4. The mechanism of drugs targeting FAO in cancers. CPT in FAO as an important target in tumor therapy. There are also potential targets for β -oxidation and ACSLs.

In addition to above drugs, several potential FAO-related targeted drugs are in the experimental stage. Chemical inhibition of ACSLs activity by triacsin C (inhibits ACSL1, ACSL3, and ACSL4, but not ACSL5 or ACSL6) induces apoptosis in lung, colon, and brain cancer cells [110]. 2-bromopalmitate (2-BP) is an irreversible inhibitor of many membrane-associated enzymes. Reported as an inhibitor of β -oxidation, 2-BP can also alter lipid metabolism through CPT1, thereby affecting tumor growth [28,29]. High-dose dexamethasone can also delay tumor growth and promote apoptosis by inhibiting CPT1A [111].

8. The Role of Polyunsaturated Fatty Acids in Tumor

Notably, polyunsaturated fatty acids (PUFAs) have been shown to play a vital role in tumor treatment. According to the position and function of double bonds, PUFAs are divided into ω -6 PUFAs, including linoleic acid and arachidonic acid and ω -3 PUFAs, containing linolenic acid, docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA). Studies have showed that ω -3 PUFAs are considered to be an immune nutrient to use in the nutritional treatment of cancer patients [112]. On the one hand, ω -3 PUFAs showed anti-inflammatory and analgesic effects by inhibiting the expression of NF- κ B [113]. On the other hand, it can be used as an agonist of G protein-coupled receptors (free fatty acid receptor 1, FFA1 and free fatty acid receptor 4, FFA4) [114,115]. Therefore, tumor patients accompanied

by cachexia, pain and other complications could benefit from ω -3 PUFAs administration.

In addition to the effect for tumor complications, recent researches have pointed that PUFAs also play a vital role in suppression of tumor, including breast cancer, colorectal cancer, liver cancer. The influence of PUFAs on tumor could be summarized as follows: (1) Inhibition of tumor cell cycle. DHA disturbed cell cycle by suppressing DNA synthesis in liver cancer cells and melanoma cells [116]. Furthermore, Istfan NW demonstrated the duration of S phase of tumor cells increased significantly when ω -3 PUFAs were consumed [117]. (2) Induction of tumor cell apoptosis. Studies have showed PUFAs cause apoptosis in many ways, especially PUFAs inhibit the expression of Bcl2 and promote Bax expression [118,119]. (3) Suppression of tumor related angiogenesis. ω -6 PUFAs reduced the content of leptin in adipocytes, resulting in the decrease of VEGF expression to prevent angiogenesis [120]. (4) The influence of immune system. PUFAs regulated the differentiation of directional thymocyte lineage and mediated inflammatory response by increasing the production of CD8+ T cells [121]. Furthermore, PUFAs in peripheral lymph regulated the specific proliferation of T cells and the secretion of cytokines, causing the inhibition of Th2 response [122]. (5) Lipid peroxidation mediated cell death. Lipid peroxidation is achieved by two main pathways, by enzymatic or by non-enzymatic oxidation, respectively [123]. Lipid peroxidation was accumulated in cancer cells inducing iron-dependent cell death, which was called ferroptosis

[124]. In addition, the non-enzymatic peroxidation of PUFAs and of their 12/15-lipoxygenase-derived hydroperoxy metabolites caused the generation of the reactive aldehyde species 4-hydroxyalkenals, in particular 4-hydroxynonenal [125]. Those metabolites showed cytotoxic effect to kill tumor cells [126]. (6) Other mechanisms. Some studies have found that PUFAs inhibit the expression of MMPs in gastric cancer and interferes with tumor cell invasion and metastasis [127]. Simultaneously, ω -6 PUFAs was pointed out through PPAR γ regulated downstream target genes to reduce synthesis of inflammatory mediators [128,129]. In general, PUFAs showed an inhibitory effect on tumor cells, although this effect was thought to be related to the ratio of ω -3 and ω -6 [130,131], however, this is still a potential strategy in tumor treatment, which is worthy of further discussion.

9. Conclusions

FAO plays an extremely important role in supporting tumor progression. Research on FAO has great potential in the diagnosis and treatment of tumors. This review focused on the key enzymes that may be used as tumor treatment targets in the process of fatty acid β -oxidation and described that the abnormal expression of enzymes in the process of fatty acid activation, transport, and β -oxidation mediates the progression of a variety of tumors. Inhibiting the expression of key enzyme-related genes or enzyme activity could hinder tumor cell proliferation, migration, and other malignant functions. Studies have shown that knocking down FAO-related genes induces tumor cell apoptosis; however, the specific mechanism of action is not particularly clear, and further research is needed. In addition to key enzymes, this article also summarized that FAO provided a large amount of ATP for tumors to support uncontrolled proliferation and maintained cell redox homeostasis by producing NADPH. Abnormal fatty acid metabolism has attracted the attention and discussion of an increasing number of researchers. Compared with extensive research on de novo fatty acid synthesis and fatty acid absorption, FAO is equally important to tumor survival and progression, and it plays a role that cannot be ignored. Therefore, targeting abnormal FAO in tumors may be a new strategy and idea for tumor treatment.

At present, FAO inhibitors have been used in the clinic, but they are mainly used to treat heart disease [132–134]. Their application in tumors is still in preclinical research or encounters bottlenecks, such as drug toxicity, and the *in vivo* effect is not as good as the *in vitro* effect. On the other hand, FAO has been proven to be indirectly activated by PPAR activators [133], AMPK activators [72], or ACC inhibitors [135], so there are indirect strategies for these targets, but the various pathways activated by these methods complicate the interpretation of the results. Therefore, further direct targeting of FAO has great significance and potential.

Abbreviations

FA, fatty acids; FAO, fatty acid β -oxidation; ACSLs, long-chain fatty acyl-CoA synthetases; AR, androgen receptor; CPT1, carnitine palmitoyl transferase 1; ROS, reactive oxygen species; ACAD, acyl-CoA dehydrogenase; ECHS1, enoyl-CoA hydratase short-chain 1; PRDX3, peroxidase 3; DECR1, 2,4-dienoyl CoA reductase 1; PUFAs, polyunsaturated fatty acids; TCA cycle, tricarboxylic acid cycle; Treg, regulatory T cells; 3-KAT, 3-ketoacyl CoA thiolase; FASN, fatty acid synthetase; PGC1 α , PPAR coactivator-1 α ; CEBPB, CCAAT/enhancer binding protein β ; JAK/STAT3, janus kinase (JAK)/Signal transducer and activator of transcription 3 (STAT3); OXPHOS, oxidative phosphorylation; PPAR α , peroxisome proliferator-activated receptor alpha; CCAT1, colon cancer associated transcript 1; SIK, salt-inducible kinase; PLA2, phospholipase A2; MCAD, medium-chain acyl-CoA dehydrogenase; LCAD, long-chain acyl-CoA dehydrogenase; HIF-1 α , hypoxia inducible factor 1 subunit alpha; AMPK, protein kinase AMP-activated catalytic subunit alpha 1; NDRG2, NDRG family member 2; RARRES1, retinoic acid receptor responder 1; REDD1, DNA-damage-inducible transcript 4.

Author contributions

HC and FZ designed the research study. HC performed the research. MT and YS provided help and advice on. ZY and SY analyzed the data. HC wrote the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Acknowledgment

We apologize to colleagues whose work is not cited due to space constraints. And we also thank anonymous reviewers for excellent criticism of the article and all the authors in the reference list.

Funding

This research was funded by Natural Science Foundation of Chongqing, China, grant number cstc2020jcyj-msxmX0485 and Medical Science and Technology Innovation Fund of Chongqing General Hospital, grant number 2019ZDXM01 and Y2020ZDXM08.

Conflict of interest

The authors declare no conflict of interest.

References

- [1] Yoshida GJ. Metabolic reprogramming: the emerging concept and associated therapeutic strategies. *Journal of Experimental & Clinical Cancer Research*. 2015; 34: 111.

- [2] Warburg O, Wind F, Negelein E. The METABOLISM of TUMORS in the BODY. *The Journal of General Physiology*. 1927; 8: 519–530.
- [3] Nassar ZD, Mah CY, Dehairs J, Burvenich IJ, Irani S, Centenera MM, *et al*. Human DECR1 is an androgen-repressed survival factor that regulates PUFA oxidation to protect prostate tumor cells from ferroptosis. *eLife*. 2020; 9: e54166.
- [4] Nagarajan SR, Butler LM, Hoy AJ. The diversity and breadth of cancer cell fatty acid metabolism. *Cancer & Metabolism*. 2021; 9: 2.
- [5] Cheng C, Geng F, Cheng X, Guo D. Lipid metabolism reprogramming and its potential targets in cancer. *Cancer Communications*. 2018; 38: 27.
- [6] Guppy M, Leedman P, Zu X, Russell V. Contribution by different fuels and metabolic pathways to the total ATP turnover of proliferating MCF-7 breast cancer cells. *The Biochemical Journal*. 2002; 364: 309–315.
- [7] Resh MD. Fatty acylation of proteins: the long and the short of it. *Progress in Lipid Research*. 2016; 63: 120–131.
- [8] Lien EC, Dibble CC, Toker A. PI3K signaling in cancer: beyond AKT. *Current Opinion in Cell Biology*. 2017; 45: 62–71.
- [9] Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. *Cell*. 2011; 144: 646–674.
- [10] Zadra G, Loda M. Metabolic Vulnerabilities of Prostate Cancer: Diagnostic and Therapeutic Opportunities. *Cold Spring Harbor Perspectives in Medicine*. 2018; 8: a030569.
- [11] Watt MJ, Clark AK, Selth LA, Haynes VR, Lister N, Rebello R, *et al*. Suppressing fatty acid uptake has therapeutic effects in preclinical models of prostate cancer. *Science Translational Medicine*. 2019; 11: eaau5758.
- [12] Balaban S, Nassar ZD, Zhang AY, Hosseini-Beheshti E, Centenera MM, Schreuder M, *et al*. Extracellular Fatty Acids are the Major Contributor to Lipid Synthesis in Prostate Cancer. *Molecular Cancer Research*. 2019; 17: 949–962.
- [13] Schlaepfer IR, Rider L, Rodrigues LU, Gijón MA, Pac CT, Romero L, *et al*. Lipid catabolism via CPT1 as a therapeutic target for prostate cancer. *Molecular Cancer Therapeutics*. 2014; 13: 2361–2371.
- [14] Ma Y, Temkin SM, Hawkrigde AM, Guo C, Wang W, Wang X, *et al*. Fatty acid oxidation: an emerging facet of metabolic transformation in cancer. *Cancer Letters*. 2018; 435: 92–100.
- [15] Lin H, Patel S, Affleck VS, Wilson I, Turnbull DM, Joshi AR, *et al*. Fatty acid oxidation is required for the respiration and proliferation of malignant glioma cells. *Neuro-Oncology*. 2017; 19: 43–54.
- [16] Wang M, Wu H, Huang S, Zhang H, Qin C, Zhao L, *et al*. HBx regulates fatty acid oxidation to promote hepatocellular carcinoma survival during metabolic stress. *Oncotarget*. 2016; 7: 6711–6726.
- [17] Cook KL, Soto-Pantoja DR, Clarke PAG, Cruz MI, Zwart A, Wärrri A, *et al*. Endoplasmic Reticulum Stress Protein GRP78 Modulates Lipid Metabolism to Control Drug Sensitivity and Antitumor Immunity in Breast Cancer. *Cancer Research*. 2016; 76: 5657–5670.
- [18] Rodríguez-Enríquez S, Hernández-Esquivel L, Marín-Hernández A, El Hafidi M, Gallardo-Pérez JC, Hernández-Reséndiz I, *et al*. Mitochondrial free fatty acid β -oxidation supports oxidative phosphorylation and proliferation in cancer cells. *The International Journal of Biochemistry & Cell Biology*. 2015; 65: 209–221.
- [19] Liu QQ, Huo HY, Ao S, Liu T, Yang L, Fei ZY, *et al*. TGF- β 1-induced epithelial-mesenchymal transition increases fatty acid oxidation and OXPHOS activity via the p-AMPK pathway in breast cancer cells. *Oncology Reports*. 2020; 44: 1206–1215.
- [20] Lee C, Jeong S, Jang C, Bae H, Kim YH, Park I, *et al*. Tumor metastasis to lymph nodes requires YAP-dependent metabolic adaptation. *Science*. 2019; 363: 644–649.
- [21] Li M, Xian H, Tang Y, Liang X, Tang Y. Fatty acid oxidation: driver of lymph node metastasis. *Cancer Cell International*. 2021; 21: 339.
- [22] Wong BW, Wang X, Zecchin A, Thienpont B, Cornelissen I, Kalucka J, *et al*. The role of fatty acid β -oxidation in lymphangiogenesis. *Nature*. 2017; 542: 49–54.
- [23] Pascual G, Avgustinova A, Mejetta S, Martín M, Castellanos A, Attolini CS, *et al*. Targeting metastasis-initiating cells through the fatty acid receptor CD36. *Nature*. 2017; 541: 41–45.
- [24] Schafer ZT, Grassian AR, Song L, Jiang Z, Gerhart-Hines Z, Irie HY, *et al*. Antioxidant and oncogene rescue of metabolic defects caused by loss of matrix attachment. *Nature*. 2009; 461: 109–113.
- [25] Buzzai M, Bauer DE, Jones RG, Deberardinis RJ, Hatzivasiliou G, Elstrom RL, *et al*. The glucose dependence of Akt-transformed cells can be reversed by pharmacologic activation of fatty acid beta-oxidation. *Oncogene*. 2005; 24: 4165–4173.
- [26] Su P, Wang Q, Bi E, Ma X, Liu L, Yang M, *et al*. Enhanced Lipid Accumulation and Metabolism are Required for the Differentiation and Activation of Tumor-Associated Macrophages. *Cancer Research*. 2020; 80: 1438–1450.
- [27] Namgaladze D, Brüne B. Macrophage fatty acid oxidation and its roles in macrophage polarization and fatty acid-induced inflammation. *Biochimica Et Biophysica Acta*. 2016; 1861: 1796–1807.
- [28] Gerriets VA, Kishton RJ, Johnson MO, Cohen S, Siska PJ, Nichols AG, *et al*. Foxp3 and Toll-like receptor signaling balance Treg cell anabolic metabolism for suppression. *Nature Immunology*. 2016; 17: 1459–1466.
- [29] Procaccini C, Carbone F, Di Silvestre D, Brambilla F, De Rosa V, Galgani M, *et al*. The Proteomic Landscape of Human Ex Vivo Regulatory and Conventional T Cells Reveals Specific Metabolic Requirements. *Immunity*. 2016; 44: 712.
- [30] Choi H, Jhe Y, Kim J, Lim JY, Lee JE, Shin M, *et al*. FoxM1-dependent and fatty acid oxidation-mediated ROS modulation is a cell-intrinsic drug resistance mechanism in cancer stem-like cells. *Redox Biology*. 2020; 36: 101589.
- [31] Bell JA, Reed MA, Consitt LA, Martin OJ, Haynie KR, Hulver MW, *et al*. Lipid Partitioning, Incomplete Fatty Acid Oxidation, and Insulin Signal Transduction in Primary Human Muscle Cells: Effects of Severe Obesity, Fatty Acid Incubation, and Fatty Acid Translocase/CD36 Overexpression. *The Journal of Clinical Endocrinology & Metabolism*. 2010; 95: 3400–3410.
- [32] Adeva-Andany MM, Carneiro-Freire N, Seco-Filgueira M, Fernández-Fernández C, Mouriño-Bayolo D. Mitochondrial β -oxidation of saturated fatty acids in humans. *Mitochondrion*. 2019; 46: 73–90.
- [33] Galicia-Vázquez G, Aloyz R. Ibrutinib Resistance is Reduced by an Inhibitor of Fatty Acid Oxidation in Primary CLL Lymphocytes. *Frontiers in Oncology*. 2018; 8: 411.
- [34] Kuo C, Ann DK. When fats commit crimes: fatty acid metabolism, cancer stemness and therapeutic resistance. *Cancer Communications*. 2018; 38: 47.
- [35] Aiderus A, Black MA, Dunbier AK. Fatty acid oxidation is associated with proliferation and prognosis in breast and other cancers. *BMC Cancer*. 2018; 18: 805.
- [36] Rossi Sebastiano M, Konstantinidou G. Targeting Long Chain Acyl-CoA Synthetases for Cancer Therapy. *International Journal of Molecular Sciences*. 2019; 20: 3624.
- [37] Wright HJ, Hou J, Xu B, Cortez M, Potma EO, Tromberg BJ, *et al*. CDCP1 drives triple-negative breast cancer metastasis through reduction of lipid-droplet abundance and stimulation of fatty acid oxidation. *Proceedings of the National Academy of Sciences of the United States of America*. 2017; 114: E6556–

E6565.

- [38] Ma Y, Zha J, Yang X, Li Q, Zhang Q, Yin A, *et al.* Long-chain fatty acyl-CoA synthetase 1 promotes prostate cancer progression by elevation of lipogenesis and fatty acid beta-oxidation. *Oncogene*. 2021; 40: 1806–1820.
- [39] Al-Rashed F, Thomas R, Al-Roub A, Al-Mulla F, Ahmad R. LPS Induces GM-CSF Production by Breast Cancer MDA-MB-231 Cells via Long-Chain Acyl-CoA Synthetase 1. *Molecules*. 2020; 25: 4709.
- [40] Ma Y, Zhang X, Alsaidan OA, Yang X, Sulejmani E, Zha J, *et al.* Long-Chain Acyl-CoA Synthetase 4-Mediated Fatty Acid Metabolism Sustains Androgen Receptor Pathway-Independent Prostate Cancer. *Molecular Cancer Research*. 2021; 19: 124–135.
- [41] Fernández LP, Merino M, Colmenarejo G, Moreno-Rubio J, Sánchez-Martínez R, Quijada-Freire A, *et al.* Metabolic enzyme ACSL3 is a prognostic biomarker and correlates with anticancer effectiveness of statins in non-small cell lung cancer. *Molecular Oncology*. 2020; 14: 3135–3152.
- [42] Dattilo MA, Benzo Y, Herrera LM, Prada JG, Castillo AF, Orlando UD, *et al.* Regulatory mechanisms leading to differential Acyl-CoA synthetase 4 expression in breast cancer cells. *Scientific Reports*. 2019; 9: 10324.
- [43] Chen J, Ding C, Chen Y, Hu W, Yu C, Peng C, *et al.* ACSL4 reprograms fatty acid metabolism in hepatocellular carcinoma via c-Myc/SREBP1 pathway. *Cancer Letters*. 2021; 502: 154–165.
- [44] Klaus C, Schneider U, Hedberg C, Schütz AK, Bernhagen J, Waldmann H, *et al.* Modulating effects of acyl-CoA synthetase 5-derived mitochondrial Wnt2B palmitoylation on intestinal Wnt activity. *World Journal of Gastroenterology*. 2014; 20: 14855–14864.
- [45] Ding S, Tang S, Wang M, Wu D, Guo H. Acyl-CoA Synthetase 5 Promotes the Growth and Invasion of Colorectal Cancer Cells. *Canadian Journal of Gastroenterology and Hepatology*. 2017; 2017: 1–14.
- [46] Gharib E, Nasri Nasrabadi P, Reza Zali M. MiR-497-5p mediates starvation-induced death in colon cancer cells by targeting acyl-CoA synthetase-5 and modulation of lipid metabolism. *Journal of Cellular Physiology*. 2020; 235: 5570–5589.
- [47] Setoyama D, Fujimura Y, Miura D. Metabolomics reveals that carnitine palmitoyltransferase-1 is a novel target for oxidative inactivation in human cells. *Genes to Cells*. 2013; 18: 1107–1119.
- [48] Casals N, Zammit V, Herrero L, Fadó R, Rodríguez-Rodríguez R, Serra D. Carnitine palmitoyltransferase 1C: from cognition to cancer. *Progress in Lipid Research*. 2016; 61: 134–148.
- [49] Zaugg K, Yao Y, Reilly PT, Kannan K, Kiarash R, Mason J, *et al.* Carnitine palmitoyltransferase 1C promotes cell survival and tumor growth under conditions of metabolic stress. *Genes & Development*. 2011; 25: 1041–1051.
- [50] Carrasco P, Sahún I, McDonald J, Ramirez S, Jacas J, Gratacós E, *et al.* Ceramide levels regulated by carnitine palmitoyltransferase 1C control dendritic spine maturation and cognition. *The Journal of Biological Chemistry*. 2012; 287: 21224–21232.
- [51] Lee J, Wolfgang MJ. Metabolomic profiling reveals a role for CPT1c in neuronal oxidative metabolism. *BMC Biochemistry*. 2012; 13: 23.
- [52] Qu Q, Zeng F, Liu X, Wang QJ, Deng F. Fatty acid oxidation and carnitine palmitoyltransferase i: emerging therapeutic targets in cancer. *Cell Death & Disease*. 2016; 7: e2226.
- [53] Ricciardi MR, Mirabilli S, Allegretti M, Licchetta R, Calarco A, Torrisi MR, *et al.* Targeting the leukemia cell metabolism by the CPT1a inhibition: functional preclinical effects in leukemias. *Blood*. 2015; 126: 1925–1929.
- [54] Han S, Wei R, Zhang X, Jiang N, Fan M, Huang JH, *et al.* CPT1A/2-Mediated FAO Enhancement-A Metabolic Target in Radioresistant Breast Cancer. *Frontiers in Oncology*. 2019; 9: 1201.
- [55] Joshi M, Kim J, D’Alessandro A, Monk E, Bruce K, Elajaili H, *et al.* CPT1A Over-Expression Increases Reactive Oxygen Species in the Mitochondria and Promotes Antioxidant Defenses in Prostate Cancer. *Cancers*. 2020; 12: 3431.
- [56] Wang Y, Zeng Z, Lu J, Wang Y, Liu Z, He M, *et al.* CPT1a-mediated fatty acid oxidation promotes colorectal cancer cell metastasis by inhibiting anoikis. *Oncogene*. 2018; 37: 6025–6040.
- [57] Niu Y, Yuan H, Fu L. Aerobic exercise’s reversal of insulin resistance by activating AMPK α -ACC-CPT1 signaling in the skeletal muscle of C57BL/6 mice. *International Journal of Sport Nutrition and Exercise Metabolism*. 2010; 20: 370–380.
- [58] Li Q, Lai X, Sun L, Cao J, Ling C, Zhang W, *et al.* Antiobesity and anti-inflammation effects of Hakka stir-fried tea of different storage years on high-fat diet-induced obese mice model via activating the AMPK/ACC/CPT1 pathway. *Food & Nutrition Research*. 2020; 64.
- [59] Ceccarelli SM, Chomienne O, Gubler M, Arduini A. Carnitine palmitoyltransferase (CPT) modulators: a medicinal chemistry perspective on 35 years of research. *Journal of Medicinal Chemistry*. 2011; 54: 3109–3152.
- [60] Wang T, Fahrman JF, Lee H, Li Y, Tripathi SC, Yue C, *et al.* JAK/STAT3-Regulated Fatty Acid β -Oxidation is Critical for Breast Cancer Stem Cell Self-Renewal and Chemoresistance. *Cell Metabolism*. 2018; 27: 136–150.e5.
- [61] Huang D, Li T, Li X, Zhang L, Sun L, He X, *et al.* HIF-1-mediated suppression of acyl-CoA dehydrogenases and fatty acid oxidation is critical for cancer progression. *Cell Reports*. 2014; 8: 1930–1942.
- [62] Liu X, Feng R, Du L. The role of enoyl-CoA hydratase short chain 1 and peroxiredoxin 3 in PP2-induced apoptosis in human breast cancer MCF-7 cells. *FEBS Letters*. 2010; 584: 3185–3192.
- [63] Blomme A, Ford CA, Mui E, Patel R, Ntala C, Jamieson LE, *et al.* 2,4-dienoyl-CoA reductase regulates lipid homeostasis in treatment-resistant prostate cancer. *Nature Communications*. 2020; 11: 2508.
- [64] De Santis MC, Porporato PE, Martini M, Morandi A. Signaling Pathways Regulating Redox Balance in Cancer Metabolism. *Frontiers in Oncology*. 2018; 8: 126.
- [65] Panieri E, Santoro MM. ROS homeostasis and metabolism: a dangerous liason in cancer cells. *Cell Death & Disease*. 2016; 7: e2253.
- [66] Kong H, Chandel NS. Regulation of redox balance in cancer and T cells. *The Journal of Biological Chemistry*. 2018; 293: 7499–7507.
- [67] Lubos E, Loscalzo J, Handy DE. Glutathione peroxidase-1 in health and disease: from molecular mechanisms to therapeutic opportunities. *Antioxidants & Redox Signaling*. 2011; 15: 1957–1997.
- [68] Li X, Wang Z, Zheng Y, Guan Y, Yang P, Chen X, *et al.* Nuclear Receptor Nur77 Facilitates Melanoma Cell Survival under Metabolic Stress by Protecting Fatty Acid Oxidation. *Molecular Cell*. 2018; 69: 480–492.e7.
- [69] Carracedo A, Cantley LC, Pandolfi PP. Cancer metabolism: fatty acid oxidation in the limelight. *Nature Reviews. Cancer*. 2013; 13: 227–232.
- [70] Pike LS, Smift AL, Croteau NJ, Ferrick DA, Wu M. Inhibition of fatty acid oxidation by etomoxir impairs NADPH production and increases reactive oxygen species resulting in ATP depletion and cell death in human glioblastoma cells. *Biochimica Et Biophysica Acta*. 2011; 1807: 726–734.
- [71] Kalucka J, Bierhansl L, Conchinha NV, Missiaen R, Elia I,

- Brüning U, *et al.* Quiescent Endothelial Cells Upregulate Fatty Acid β -Oxidation for Vasculoprotection via Redox Homeostasis. *Cell Metabolism*. 2018; 28: 881–894.e13.
- [72] Jeon S, Chandel NS, Hay N. AMPK regulates NADPH homeostasis to promote tumour cell survival during energy stress. *Nature*. 2012; 485: 661–665.
- [73] Bovilla VR, Kuruburu MG, Bettada VG, Krishnamurthy J, Sukocheva OA, Thimmulappa RK, *et al.* Targeted Inhibition of Anti-Inflammatory Regulator Nrf2 Results in Breast Cancer Retardation *In vitro* and *In vivo*. *Biomedicines*. 2021; 9: 1119.
- [74] Junttila MR, de Sauvage FJ. Influence of tumour microenvironment heterogeneity on therapeutic response. *Nature*. 2013; 501: 346–354.
- [75] Lee J, Yoon J, Kim B, Kim S, Kim MA, Lim H, *et al.* Tumor evolution and intratumor heterogeneity of an epithelial ovarian cancer investigated using next-generation sequencing. *BMC Cancer*. 2015; 15: 85.
- [76] Michalek RD, Gerriets VA, Jacobs SR, Macintyre AN, MacIver NJ, Mason EF, *et al.* Cutting edge: distinct glycolytic and lipid oxidative metabolic programs are essential for effector and regulatory CD4⁺ T cell subsets. *Journal of Immunology*. 2011; 186: 3299–3303.
- [77] Pacella I, Procaccini C, Focaccetti C, Miacci S, Timperi E, Faichia D, *et al.* Fatty acid metabolism complements glycolysis in the selective regulatory T cell expansion during tumor growth. *Proceedings of the National Academy of Sciences of the United States of America*. 2018; 115: E6546–E6555.
- [78] Vats D, Mukundan L, Odegaard JI, Zhang L, Smith KL, Morel CR, *et al.* Oxidative metabolism and PGC-1 β attenuate macrophage-mediated inflammation. *Cell Metabolism*. 2006; 4: 13–24.
- [79] Huang SC, Everts B, Ivanova Y, O’Sullivan D, Nascimento M, Smith AM, *et al.* Cell-intrinsic lysosomal lipolysis is essential for alternative activation of macrophages. *Nature Immunology*. 2014; 15: 846–855.
- [80] Jiang M, Li X, Zhang J, Lu Y, Shi Y, Zhu C, *et al.* Dual Inhibition of Endoplasmic Reticulum Stress and Oxidation Stress Manipulates the Polarization of Macrophages under Hypoxia to Sensitize Immunotherapy. *ACS Nano*. 2021; 15: 14522–14534.
- [81] Cubillos-Ruiz JR, Silberman PC, Rutkowski MR, Chopra S, Perales-Puchalt A, Song M, *et al.* ER Stress Sensor XBP1 Controls Anti-tumor Immunity by Disrupting Dendritic Cell Homeostasis. *Cell*. 2015; 161: 1527–1538.
- [82] Chen H, Sun Y, Yang Z, Yin S, Li Y, Tang M, *et al.* Metabolic heterogeneity and immunocompetence of infiltrating immune cells in the breast cancer microenvironment (Review). *Oncology Reports*. 2021; 45: 846–856.
- [83] Lazar I, Clement E, Dauvillier S, Milhas D, Ducoux-Petit M, LeGonidec S, *et al.* Adipocyte Exosomes Promote Melanoma Aggressiveness through Fatty Acid Oxidation: a Novel Mechanism Linking Obesity and Cancer. *Cancer Research*. 2016; 76: 4051–4057.
- [84] Peng S, Chen D, Cai J, Yuan Z, Huang B, Li Y, *et al.* Enhancing cancer-associated fibroblast fatty acid catabolism within a metabolically challenging tumor microenvironment drives colon cancer peritoneal metastasis. *Molecular Oncology*. 2021; 15: 1391–1411.
- [85] Senni N, Savall M, Cabrero Granados D, Alves-Guerra M, Sartor C, Lagoutte I, *et al.* B-catenin-activated hepatocellular carcinomas are addicted to fatty acids. *Gut*. 2019; 68: 322–334.
- [86] Padanad MS, Konstantinidou G, Venkateswaran N, Melegari M, Rindhe S, Mitsche M, *et al.* Fatty Acid Oxidation Mediated by Acyl-CoA Synthetase Long Chain 3 is Required for Mutant KRAS Lung Tumorigenesis. *Cell Reports*. 2016; 16: 1614–1628.
- [87] Camarda R, Williams J, Goga A. In vivo Reprogramming of Cancer Metabolism by MYC. *Frontiers in Cell and Developmental Biology*. 2017; 5: 35.
- [88] Antonosante A, d’Angelo M, Castelli V, Catanesi M, Iannotta D, Giordano A, *et al.* The Involvement of PPARs in the Peculiar Energetic Metabolism of Tumor Cells. *International Journal of Molecular Sciences*. 2018; 19: 1907.
- [89] Li J, Huang Q, Long X, Zhang J, Huang X, Aa J, *et al.* CD147 reprograms fatty acid metabolism in hepatocellular carcinoma cells through Akt/mTOR/SREBP1c and P38/PPAR α pathways. *Journal of Hepatology*. 2015; 63: 1378–1389.
- [90] Chen J, Alduais Y, Zhang K, Zhu X, Chen B. CCAT1/FABP5 promotes tumour progression through mediating fatty acid metabolism and stabilizing PI3K/AKT/mTOR signalling in lung adenocarcinoma. *Journal of Cellular and Molecular Medicine*. 2021; 25: 9199–9213.
- [91] Kamarajugadda S, Becker JR, Hanse EA, Mashek DG, Mashek MT, Hendrickson AM, *et al.* Cyclin D1 represses peroxisome proliferator-activated receptor alpha and inhibits fatty acid oxidation. *Oncotarget*. 2016; 7: 47674–47686.
- [92] Patra KC, Kato Y, Mizukami Y, Widholz S, Boukhali M, Revenco I, *et al.* Mutant GNAS drives pancreatic tumorigenesis by inducing PKA-mediated SIK suppression and reprogramming lipid metabolism. *Nature Cell Biology*. 2018; 20: 811–822.
- [93] Lue H, Podolak J, Kolahi K, Cheng L, Rao S, Garg D, *et al.* Metabolic reprogramming ensures cancer cell survival despite oncogenic signaling blockade. *Genes & Development*. 2017; 31: 2067–2084.
- [94] Samovski D, Sun J, Pietka T, Gross RW, Eckel RH, Su X, *et al.* Regulation of AMPK activation by CD36 links fatty acid uptake to β -oxidation. *Diabetes*. 2015; 64: 353–359.
- [95] Assaily W, Rubinger DA, Wheaton K, Lin Y, Ma W, Xuan W, *et al.* ROS-mediated p53 induction of Lpin1 regulates fatty acid oxidation in response to nutritional stress. *Molecular Cell*. 2011; 44: 491–501.
- [96] Pan T, Zhang M, Zhang F, Yan G, Ru Y, Wang Q, *et al.* NDRG2 overexpression suppresses hepatoma cells survival during metabolic stress through disturbing the activation of fatty acid oxidation. *Biochemical and Biophysical Research Communications*. 2017; 483: 860–866.
- [97] Maimouni S, Issa N, Cheng S, Ouaari C, Cheema A, Kumar D, *et al.* Tumor suppressor RARRES1- A novel regulator of fatty acid metabolism in epithelial cells. *PLoS ONE*. 2018; 13: e0208756.
- [98] Qiao S, Koh S, Vivekanandan V, Salunke D, Patra KC, Zaganjor E, *et al.* REDD1 loss reprograms lipid metabolism to drive progression of RAS mutant tumors. *Genes & Development*. 2020; 34: 751–766.
- [99] Corn KC, Windham MA, Rafat M. Lipids in the tumor microenvironment: from cancer progression to treatment. *Progress in Lipid Research*. 2020; 80: 101055.
- [100] Martinez-Outschoorn UE, Peiris-Pagés M, Pestell RG, Sotgia F, Lisanti MP. Cancer metabolism: a therapeutic perspective. *Nature Reviews. Clinical Oncology*. 2017; 14: 11–31.
- [101] Wang J, Xiang H, Lu Y, Wu T, Ji G. The role and therapeutic implication of CPTs in fatty acid oxidation and cancers progression. *American Journal of Cancer Research*. 2021; 11: 2477–2494.
- [102] Selby PL, Sherratt HS. Substituted 2-oxiranecarboxylic acids: a new group of candidate hypoglycaemic drugs. *Trends in Pharmacological Sciences*. 1989; 10: 495–500.
- [103] Cabrero A, Merlos M, Laguna JC, Carrera MV. Downregulation of acyl-CoA oxidase gene expression and increased NF-kappaB activity in etomoxir-induced cardiac hypertrophy. *Journal of Lipid Research*. 2003; 44: 388–398.
- [104] Rufer AC, Thoma R, Hennig M. Structural insight into function and regulation of carnitine palmitoyltransferase. *Cellular*

and Molecular Life Sciences. 2009; 66: 2489–2501.

- [105] Conti R, Mannucci E, Pessotto P, Tassoni E, Carminati P, Giannessi F, *et al.* Selective reversible inhibition of liver carnitine palmitoyl-transferase 1 by teglicar reduces gluconeogenesis and improves glucose homeostasis. *Diabetes*. 2011; 60: 644–651.
- [106] Mao S, Ling Q, Pan J, Li F, Huang S, Ye W, *et al.* Inhibition of CPT1a as a prognostic marker can synergistically enhance the antileukemic activity of ABT199. *Journal of Translational Medicine*. 2021; 19: 181.
- [107] Huang D, Chowdhury S, Wang H, Savage SR, Ivey RG, Kennedy JJ, *et al.* Multiomic analysis identifies CPT1a as a potential therapeutic target in platinum-refractory, high-grade serous ovarian cancer. *Cell Reports Medicine*. 2021; 2: 100471.
- [108] Jariwala N, Mehta GA, Bhatt V, Hussein S, Parker K, Yunus N, *et al.* CPT1a and fatty acid β -oxidation are essential for tumor cell growth and survival in hormone receptor-positive breast cancer. *NAR Cancer*. 2021; 3: zcab035.
- [109] Samudio I, Harmancey R, Fiegl M, Kantarjian H, Konopleva M, Korchin B, *et al.* Pharmacologic inhibition of fatty acid oxidation sensitizes human leukemia cells to apoptosis induction. *The Journal of Clinical Investigation*. 2010; 120: 142–156.
- [110] Mashima T, Sato S, Okabe S, Miyata S, Matsuura M, Sugimoto Y, *et al.* Acyl-CoA synthetase as a cancer survival factor: its inhibition enhances the efficacy of etoposide. *Cancer Science*. 2009; 100: 1556–1562.
- [111] Xu L, Xia H, Ni D, Hu Y, Liu J, Qin Y, *et al.* High-Dose Dexamethasone Manipulates the Tumor Microenvironment and Internal Metabolic Pathways in Anti-Tumor Progression. *International Journal of Molecular Sciences*. 2020; 21: 1846.
- [112] Freitas RDS, Campos MM. Protective Effects of Omega-3 Fatty Acids in Cancer-Related Complications. *Nutrients*. 2019; 11: 945.
- [113] Spencer L, Mann C, Metcalfe M, Webb M, Pollard C, Spencer D, *et al.* The effect of omega-3 FAs on tumour angiogenesis and their therapeutic potential. *European Journal of Cancer*. 2009; 45: 2077–2086.
- [114] Briscoe CP, Tadayyon M, Andrews JL, Benson WG, Chambers JK, Eilert MM, *et al.* The orphan G protein-coupled receptor GPR40 is activated by medium and long chain fatty acids. *The Journal of Biological Chemistry*. 2003; 278: 11303–11311.
- [115] Hirasawa A, Tsumaya K, Awaji T, Katsuma S, Adachi T, Yamada M, *et al.* Free fatty acids regulate gut incretin glucagon-like peptide-1 secretion through GPR120. *Nature Medicine*. 2005; 11: 90–94.
- [116] Lee CY, Sit W, Fan S, Man K, Jor IW, Wong LL, *et al.* The cell cycle effects of docosahexaenoic acid on human metastatic hepatocellular carcinoma proliferation. *International Journal of Oncology*. 2010; 36: 991–998.
- [117] Hennessy AA, Ross RP, Devery R, Stanton C. The health promoting properties of the conjugated isomers of α -linolenic acid. *Lipids*. 2011; 46: 105–119.
- [118] Calder PC. Omega-3 fatty acids and inflammatory processes. *Nutrients*. 2010; 2: 355–374.
- [119] Pizato N, Bonatto S, Yamazaki RK, Aikawa J, Nogata C, Mund RC, *et al.* Ratio of n6 to n-3 fatty acids in the diet affects tumor growth and cachexia in Walker 256 tumor-bearing rats. *Nutrition and Cancer*. 2005; 53: 194–201.
- [120] de Luis DA, Aller R, Izaola O, Gonzalez Sagrado M, Conde R, de la Fuente B, *et al.* Effect of Lys656Asn Polymorphism of Leptin Receptor Gene on Cardiovascular Risk Factors and Serum Adipokine Levels after a High Polyunsaturated Fat Diet in Obese Patients. *Journal of Clinical Laboratory Analysis*. 2015; 29: 432–436.
- [121] Maes M, Mihaylova I, Leunis J. In chronic fatigue syndrome, the decreased levels of omega-3 poly-unsaturated fatty acids are related to lowered serum zinc and defects in T cell activation. *Neuro Endocrinology Letters*. 2005; 26: 745–751.
- [122] Hichami A, Grissa O, Mrizak I, Benammar C, Khan NA. Role of T-Cell Polarization and Inflammation and their Modulation by n-3 Fatty Acids in Gestational Diabetes and Macrosomia. *Journal of Nutrition and Metabolism*. 2016; 2016: 3124960.
- [123] Jaganjac M, Cindrić M, Jakovčević A, Žarković K, Žarković N. Lipid peroxidation in brain tumors. *Neurochemistry International*. 2021; 149: 105118.
- [124] Lee J, Nam M, Son HY, Hyun K, Jang SY, Kim JW, *et al.* Polyunsaturated fatty acid biosynthesis pathway determines ferroptosis sensitivity in gastric cancer. *Proceedings of the National Academy of Sciences*. 2020; 117: 32433–32442.
- [125] Cohen G, Riahi Y, Sasson S. Lipid peroxidation of polyunsaturated fatty acids in normal and obese adipose tissues. *Archives of Physiology and Biochemistry*. 2011; 117: 131–139.
- [126] Riahi Y, Cohen G, Shamni O, Sasson S. Signaling and cytotoxic functions of 4-hydroxyalkenals. *American Journal of Physiology. Endocrinology and Metabolism*. 2010; 299: E879–E886.
- [127] Khojastehfard M, Dolatkah H, Somi M, Nazari Soltan Ahmad S, Estakhri R, Sharifi R, *et al.* The Effect of Oral Administration of PUFAs on the Matrix Metalloproteinase Expression in Gastric Adenocarcinoma Patients Undergoing Chemotherapy. *Nutrition and Cancer*. 2019; 71: 444–451.
- [128] Rashidi M, Khalilnezhad A, Amani D, Jamshidi H, Muhammadnejad A, Bazi A, *et al.* Umbelliprenin shows antitumor, antiangiogenesis, antimetastatic, anti-inflammatory, and immunostimulatory activities in 4T1 tumor-bearing Balb/c mice. *Journal of Cellular Physiology*. 2018; 233: 8908–8918.
- [129] Ravnskjaer K, Frigerio F, Boergesen M, Nielsen T, Maechler P, Mandrup S. PPARdelta is a fatty acid sensor that enhances mitochondrial oxidation in insulin-secreting cells and protects against fatty acid-induced dysfunction. *Journal of Lipid Research*. 2010; 51: 1370–1379.
- [130] Rao CV, Hirose Y, Indranie C, Reddy BS. Modulation of experimental colon tumorigenesis by types and amounts of dietary fatty acids. *Cancer Research*. 2001; 61: 1927–1933.
- [131] Amirrasoul H, Asefy Z, Kazerouni F, Taghikhani M. Study of serum cystatin C as a reliable marker for metabolic syndrome. *Iranian Journal of Diabetes and Lipid Disorders*. 2011; 10: 1–4.
- [132] Caro P, Kishan AU, Norberg E, Stanley IA, Chapuy B, Ficarro SB, *et al.* Metabolic signatures uncover distinct targets in molecular subsets of diffuse large B cell lymphoma. *Cancer Cell*. 2012; 22: 547–560.
- [133] Ito K, Carracedo A, Weiss D, Arai F, Ala U, Avigan DE, *et al.* A PML–PPAR- δ pathway for fatty acid oxidation regulates hematopoietic stem cell maintenance. *Nature Medicine*. 2012; 18: 1350–1358.
- [134] Carracedo A, Weiss D, Leliaert AK, Bhasin M, de Boer VCJ, Laurent G, *et al.* A metabolic prosurvival role for PML in breast cancer. *Journal of Clinical Investigation*. 2012; 122: 3088–3100.
- [135] Zordoky BN, Nagendran J, Pulinilkunnil T, Kiensberger PC, Masson G, Waller TJ, *et al.* AMPK-dependent inhibitory phosphorylation of ACC is not essential for maintaining myocardial fatty acid oxidation. *Circulation Research*. 2014; 115: 518–524.