Review

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

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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 Mg²⁺, 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 [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-κB [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
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 \[47\].

CPT1 family consists of three subtypes: CPT1A, CPT1B, and CPT1C. CPT1C is mainly expressed 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-
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 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-1α 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 peroxidas 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]. Nissm 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 up-regulated 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
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 PPARα 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 PPARα 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 control 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 focused 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-κB 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 hematologic 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 1. FAO was regulated by oncogenes and tumor suppressor genes.

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

PPARα, 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-1α, 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.
<table>
<thead>
<tr>
<th>Agent</th>
<th>Target</th>
<th>Tumor type and mechanism</th>
<th>Risks</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Etomoxir</strong></td>
<td>CPT1A and CPT1B</td>
<td>Colorectal cancer: CPT1↓-anoikis↑/anchorage-independent growth↑</td>
<td>High liver transaminase level, cardiac hypertrophy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Leukemia: FAO↓-Bcl-2↓</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nasopharyngeal: PGC1α+CEBPB-CPT1A↑-FAO↑</td>
<td></td>
</tr>
<tr>
<td>ST1326</td>
<td>CPT1A</td>
<td>Leukemia: CPT1A↓-Mcl-1↓</td>
<td>Hepatotoxicity</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Breast cancer: JAK/STAT3↓-CPT1B↓-FAO↓</td>
<td>Transient effects: Predominantly are dizziness, headache, and nausea</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ovarian cancer: CPT1↓-FAO/OXPHOS↓</td>
<td>Long term side effects: Hepatotoxicity and neurotoxicity</td>
</tr>
<tr>
<td>Perhexiline</td>
<td>CPT1 and CPT2</td>
<td>Leukemia: CPT1↓-cardiolipin↓</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ovarian cancer: CPT1↓-FAO/OXPHOS↓</td>
<td></td>
</tr>
<tr>
<td>Ranolazine</td>
<td>FAO/3-KAT</td>
<td>Breast cancer: FAO↓-tumor growth and cell proliferation↑/ apoptosis↑</td>
<td>Excessive product can cause dizziness, nausea, vomiting, diplopia, paresthesia, confusion and loss of delayed consciousness</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Prostate cancer: FAO↓-CD8+ T-cells Tim3 content↓/macrophages↑</td>
<td></td>
</tr>
<tr>
<td>6-gingerol</td>
<td>CPT-1/FASN</td>
<td>Colorectal cancer: FASN↓-PI3K/AKT/mTOR↓</td>
<td>nausea, stomachache</td>
</tr>
<tr>
<td></td>
<td></td>
<td>FASN-overproduction of malonyl-CoA↓-CPT1↓-ROS↑</td>
<td></td>
</tr>
</tbody>
</table>

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; PGC1α, PPAR coactivator-1α; 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; PPARα, peroxisome proliferator-activated receptor alpha.
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-κB [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]. Furhter, Iistfan 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, enzymatic or by non-enzymatic oxidation, respectively [123]. Lipid peroxidation was accumulated in cancer cells inducing iron-dependent cell death, which was called ferroptosis.
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-hydroxynonenals, in particular 4-hydroxynonenal [125]. Those metabolites showed cytotoxic effect to kill tumor cells [126]. (6) Other mechanims. 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 PPARγ 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 NAPDH. 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-ketoyl CoA thiolase; FASN, fatty acid synthetase; PGC1α, PPAR coactivator-1α; CEBPB, CCAAT enhancer binding protein β; JAK/STAT3, janus kinase (JAK)/Signal transducer and activator of transcription 3 (STAT3); OXPHOS, oxidative phosphorylation; PPARo, 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-1α, 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-xsmx0485 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.

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