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Fatty acid oxidation: An emerging facet of metabolic transformation in cancer

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Abstract

Cancer cells undergo metabolic reprogramming such as enhanced aerobic glycolysis, mutations in the tricarboxylic acid cycle enzymes, and upregulation of *de novo* lipid synthesis and glutaminolysis. These alterations are pivotal to the development and maintenance of the malignant phenotype of cancer cells in unfavorable tumor microenvironment or metastatic sites. Although mitochondrial fatty acid β-oxidation (FAO) is a primary bioenergetic source, it has not been generally recognized as part of the metabolic landscape of cancer. The last few years, however, have seen a dramatic change in the view of cancer relevance of the FAO pathway. Many recent studies have provided significant evidence to support a “lipolytic phenotype” of cancer. FAO, like other well-defined metabolic pathways involved in cancer, is dysregulated in diverse human malignancies. Cancer cells rely on FAO for proliferation, survival, stemness, drug resistance, and metastatic progression. FAO is also reprogrammed in cancer-associated immune and other host cells, which may contribute to immune suppression and tumor-promoting microenvironment. This article reviews and puts into context our current understanding of multi-faceted roles of FAO in oncogenesis as well as anti-cancer therapeutic opportunities posed by the FAO pathway.

Keywords

Fatty acid β-oxidation; Cancer; Lipolytic phenotype; ATP; NADPH

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Conflicts of interest

The authors declare that they have no conflicts of interest with the contents of this article.

1. Introduction

During the process of transformation from normal precursors, cancer cells acquire the ability of rewiring the metabolism of their own as well as diverse types of immune and stromal cells in the tumor microenvironment to meet the demands of uncontrolled growth and metastatic progression [1]. As early as in 1920s, Warburg observed that neoplastic cells prefer glycolysis to form lactate as the final product instead of mitochondrial oxidation, even in the presence of abundant oxygen [2]. Since then, much progress has been made in understanding metabolic reprogramming in cancer. Although limited in generating ATP, the Warburg effect of aerobic glycolysis offers an advantage in supplying cancer cells with quick ATP and biosynthetic intermediates for rapid proliferation [3]. In addition to the Warburg effect, increases in glutaminolysis and *de novo* fatty acid synthesis are also prominent hallmarks of cancer. Glutaminolysis feeds the tricarboxylic acid (TCA) cycle and contributes nitrogen and carbon skeletons to nucleotide and amino acid synthesis [4]. On the other hand, heightened *de novo* fatty acid synthesis from acetyl-CoA and reducing power (NADPH) is required for membrane biogenesis in rapidly dividing cancer cells [5].

In contrast to the lipogenic phenotype, the role of mitochondrial fatty acid β-oxidation (FAO) in cancer has not been well defined. Although FAO is one of the major sources of ATP production, most previous studies of cancer bioenergetics have focused on the Warburg effect [3,6,7]. In addition to ATP, FAO is involved in production of cytosolic NADPH [8–10], the reducing power to support biosynthesis and to counteract oxidative stress. However, there are other alternative or redundant routes to replenish cytosolic NADPH including the pentose phosphate pathway and the conversion of malate to pyruvate catalyzed by malic enzyme [10]. Another argument against the oncogenic involvement of FAO is that lipogenesis and FAO are mutually exclusive processes coordinated by the level of malonyl-CoA [10–12]. Malonyl-CoA, an intermediate of fatty acid biosynthesis, acts as an allosteric inhibitor of the FAO rate-setting enzyme carnitine palmitoyltransferase 1 (CPT1), presumably preventing FAO from occurring simultaneously with active lipogenesis [10–12]. Finally, in sharp contrast to the well-studied glycolysis, glutaminolysis, and lipogenesis cascades where key enzymes or their regulators are known to be overexpressed, mutated, or dysregulated in connection to oncoproteins or tumor suppressors [13–18], limited evidence suggests that the FAO pathway is “reprogrammed” in cancer or pathophysiologically linked to activation of specific oncogenes or loss of tumor suppressors. However, recent advances in the field have substantially changed the view on the relevance of FAO to cancer. Multiple lines of evidence now suggest that abnormal FAO activity is involved in diverse aspects of oncogenesis [19]. Many cancer cells rely on FAO for proliferation, survival, stemness, drug resistance or metastasis. The key enzymes or regulators of FAO have therefore emerged as promising targets for cancer therapy. The review aims to dissect the multi-faceted roles of FAO in cancer and non-cancerous cells in the tumor microenvironment.

2. FAO basics

FAO is a multi-step catabolic process that allows for the mitochondrial conversion of long chain fatty acids into acetyl-CoA which will be fully oxidized through the TCA cycle and the electron transport chain (ETC) to produce ATP (Fig. 1). Fatty acids enter mammalian

cells through fatty acid transport proteins such as CD36 and fatty-acid-binding proteins that facilitate the transfer of fatty acids between extra-and intra-cellular membranes [20]. Before shuttling into the mitochondrion for oxidation, fatty acids are activated to fatty acyl-CoA by fatty acyl CoA synthetase. On the outer mitochondrial membrane, fatty acyl-CoA is converted to fatty acyl-carnitine by the action of CPT1. Carnitine/acylcarnitine translocase (CACT), located on the inner mitochondrial membrane shuttles acylcarnitine into the mitochondrial matrix. Carnitine palmitoyltransferase II (CPT2) on the matrix side of the inner membrane reconverts acylcarnitine to acyl-CoA. In the mitochondrion, acyl CoA is cleaved into acetyl CoA by a repeated 4-step cycle catalyzed sequentially by activities of acyl-CoA dehydrogenase, hydroxyacyl-CoA dehydrogenase, enoyl-CoA hydratase and 3-ketoacyl-CoA thiolase (3-KAT). The breakdown product acetyl-CoA enters the TCA cycle which is coupled to oxidative phosphorylation to generate ATP (Fig. 1).

In addition to bioenergetic production, FAO-generated acetyl CoA enters TCA to form citrate, which can be exported to the cytoplasm to engage NADPH-producing oxidation of isocitrate to α-ketoglutarate by isocitrate dehydrogenase [10] (Fig. 1). Indeed, as demonstrated by several groups, FAO is involved in regulation of cytosolic NADPH [8–10], the reducing agent to support biosynthesis and redox homeostasis. Several recent studies have identified FAO-generated acetyl CoA to be carbon source for incorporation into aspartate (a nucleotide precursor), uridine monophosphate (a precursor of pyrimidine nucleoside triphosphates) and subsequently cellular DNA in endothelial cells [21–23] (Fig. 1). However, this catabolic fate of fatty acid has not been extrapolated to other cell types or tissues yet.

The cellular FAO rate is regulated at multiple sites of fatty acid trafficking and the subsequent breakdown via transcriptional and post-transcriptional mechanisms. CPT1 is considered to be the rate-limiting enzyme that is allosterically inhibited by malonyl-CoA [21]. There are three members of the CPT1 family, CPT1A (liver form), CPT1B (muscle form) and CPT1C (brain form, enzymatic inactive) encoded by three paralogous genes. Compared to CPT1B, CPT1A is 30–100-fold more resistant to allosteric inhibition by malonyl CoA [12,24] and is therefore more likely to be enzymatically active in cancer cells exhibiting high activities of both lipogenesis and FAO. Although the atypical CPT1C has been reported to be expressed in various cell types and functions to cope with metabolic stresses [25,26], the location in endoplasmic reticulum (ER) of neurons and the lack of an enzymatic activity in mitochondria make it unlikely that CPT1C plays a direct role in mitochondrial FAO [21,27,28].

The most prominent transcriptional regulators of FAO are peroxisome proliferator-activated receptors (PPARs) of the ligand-activated nuclear receptor superfamily. They act as environmental fat sensors and transcriptional activators of FAO enzymes [29]. PPARα has been shown to stimulate CPT1A transcription in the liver by binding to the peroxisome proliferator response element on the *CPT1A* gene promoter [30]. PPARδ drives expression of various FAO enzymes to promote FAO in hematopoietic stem cells [31]. In addition, the FAO rate is tightly controlled by the activity of AMP-activated protein kinases (AMPKs). AMPKs regulate cellular metabolic states by shutting down energy-consuming anabolic processes and activating energy-yielding catabolic ones [32]. Activation of AMPK

stimulates FAO primarily through phosphorylation and inactivation of its downstream target acetyl-CoA carboxylase (ACC) [33], the enzyme that synthesizes malonyl CoA to inhibit CPT1 and FAO in physiological conditions [10–12]. It seems that two isoforms of ACC (ACC1 and ACC2) differ in cellular locations and functions [34]. ACC1 is present in the cytosol and produces malonyl-CoA mainly as substrate for fatty acid synthesis. In contrast, ACC2 is located on the outer mitochondrial membrane responsible for synthesizing malonyl-CoA serving as a CPT1 inhibitor [35]. In cancer cells, ACC2 has been reported to be repressed by sirtuin-mediated histone deacetylation or loss of prolyl hydroxylase 3 [36,37], potentially explaining the simultaneous occurrence of active lipogenesis and FAO in neoplastic cells.

3. Dysregulation of FAO in cancer

A critical question concerning the role of FAO in cancer pathogenicity is whether the FAO enzymes or their regulators are dysregulated as those in the glycolysis and glutaminolysis pathways. Mutations of FAO enzymes have not been detected at significant rates in cancer. Substantial studies, however, have revealed overexpression of various FAO enzymes including CD36 [38], CPT1A [39,40], CPT1B [40,41], CPT1C [25], CPT-2 [40], carnitine transporter CT2 [42], and Acyl-CoA synthetase long chain 3 [43] in multiple malignancies relative to their normal counterparts. For instance, 3- to 4-fold increases in expression of CPT-1 A, CPT-1B, and CPT-2 were observed in chronic lymphocytic leukemia (CLL) cells compared to normal stromal cells [40]. Over-expression of some FAO enzymes such as CPT1A correlates strongly with poor patient outcomes of cancer including acute myeloid leukemia (AML) and ovarian cancer [39,44].

Consistent with cancer-associated overexpression of key FAO enzymes, many types of cancer exhibit a high activity of FAO such as KRas mutant lung cancer [43], triple negative breast cancer (TNBC) [45,46], AML [42], hepatitis B-induced hepatocellular carcinoma [47], glioma [48], and low-grade astrocytoma [48]. Most significantly, several groups have recently reported that expression of a number of FAO enzymes was activated by prominent oncoproteins. For instance, a metabolomics study revealed that FAO enzymes and metabolic intermediates were upregulated in a subset of TNBC that overexpress c-Myc [49], an oncogenic transcription factor disproportionately elevated in TNBC. Inhibition of FAO blocked Myc-driven tumorigenesis [49]. Such a role of c-Myc in activation of FAO has been further confirmed in MCF-10A-Ras cells where FAO enzymes were upregulated by the c-Myc/PGC-1β/ERRα signaling [50]. In addition, another group recently identified CPT1B as a downstream target of the JAK/STAT3 transcription factor in breast cancer. The JAK/STAT3-CPT1B axis was activated in response to mammary adipocyte-derived leptin [41]. Collectively these studies suggest that FAO is activated in cancer as a result of c-Myc over-expression or JAK/STAT3 activation. Furthermore, FAO can act upstream of oncoproteins to regulate their functions. In metastatic TNBC with elevated levels of FAO, the knocking down of CPT enzymes resulted in inhibition of Src and Src-mediated metastasis [51], suggesting that FAO activity may be instrumental in maintaining activated status of certain oncoproteins, another mode of FAO involvement in oncogenic processes.

4. Reliance on FAO for cancer cell growth and survival

Multiple types of cancer have been demonstrated to rely on FAO for cell growth and survival. Most previous observations implicating FAO in oncogenesis were based on pharmacological inhibition of CPT1. CPT1 inhibitors suppressed growth and/or viability of cell lines of myeloid leukemia [9,52], ovarian cancer [44], hepatocellular carcinoma [53], prostate cancer [54,55], glioma [8], and multiple myeloma [56]. The effects of these CPT1 inhibitors in ovarian [44] and prostate [54] cancer cells were validated by siRNA or shRNA silencing approach. In an integrated genomics study published in 2014, Gatza et al. identified 8 genes essential for the luminal subtype of breast cancer [57]. CPT1A, but not other CPT1 isoforms, was among this short panel of the 8 growth-dependent genes [57]. Mechanistically, many types of cancer seem to rely on FAO as an essential ATP source to fuel rapid growth [8,9,44,58]. This is particularly relevant in ovarian cancer wherein inhibition of CPT1 reduced cellular ATP levels and activated AMPK, which was associated with cell cycle arrest at G1/G0 [44]. The meta-static spread of ovarian cancer characteristically first involves the abdominal fatty tissue of the omentum. Upon interactions, fatty acids are hydrolyzed and released from omental adipocytes [58]. Ovarian tumor cells depend on these adipocyte-derived fatty acids to support rapid growth and continued peritoneal dissemination [58]. More recent studies from colon and breast cancer suggest that cancer cells have a clear predilection for spreading to adipocyte-rich tissues [59,60]. Uptake of fatty acids from surrounding adipocytes promoted FAO in cancer cells [59,61] (Fig. 2).

Compared to other malignancies, prostate cancer is less glycolytic [62,63]. The ^{18}F-fluorodeoxyglucose with positron emission tomography (FDG-PET) has limited value in diagnostic imaging of prostate cancer [64–66]. Pharmacological interference with FAO led to not only growth inhibition but also metabolic switch to more glycolysis and therefore enhanced sensitivity to FDG-PET scan as demonstrated in mouse xenografts of human prostate cancer cell lines [54,55]. Glioma may be another example of cancer with limited glycolysis. Less than 50% of acetyl-CoA in glioma was derived from glucose as demonstrated in a study of human nuclear magnetic resonance (NMR) spectroscopy [67]. Pharmacological inhibition of FAO decreased cell proliferation, Ki-67 positive index, and S + G2/M phases of cell cycle, as well as delayed emergence and progression of glioma *in vivo* [48]. In glioma patient-derived tumor xenografts, FAO was demonstrated to support major respiration activity compared to glucose catabolism [48].

Besides the impact on cellular proliferation, inhibition of FAO was also linked to induction of apoptosis or reduced viability in cell lines of myeloid leukemia, glioma, and hepatocellular carcinoma [47,48,52]. The anti-survival effect of FAO inhibition was most likely resulted from perturbation of NADPH homeostasis, reactive oxidative species (ROS) production, oxidative stress, and/or mitochondrial damages [9,52]. There is also evidence that FAO flux or FAO enzymes regulated expression or functions of the Bcl-2 family proteins or other death/survival mediators [68,69]. Other studies suggested the involvement of FAO metabolic intermediates as functional effectors of cell survival [8,9,22]. In addition, FAO inhibition could lead to cytotoxic accumulation of long-chain fatty acids (lipotoxicity) and the subsequent ER stress, and ultimately cell death [70,71].

5. FAO and metastasis

Cancer metastasis encompasses multiple steps including local invasion of tumor cells into adjacent tissues, intravasation of cancer cells into blood or lymphatic vessels, survival of cancer cells in the circulatory and lymphatic systems, extravasation, and colonization of cancer cells in target organs. FAO has been implicated in promotion of many of these steps leading to a metastatic phenotype (Fig. 2) [22,23,38,59,72,73].

Local invasion of cancer cells is facilitated by epithelial-to-mesenchymal transition (EMT), a process critical for normal embryonic morphogenesis. A metabolomics profiling study of immortalized breast epithelial cell lines with stem cell properties and their EMT-derived mesenchymal phenotype revealed that FAO was more active, driven by PPAR, in the mesenchymal phenotype, whereas amino acid metabolism and glycolysis were at higher levels in the epithelial counterpart [74]. In line with this, FAO induction in colon cancer cells by co-cultivation with adipocytes was associated with induction of EMT as indicated by decreased E-cadherin but increased vimentin expression [59].

Once migration into the lumina of lymphatic or blood vessels, the first challenge for the survival of cancer cells is the detachment-triggered metabolic stress. When detached from the extracellular matrix, normal or non-metastatic cells undergo anoikis, a caspase-mediated apoptosis [72,73,75]. The detachment results in ATP deficiency as a result of decreased glucose uptake and catabolism, associated with a decrease in NADPH and increase in ROS [72]. Several independent studies showed that cancer cells upregulated FAO to overcome anoikis [73,75,76]. Upon loss of attachment, FAO in breast cancer cells was stimulated to increase ATP and cell survival by overexpression of the promyelocytic leukemia (PML) gene [75]. The PML protein is a driver of FAO as further elaborated below.

FAO may also contribute to the development of the metastatic phenotype through its potential role in regulation of cancer stem cells (CSCs). CSCs are capable of self-renewing and differentiating into the non-stem cancer cells. They are also responsible for tumor metastasis and resistance to therapies. Ito et al. reported that the PML-PPARδ-FAO axis was required for asymmetric division of hematopoietic stem cells [31]. Genetic interference with this pathway resulted in the exhaustion of the stem cell pool. Another work showed that a deficient mutation in trimethyllysine hydroxylase, a key enzyme in biosynthesis of the CPT1 substrate carnitine, reduced neural stem cells in the mouse embryonic neocortex, an abnormality shared by silencing CPT1A or limiting fatty acid availability [77]. These observations indicate that normal tissue stem cells benefit from active FAO for phenotypic maintenance.

Such a role for FAO in cancer stemness has gained some recent attention. The first observation alluding to the possibility was from Samudio et al. who reported that treatment with etomoxir decreased the number of quiescent leukemia progenitor cells in approximately 50% of primary human AML samples [52]. Another study reported that leukemic stem cells could be divided into two distinct populations based on the expression of the fatty acid transporter CD36 [78]. CD36-positive leukemic stem cells displayed a higher FAO rate and more resistance to drugs than CD36-negative leukemic stem cells, indicating that FAO

activity was a determinant of cancer stem cell properties. In a most recent study, Wang et al. reported that the Leptin-JAK/STAT3 pathway upregulated expression of CPT1B, FAO activity and stem cell self-renewal in breast cancer [41].

6. FAO in drug resistance

Systemic treatment of cancer inevitably induces drug resistance of tumor cells, which prevents most cancer therapies from being curative [79]. Accumulating studies showed that FAO activation is an important mechanism employed by cancer cells to develop drug resistance (Fig. 2). FAO activity has been demonstrated to be elevated in cancer cells in response to treatment with the therapeutic reagents dexamethasone [80], L-asparaginase [81], imatinib or rapamycin [82,83], cytarabine [84], and tamoxifen [85].

Multiple mechanisms have been proposed to explain drug-induced FAO activation and FAO-mediated drug resistance. Dexamethasone induced FAO in CLL cells via upregulation of PPARα [80]. Treatment with L-asparaginase, a chemotherapeutic agent for childhood acute lymphoblastic leukemia, inhibited the RagB (a Ras-related GTPase)-mTORC1 pathway, leading to metabolic stress and FAO activation [81]. Intriguingly, although it has been previously shown to be enzymatically inactive, CPT1C is upregulated and involved in survival of breast, brain, and lung cancers, especially under conditions of hypoxia or nutrient stress [25,86]. Recently, CPT1C upregulation was found to be linked to increased FAO in BCR-ABL positive leukemia cells, responsible for imatinib or rapamycin resistance [82,83]. Although the functional relationship of CPT1C to FAO is yet to be elucidated, these studies make CPT1C, an atypical isoform of CPT1, a promising anti-cancer target. In AML cells, resistance to cytarabine was found to be mediated by increases in expression of the fatty acid transporter CD36 and FAO rates [84]. In addition, retinoblastoma (Rb) deficiency in breast cancer cells upregulated FAO-related genes, which might contribute to resistance to tamoxifen [85]. In these studies, addition of FAO inhibitors completely or partially inhibited the drug resistances of cancer cells [80,81,83,84,87,88].

7. Beyond cancer cells

While the crucial role for FAO in cancer cells has been recognized, the emerging correlative studies also suggest association of FAO with tumor-promoting functions of non-cancerous cells in the tumor micro-environment (Fig. 2). For example, it was recently shown that FAO was involved in supporting cellular DNA synthesis of endothelium [22,23], suggesting that blockade of FAO may prevent vessel sprouting and tumor angiogenesis through targeting endothelial cells within a tumor.

Depending on the cellular context, FAO activity may be immune promoting or inhibitory. Cellular immune responses against tumors are typically mediated by CD8 T cells. Tumor necrosis factor receptor-associated factor 6 (TRAF6) regulated long-lived memory CD8 T cell development by promoting FAO [89]. Similarly, activation of FAO was reported to be a mechanism by which IL-15 regulated the memory phenotype of $CD8^+$ T cells [90]. Restoration of FAO increased CD8 memory cells and improved the potency of anticancer

vaccination [89]. It will be interesting to determine whether FAO is repressed in CD8 memory cells in cancer.

On the other hand, activation of the FAO pathway in other immune cells, such as regulatory $CD4^+$ T cells (T_{reg}), M2 macrophages, myeloid-derived suppressor cells (MDSCs), and dendritic cells (DCs), may be a potential mechanism for cancer cells to escape from immune surveillance. Distinct subsets of helper $CD4^+$ T cells require specific metabolic programs to meet their differing energetic and biosynthetic demands. Effector $CD4^+$ T cells (T_{eff}) relied on glycolytic metabolism, whereas T_{reg} demonstrated higher levels of FAO [91]. Etomoxir suppressed T_{reg} population while addition of exogenous fatty acids promoted their differentiation or survival [91]. High infiltration of T_{reg} cells in tumors correlated with poor prognosis in multiple cancers [92]. Several groups reported that M2 macrophages used FAO to fuel mitochondrial oxidative phosphorylation. Inhibition of FAO could prevent M2 polarization of macrophages [93,94], Heightened FAO is believed to provide survival advantage to M2 macrophages over M0 and M1 phenotypes [94]. However, a recent report using a genetic model disrupting FAO in the myeloid lineage did not support such a function of FAO in M2 polarization and differentiation [95]. Intriguingly, the rate of FAO in MDSCs, a major component of tumor-associated immunosuppressive network [96,97], correlated positively with their T-cell inhibitory activity [98]. A recent study showed that FAO inhibition could delay tumor growth and enhance the antitumor effect of adoptive T-cell therapy [98]. Earlier studies indicated that abnormal lipid accumulation in tumor-associated DCs contributed to their tolerogenic phenotype [99,100]. The dysfunction of these DCs was thought to be due to the excessive lipid burden but the results could be equally explained by the role of the abundant intracellular fat store in supplying substrates for active FAO, which could metabolically and functionally alter tumor-associated DCs. Indeed, a more recent observation demonstrated that FAO increased the activity of indoleamine 2,3-dioxgenase-1 (IDO), culminating in enhanced tolerization of DCs and generation of T_{reg} cells [101]. Blockade of FAO enhanced antitumor immunity and improved the efficacy of anti-PD-1 inhibitors [101].

8. FAO as a druggable metabolic pathway for cancer treatment

Physiologically, the FAO flux in normal tissues including the high energy-demanding skeletal muscle and heart as well as the liver, the central organ of lipid metabolism, is controlled by the availability of glucose in the circulation [102]. FAO is activated when the environmental glucose becomes limited. On the other hand, inhibition of FAO switches energy metabolism from fatty acid to glucose oxidation, a condition typically alleviating oxygen shortage and insulin resistance, as exemplified by therapeutic benefits of a number of FAO inhibitors in patients with type II diabetes or myocardial ischemia [103–108]. Apparently, normal tissues differ from cancer. FAO is required constitutively for rapid proliferation of malignant cells as recently shown in multiple types of cancer [19,63]. Differential dependence of cancerous and normal tissues on FAO could provide a sufficient therapeutic window to target cancer cells with little side effect on normal ones. The cancer-special dependence on FAO may be related to the glycolytic phenotype of neoplastic cells. Unlike mitochondrial glucose oxidation, glycolysis is limited in ATP generation [3,6] and can’t fully replace the bioenergetic function of FAO. This may explain why glycolysis and

FAO occur simultaneously in cancer. The hyperactive catabolism of both glucose and fatty acids could be also a major cause of weight loss and cachexia associated with cancer progression in patients [109,110].

FAO inhibitors are generally safe and well tolerated *in vivo* [103–108] (Table 1). Some of them belong to a new class of drugs termed “metabolic modulators” which are already in clinical use for treatment of angina pectoris in USA or other parts of the world [10,104–108]. These include perhexiline (CPT1/CPT2 dual inhibitor) and trimetazidine or ranolazine [inhibitor of 3-KAT of the trifunctional protein TFP (hydroxyacyl-CoA dehydrogenase/enoyl-CoA hydratase/3-KAT)] [106,107] (Table 1). The TFP complex catalyzes the last three steps of β-oxidation within the mitochondrion. Although the exact targets of these medicines remain controversial, substantial *in vitro* and *in vivo* data indicate that their clinical benefits are at least partially mediated through inhibiting FAO to improve myocardial glucose oxidation [10,104–108]. However, the activities of these metabolic modulators against malignant diseases have not been tested. If proved effective, these medicines could be readily repurposed to treat cancer or as adjuvants to enhance efficacies of other anti-cancer drugs.

Of note, relatively high doses (high micro-to millimolar) are required for these FAO inhibitors to efficiently reduce FAO. This common feature of diverse FAO inhibitors seems to be related to the limited conversion of the compounds (pro-drugs) to their active metabolites after entering cells. For example, oxfenicine (4-Hydroxy-L-phenylglycine) is intracellularly transaminated to the active 4-hydro-xyphenylglyoxylate to inhibit CPT1 [111]. Etomoxir is attached to CoA to turn to an active CPT1 inhibitor [112]. Although etomoxir is well tolerated in experimental rodents and has been a most commonly used FAO inhibitor in scientific research, its clinical development for treatment of type II diabetes was terminated in phase II clinical trials because of adverse side effects in the liver and heart [113]. One possibility for the undesired side effects is that the high doses of etomoxir target all CPT1 isoforms including CPT1B in the heart.

An aminocarnitine derivative (ST1326) has been recently found to be a CPT1A-specific inhibitor [114]. ST1326 was shown to be effective in inducing apoptosis and growth arrest in lymphoma and leukemia cells including primary leukemia cells [114,115]. It also suppressed lymphomagenesis in mice [114,115]. In addition, certain natural compounds such as Avocatin B, an odd-numbered carbon lipid isolated from avocado fruit, has been recently shown to interfere with growth and viability of AML cells through inhibiting mitochondrial FAO and NADPH production leading to overproduction of ROS and oxidative stress [9].

9. Future perspectives

While recent advances in the field have generated considerable enthusiasm, the concept of “lipolytic phenotype” of cancer remains to be fully evaluated. As requirement for FAO may vary considerably among malignancies, it will not be surprising if the pathway turns out to be more critical to certain types of cancer than others. In particular, the less glycolytic prostate cancer and those that grow from adipocyte-rich environments such as breast and ovarian carcinomas are more likely to be FAO-addicted forms of cancers [58,60].

Furthermore, FAO might be a preferred fuel choice for cancer cells undergoing metastatic progression or during development of drug resistance. FAO activity in host cells may play roles of both friend and foe to cancer as discussed earlier.

Previous studies rely heavily on pharmacological approaches that are limited in potency and specificity, especially for *in vivo* applications [95,116]. Those clinically used for treatment of angina pectoris summarized in Table 1 are generally considered to be only partial FAO inhibitors. Although it is of interest to test these medicines in animals or patients for treatment or prevention of cancer, more potent and CPT1-isoform specific FAO inhibitors are needed to confirm the oncogenic function of FAO. Given the complexity and plasticity of cancer cell metabolism, inhibition of FAO together with glycolysis or glutaminolysis could be a more effective strategy to treat cancer. An obstacle in the field is the lack of appropriate genetic mouse models targeting a key enzyme of FAO in specific tissues or distinct immune lineages. The availability of relevant animal models should offer critical opportunities to elucidate exact roles of FAO in tumor initiation, progression and immunity.

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Abbreviations

FAO	fatty acid β-oxidation
TCA cycle	the tricarboxylic acid cycle
CPT	carnitine palmitoyltransferase
ETC	electron transport chain
CACT	carnitine/acylcarnitine translocase
3-KAT	3-ketoacyl-CoA thiolase
TFP	the trifunctional protein (hydroxyacyl-CoA dehydrogenase/enoyl-CoA hydratase/3-KAT)
ER	endoplasmic reticulum
PPAR	peroxisome proliferator-activated receptor
AMPK	AMP-activated protein kinase
ACC	acetyl-CoA carboxylase
FDG-PET	^{18}F-fluorodeoxyglucose with positron emission tomography
NMR	nuclear magnetic resonance
ROS	reactive oxidative species

CLL	chronic lymphocytic leukemia
AML	acute myeloid leukemia
TNBC	triple negative breast cancer
EMT	epithelial-to-mesenchymal transition
PML	promyelocytic leukemia
CSC	cancer stem cell
Rb	retinoblastoma
TRAF6	tumor necrosis factor receptor-associated factor 6
T_{reg}	regulatory $CD4^+$ T cell
MDSC	Myeloid-Derived Suppressor Cell
DC	dendritic cell
T_{eff}	Effector $CD4^+$ T cell
HCC	hepatocellular carcinoma
IDO	indoleamine 2,3-dioxgenase-1

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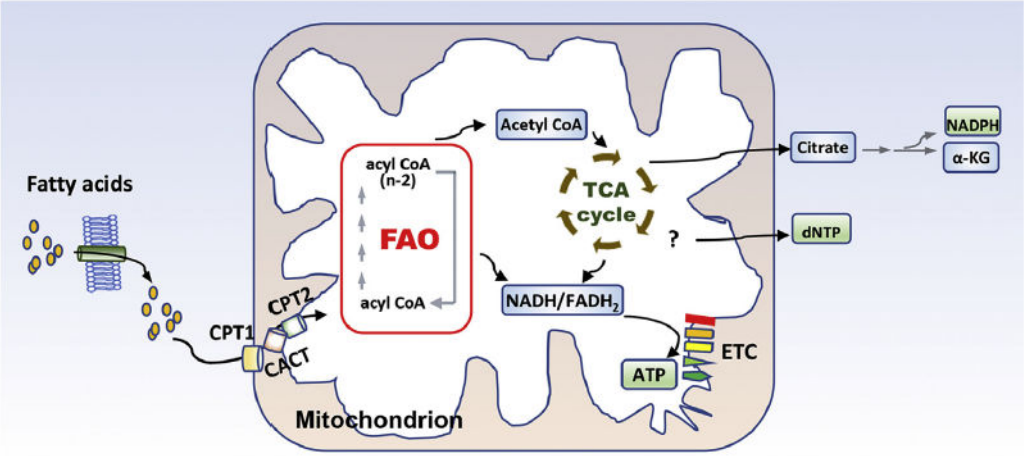

Fig. 1. FAO basics.

Long chain fatty acids enter cells via fatty acid transport proteins and then shuttled into the mitochondrion by the carnitine shuttle system. In the mitochondrion, fatty acids undergo oxidative removal of successive 2-carbon unit in the form of acetyl-CoA. Acetyl-CoA will be oxidized to CO_2 through the TCA cycle. Both FAO and the TCA cycle produce reduced electron carriers (NADH/FADH2), which will pass electrons to ETC to yield ATP. Apart from bioenergetic production, the carbon and hydrogen sources of FAO-generated acetyl CoA can be exported out of the TCA cycle to the cytoplasm to engage in NADPH and dNTP production as detailed in the text.

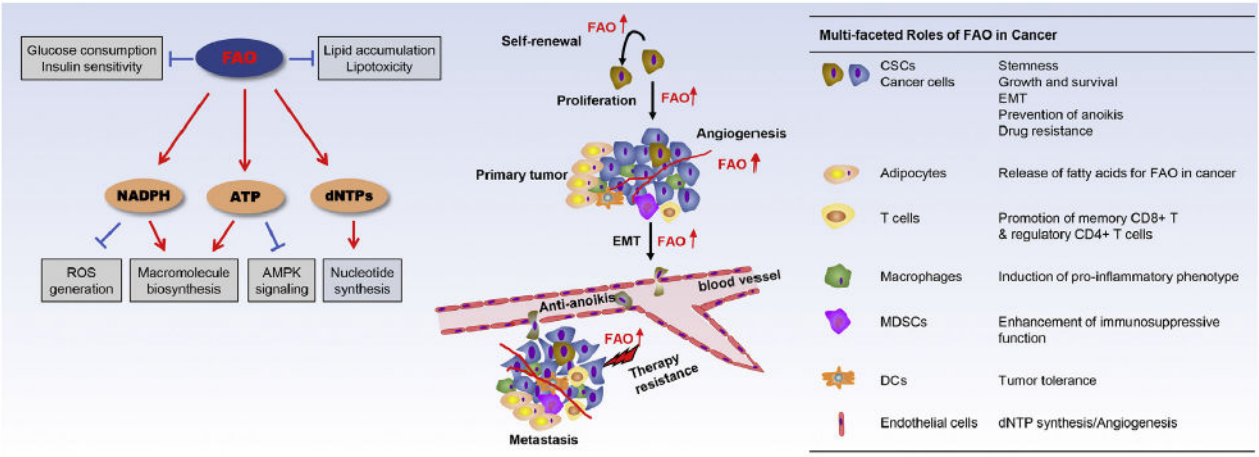

Fig. 2. FAO signaling pathways and multi-faceted roles in cancer.

Shown on the left are signaling pathways regulated by FAO in physiological conditions. FAO is implicated in multiple aspects of tumorigenesis including cancer cell growth, survival, CSC maintenance, drug resistance, and metastasis. In addition to abnormal activation in cancer cells, FAO and related lipid metabolic processes are also reprogrammed in tumor-associated immune cells, adipocytes and endothelial cells, which may contribute to immune suppression and tumor-promoting microenvironment.

Table 1

FAO modulators in clinical and research uses.

Compounds	Targeted Enzymes	Clinical applications	Research applications	Anti-cancer effects
Etomoxir	CPT1	Retired from phase II clinical trial for diabetes and heart failures	Leukemia, breast, prostate cancer cell lines in culture and xenograft model	Inhibition of cancer cell growth, survival, and tumorigenicity [49,52,54]
Oxfenicine	CPT1	No	Melanoma cell line in culture	Growth inhibition [117]
Aminocarnitine	CPT2	No	Glioma cell lines in culture	Growth inhibition [118]
Perhexiline	CPT1/CPT2	Medicine for angina pectoris in Australia and Asia	Prostate cancer cell lines, primary CLL cells, and CLL transgenic mice	Inhibition of cancer cell survival, and CLL progression in mice [40,119]
Trimetazidine	3-KAT of TFP	Medicine for angina pectoris in Europe and Asia	Glioblastoma and breast cancer cell lines in culture	Inhibition of cancer cell growth and induction of cell death [120,121]
Ranolazine	3-KAT of TFP	Medicine for angina pectoris in Europe and USA	Leukemia, lung, and colon cancer cell lines in culture and xenograft model	Inhibition of cancer cell growth, survival, and tumorigenicity in mice [37,52,98]
ST1326	CPT1A	No	Leukemia and lymphoma cell lines in culture and Eμ-myc transgenic mice	Growth inhibition and cytotoxicity in cell lines, and prevention of lymphomagenesis in mice [115]
Avocatin B	CPT1	No	Primary AML cells and cell lines in culture	ROS-dependent cell death [9]