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Review Article

The role and therapeutic implication of CPTs in fatty acid oxidation and cancers progression

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Abstract: Cancer cells must maintain metabolic homeostasis under a wide range of conditions and meet their own energy needs in order to survive and reproduce. In addition to glycolysis, cancer cells can also perform various metabolic strategies, such as fatty acid oxidation (FAO). It has been found that the proliferation, survival, drug resistance and metastasis of cancer cells depend on FAO. The carnitine palmitoyltransferase (CPT), including CPT1 and CPT2, located on the mitochondrial membrane, are important mediators of FAO. In recent years, many researchers have found that CPT has a close relationship with the metabolic development of tumor cells, not only provides energy for cancer cells development and metastasis by promoting FAO but also affects the occurrence and invasion through other signal pathways or cytokines or microRNA. This review summarized the role of CPTs in several kinds of tumors and the developed targeted inhibitors of CPTs, as well as the potential gene therapy and immunotherapy of CPTs, hoping to better explore the mechanism and role of CPTs in the future and providing useful ideas for clinical treatment.

Keywords: CPT1, CPT2, FAO, cancers, inhibitors

Introduction

Tumor cells show unique metabolic adaptation, such as enhanced glycolysis, de novo synthesis of lipids and up-regulation of glutamine decomposition [1-3]. These changes are essential for the development and maintenance of cancer cells in adverse tumor microenvironments or metastatic sites. In fact, in addition to these, there is fatty acid oxidation (FAO) [2]. Many types of cancers showed high activity of FAO, such as triple negative breast cancer [4], glioma [5], ovarian cancer (OC) [6], hepatocellular carcinoma (HCC) [7], prostate cancer (PC) [8]. In the past, although mitochondrial FAO was a major source of biological energy, it was not generally considered to be part of cancer metabolism [9]. In recent years, studies have found that FAO is an important source of nicotinamide adenine diphosphate hydride (NADH), flavin adenine dinucleotide (FADH2), nicotinamide adenine dinucleotide phosphate (NADPH) and adenosine triphosphate (ATP), all of which provide survival advantages for cancer [10, 11]. NADH and FADH2 entered the electron transport chain to produce ATP, NADPH to protect cancer cells from metabolic stress and hypoxia [10]. In addition, it was found that the proliferation, survival, drug resistance and metastasis of cancer cells were dependent on FAO [11-14]. FAO has been found to promote the migration of HCC cells by promoting the secretion of IL-1β, which plays a key role in functional human M2 macrophages [15]. Wang et al. found that FAO regulated by the Janus kinase/signal transducer and activator of transcription 3 (JAK/STAT3) was the key to self-renewal and drug resistance of breast cancer (BC) stem cells [16]. FAO was also reprogrammed in cancer-related immune cells and other host cells, which may contribute to immunosuppression and promote tumor microenvironment [6, 17, 18]. In short, FAO pathway is increasingly seen as a potential target for new cancer therapy.

The carnitine palmitoyltransferase (CPT) serves a major role in the process of FAO, including

CPT1 and CPT2 [19]. CPT1 is located in the outer of mitochondrial membrane and considered as an indispensable enzyme of FAO and converts carnitines to fatty acyl carnitines [19, 20]. CPT1 includes three isozymes, named CPT1a, CPT1b, CPT1c, which CPT1c is considered to have no enzyme activity [21-23]. CPT2 is located in the inner of the mitochondrial membrane [21]. It promotes the β-oxidation of fatty acids (FAs) by facilitating the conversion of acetyl-coenzyme A (CoA) to fatty acyl-CoA [24]. The CPT is indispensable to the oxidation of long-chain FAs. Recently, some studies have showed that the abnormal activity of CPT is associated with lots of serious diseases, such as cancers [25], non-alcoholic fatty liver disease (NAFLD) [26], diabetes [27], central nervous system diseases [28], obesity and so on [29]. The FAO provides nutrition for solid tumor cells, especially under the condition of lack of oxygen and glycolysis [30-32]. Studies have found that CPT affects the development of cancers not only through the FAO but also other signal pathways or cytokines or microRNA, for example, PC [33], leukemia [34] and BC [35, 36]. The CPT is also related to apoptosis of cancer cells [37, 38]. It was reported that truncated Bid (tBid) of bcl-2 family reduced the activity of CPT1 in a malondialdehyde-coenzyme-independent manner, leading to the increasing level of palmitoyl-CoA and apoptosis of cancer cells [39]. In addition, one study reported that high CPT1b expression was related to high-grade bladder cancer (BIC) cells, resulting in the decrease of epithelial mesenchymal transformation (EMT) in vitro and the decrease of cells growth, invasion, and EMT in vivo [40]. Interestingly, the CPT is also associated with cell senescence, and scholars have found that CPT1c regulates cancer cells senescence through mitochondrial-related metabolic reprogramming in aging human pancreatic cancer (PaC) PANC-1 cells [41]. Moreover, Gu et al. [42] found that the low expression of the CPT2 promoted malignant transformation of hepatocytes in liver of rats by increasing the level of lipids.

These results show that CPTs have different functions in FAO and cancer progression. In this paper, we summarize the mechanism of CPTs and FAO in many kinds of tumors and the treatment strategies related to CPTs, hoping to provide some ideas for clinical treatment.

The CPTs and FAO

FAO is necessary to maintain the dynamic balance of energy when it is necessary to ensure the concentration of glucose and the supply of main energy at the same time [43]. This process happens in mitochondria and includes a range of periodic reactions that can supply a large amount of energy needed by the body [44]. FAO must be activated at first. Then, FAs are catalyzed by acyl-CoA synthetases located in mitochondrial outer membrane to form acyl-CoA in the participation with ATP and CoA [43]. The activated medium and short chain acyl-CoA directly enters the mitochondria through the mitochondrial membrane for β-oxidation, while the long chain acyl-CoA must be transported to the mitochondria through the delivery system-CPT system [19, 45] to enter the process for β-oxidation. This system includes CPT1 [20], carnitine-acylcarnitine translocase located in the inner mitochondrial membrane and CPT2 [24]. CPT1 promotes the conversion of acyl-CoA to acyl-carnitine that is transported to mitochondrial interior with the help of translocase (or the carrier) on the intima of mitochondria [19]. Then, under the catalysis of CPT2, acyl-carnitine releases carnitine, and then converted to acyl-CoA to enter β-oxidation [19, 21] (**Figure 1**). The β-oxidation is an important way to FAs decomposition in the body, and CPT is an indispensable medium in β-oxidation of long-chain FAs [21, 43].

The structure and function of CPTs

As mentioned above, the CPT includes two subtypes: CPT1 and CPT2 [24, 46]. The CPT1 serves a significant role in determining the development of FAO and it is inhibited through malonyl-CoA [24]. It is the first important intermediate of lipogenesis and the key regulatory mechanism to maintain the balance of FA metabolism [47]. So far, three CPT1 isotypes have been found in different tissues, that is, CPT1a, CPT1b and CPT1c [21, 23, 24]. The CPT1a, also known as liver isotype, is expressed in brain, intestine, kidney, lung, ovary, pancreas and spleen [48-51]. The CPT1b, often referred to as muscle isoform, is with high level in skeletal muscle, heart and brown adipose tissue (BAT) [51-53]. The third isotype CPT1c is mainly expressed in the brain and has been confirmed it mainly locates in the endoplasmic reticulum [54, 55].

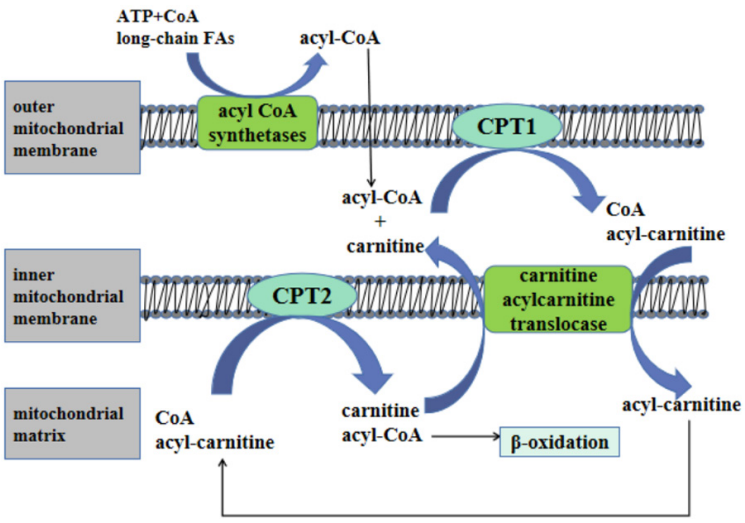

Figure 1. The role of CPT in the long-chain fatty acid oxidation. FAs are catalyzed by acyl-CoA synthetases located in mitochondrial outer membrane to form acyl-CoA in the participation with ATP and CoA. Then, long chain acyl-CoA must be transported to the mitochondria through the delivery system-CPT system to enter the process for β-oxidation. This system includes CPT1, carnitine-acylcarnitine translocase and CPT2. CPT1 promotes the conversion of acyl-CoA to acyl-carnitine that is transported to mitochondrial interior with the help of translocase on the intima of mitochondria. Then, under the catalysis of CPT2, acyl-carnitine releases carnitine, and then converted to acyl-CoA to enter β-oxidation. Abbreviations: ATP, adenosine-triphosphate; CPT1, carnitine palmitoyltransferase 1; CPT2, carnitine palmitoyltransferase 2; FA, fatty acid; CoA, coenzyme A.

According to the studies of CPT1a and CPT1b, they locate in the outer membrane of mitochondria [56, 57]. Human CPT1a gene is located on chromosome 11q, while CPT1b is located on chromosome 22q [58]. CPT1a is consisted of 773 amino acid residues (88 ku) and CPT1b consisted of 772 amino acids (88 ku) [58, 59]. The homology of amino acid sequence between them is 62% [59, 60]. Compared with CPT1b, CPT1a has a higher affinity for substrate carnitine and has more ability to resist the inhibition of malonyl-CoA [24]. In addition, one research has been predicted the three-dimensional structures of them according to the carnitine acetyltransferase, carnitine octanoyltransferase and CPT2 crystals [61]. Through functional and structural analysis, López-Viñas et al. [61] concluded that CPT1a had two malonyl-CoA sites, and the two sites shared carnitine binding sites. Furthermore, a study has found that CPT1b homozygous deficiency was fatal in mice [62]. For CPT1c, it was reported that it was located on chromosome 19q and consists of 798 amino acid residues [46]. Although it is highly homologous to CPT1a and CPT1b genes, CPT1c is mainly detected in the brain and testis [46, 54]. However, the detection of most scholars shows that its enzyme activity is very low or even no [54, 63], so it does not catalyze acyl transfer process [64, 65]. Lee et al. [66] has carried out an unbiased metabonomic analysis of the brains of wild-type and CPT1c gene knockout mice. The results showed that CPT1c did not serve a significant role in FAO, but it may has effect on neuronal oxidative metabolism [66]. Moreover, scholars have found that CPT1c is benefit to regulate the energy homeostasis [64, 67] and has a significant effect on cell senescence [25].

CPT2, consisted of 658 amino acids (74 ku), serves an essential role in FAO [24, 46]. Its gene situated in 1p32 and its protein is a homotetramer consisted of a single CPT2 [46, 68]. It was expressed in brain, heart, muscle [69-71]. The dysfunction of CPT2 directly affects β-oxidation of long-chain FAs in mitochondrial matrix [72]. This has been proved to be associated with the occurrence of a variety of lipid metabolic diseases [73], for example, neonatal CPT2 deficiency, rhabdomyolysis, NAFLD, obesity, HCC [70, 74-77] (**Table 1**).

The role of CPTs in FAO and different cancers

Metabolic transformation promotes cancer cells proliferation due to the fact that it protects cancer cells from the harm of environmental stress [1, 30]. Warburg effect is the most famous metabolic transformation, in which tumor cells limit energy consumption by up-regulating glycolysis [78, 79]. However, increasing evidences showed that tumor cells adapted to metabolic pressure by consuming FAs not only through glucose metabolism [1, 80-82] (**Figure 2**). For example, prostate tumors show low glucose consumption [55] and increased FA intake [83]. Cancer cells show strong metabolic adaptability and are more and more regarded as beneficial targets for some cancers therapy [82]. In a variety of targets, CPT in FAO as an important mediator in tumor meta-

Table 1. The information of CPT1 and CPT2

	CPT1			CPT2	Ref
Subtypes	CPT1a	CPT1b	CPT1c	no	[19-23]
Cellular location	Outer mitochondria membrance	Outer mitochondria membrance	The endoplasmic reticulum	Inner mitochondria membrance	[19, 21, 24, 54-57]
Chromosome location	11q	22q	19q	1p32	[24, 46, 58-60]
Main tissue distribution	brain, intestine, kidney, lung, ovary, pancreas, spleen	skeletal muscle, heart, BAT	brain	muscle, liver, heart	[48-51, 69-71]
Substrate	medium and long acyl-CoA esters	medium and long acyl-CoA esters	unclear	acyl-carnitine	[43-45, 64, 67, 70, 72, 74-77]
Related cancers	BC, GC, PC, OC, HCC, *NC, CC, leukemia*	*BlC*	LC, BC, PaC, TC, CC	HCC	[36, 40-42, 50, 70, 76, 84, 87, 91-94, 97, 100, 101, 108-115, 118, 119]

Abbreviation: CPT1, carnitine palmitoyltransferase 1; CPT2, carnitine palmitoyltransferase 2; LC, lung cancer; BC, breast cancer; GC, gastric cancer; PC, prostate cancer; OC, ovarian cancer; HCC, hepatocellular carcinom; PaC, pancreatic cancer; TC, thyroid carcinoma; NC, nasopharyngeal carcinoma; CC, colon cancer; BlC, bladder cancer; BAT, brown adipose tissue.

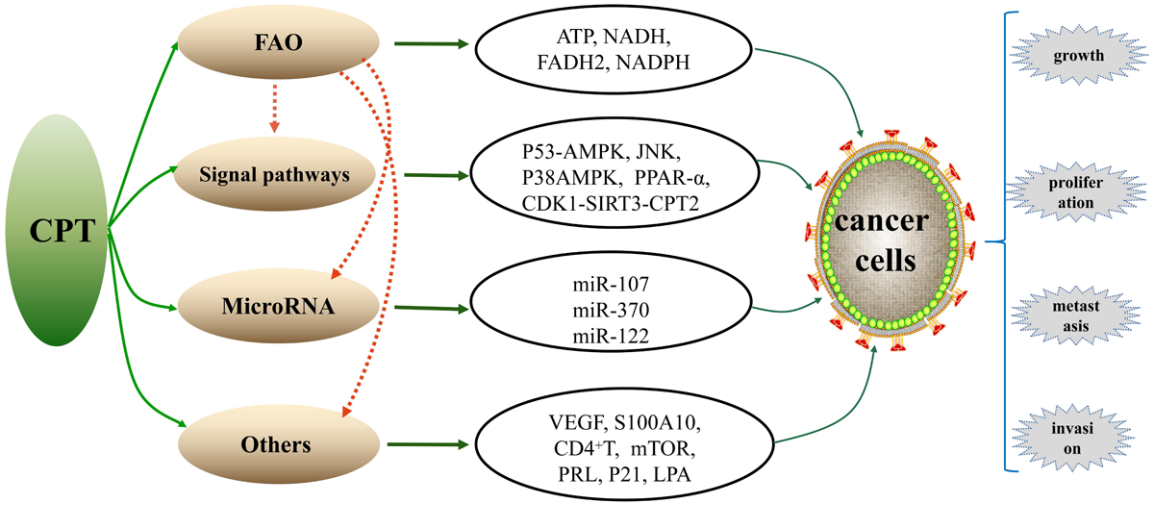

Figure 2. The mechanism of CPT in cancers. CPT not only provides energy for cancer cells through FAO, but also affects the growth, proliferation, metastasis and invasion of cancer cells through other signal pathways, signal molecules, hormones and so on. Abbreviation: ATP, adenosine triphosphate; JNK, c-Jun N-terminal kinase; NADH, nicotinamide adenine diphosphate hydride; FADH2, flavin adenine dinucleotide; NADPH, nicotinamide adenine dinucleotide phosphate; mTOR, mechanistic target of rapamycin; CPT, carnitine palmitoyltransferase; FAO, fatty acid oxidation; PRL, prolactin; VEGF, vascular endothelial-derived growth factor; AMPK, adenylate-activated protein kinase; P21, the cyclin-dependent kinase inhibitor p21WAF1; PPAR-α, peroxisome proliferator-activated receptor α; LPA, low saturated fatty acid palmitate; CDK1, cyclin-dependent kinase 1; SIRT3, sirtuin 3.

Table 2. The role of CPT1 and CPT2 in cancers

CPT	Disease	Impact	Mechanism	Ref
CPT1	Lung Cancer	Aggravate	CPT1c↑→FAO↑; P53-AMPK-CPT1c↑	[87, 84, 98]
	Breast Cancer	Aggravate	PRL→CPT1↑→FAO↑; CPT1a→VEGFC/VEGF-D/VEGFR-3→HDLEC invasion and lymphangiogenesis↑; CPT1c↑→mTOR↓→FAO, ATP↑	[85, 99, 101]
		Attenuate	miR-107↑→CPT1↓	[96]
	Gastric Cancer	Aggravate	CPT1a↑→FAO↑→EMT, proliferation, invasion↑; CPT1a→S100A10 succinylation↑	[86, 102]
	Prostate Cancer	Aggravate	androgen→CPT1↑→histone acetylation, FAO↑	[104-106]
	Ovarian Cancer	Attenuate	CPT1a inactivation→AMPK, p38, JNK↑→FoxO, p21↑→cells growth↓	[50, 107]
	Hepatocellular Carcinom	Aggravate	linoleic acid→PPAR-α, CPT1↑→CD4+T↓; LRRK2→PPAR-α, AMPK↑→CPT1a↑→FAO↑; miR-370→CPT1a↓, miR-122↑→FA↑	[88, 94, 108-110]
	Leukemia	Attenuate	Inhibit CPT1a→mitochondrial function↓→FAO↓	[34, 112-115]
	Pancreatic Cancer	Attenuate	CPT1c↓→FAO↓	[41]
	Thyroid Carcinoma	Aggravate	AMPK→CPT1c↑→FAO↑	[91]
	Nasopharyngeal Carcinoma	Aggravate	PGC1α+CEBPβ→CPT1a↑→FAO↑	[92]
	Bladder Cancer	Aggravate	CPT1b↓→FAO↓, EMT↑	[40]
	Colon Cancer	Aggravate	CPT1a, CPT1c→FAO↑	[36, 87]
CPT2	Liver Cancer	Aggravate	CPT2↓→stearoyl coenzyme A desaturase-1↑, FAO↓, JNK↓	[70, 76]
		Attenuate	LPA→CDK1-SIRT3-CPT2↑	[119]

Abbreviation: CPT1, carnitine palmitoyltransferase 1; CPT2, carnitine palmitoyltransferase 2; FAO, fatty acid oxidation; PRL, prolactin; VEGF, vascular endothelial-derived growth factor; AMPK, adenylate-activated protein kinase; HDLEC, human dermal lymphatic endothelial cell; EMT, epithelial mesenchymal transformation; FoxO, forkhead box O; P21, the cyclin-dependent kinase inhibitor p21WAF1; LRRK2, leucine-rich repetitive protein kinase 2; PPAR-α, peroxisome proliferator-activated receptor α; FA, fatty acid; PGC1α, PPAR coactivator-1α; CEBPβ, CCAAT/enhancer binding protein β; LPA, low saturated fatty acid palmitate; CDK1, cyclin-dependent kinase 1; SIRT3, sirtuin 3.

bolic mechanisms has received extensive attention [82, 84]. A large number of studies showed that abnormal CPT expression was related to tumor cells development and proliferation in BC [84, 85], gastric cancer (GC) [86], PC [33], lung cancer (LC) [87], HCC [88], OC [50] and colon cancer (CC) [36]. The CPT can not only provide energy for the growth of tumor

cells by activating FAO [10, 89, 90], but also interact with other cellular signal pathways, related molecules or microRNA functionally, which has a direct or indirect effect on the pathogenesis of cancers [50, 87, 91-94]. The roles of CPT1 and CPT2 in several cancers are shown in **Table 2**.

The role of CPT1 in FAO and different cancers

It is reported that CPT1 can activate FAO to increase the supply of ATP and protect tumor cells from the effects of glucose and hypoxia [72]. CPT1a promotes tumor cells growth by promoting FAO and activating the activity of histone acetylase in cell nucleus [95]. Secondly, CPT1 is reported that it exert some effects on cell apoptosis [37, 38]. It is reported that tBid reduces the activity of CPT1 in a malondialdehyde-coenzyme-independent manner and the result brings about the increasing palmitoyl-CoA levels and apoptosis of tumor cells [39]. In addition, some microRNA regulate cancer cells through CPT1 [96, 97]. It has been reported that miR-370 promotes triglyceride accumulation in the liver by decreasing CPT1a expression and promotes lipogenesis by activating miR-122 in HepG2 [97]. Xiong et al. [96] showed that overexpression of miR-107 directly restrained the development and metastasis in BC cells through directly targeting inhibition CPT1. Subsequently we summarize the role of CPT1 in several types of cancers.

CPT1 and LC

Zaugg et al. [87] found that compared with healthy tissues, CPT1c mRNA expression was increased in non-small cell lung cancer (NSCLC) tissues and the increasing CPT1c expression promoted FAO to provide ATP to tumor tissues. SiRNA interference with CPT1c can inhibit the growth of transplanted tumors in vivo [84]. Moreover, it was found that the agonist of MAPK could promote CPT1c mRNA expression in tumor tissue to regulate the stress response of tumor cells to metabolism [84]. Due to the mutual activation of AMPK and p53 [98], they believed that it was possible that the p53-AMPK-CPT1c axis may allow to use FA as the energy source for supporting cells development [84].

CPT1 and BC

Linher-Melville et al. [99] found that prolactin (PRL) enhanced FA β-oxidation through increasing CPT1 expression in MCF-7 and MDA-MB-231 cells, which helps to provide lots of energy to cancer cells. However, dual inhibition the glutaminase and CPT1 can inhibit FAO in mitochondria, which in turn inhibits the proliferation and development of triple negative BC cells [100]. It is reported that the expression of CPT1a is increased in recurrent BC, which is associated with the poor prognosis of BC patients [84]. Some scholars found that the overexpression of miR-107 directly restrained the proliferation and metastasis in BC cells through decreasing CPT1a expression, but the mechanism was unclear [96]. In addition, a study reported that the invasion and lymphangiogenesis of human dermal lymphoendothelial cells (HDLEC) were inhibited after the knockout of CPT1a gene in BC cells [85]. In HDLEC cells, lymphangiogenic markers expression (such as VEGFR-3, VEGF-C and VEGF-D) decreased after CPT1a gene was knocked out. Therefore, it was suggested that CPT1a was involved in BC-induced HDLEC cells invasion and lymphangiogenesis through VEGF-C/VEGF-D/VEGFR-3 signal pathway [85]. Interestingly, Pucci et al. [35] found a CPT1a mRNA transcriptional splicing variant, named variant 2 (CPT1Av2), appeared in the nucleus of BC cells. The inhibition of CPT1Av2 expression by siRNAs promotes apoptosis in BC cells. They believed that BC cells death caused by CPT1a gene silencing was related to decreased histone deacetylase activity and histone hyperacetylation [35], but this mechanism remained to be further studied. In addition, Zaugg et al. [87] found that CPT1c was overexpressed in MCF-7 BC cells, and its FAO and ATP production increased. The expression of CPT1c in extensive BC xenografts was negatively correlated with mTOR pathway activation and rapamycin sensitivity. The mTOR activation can promote tumor growth and metastasis [101], and further study the mechanism of CPT1c and mTOR, which may be of great benefit in finding positive treatment for cancers in the future.

CPT1 and GC

Some scholars have reported that CPT1a expression is significantly up-regulated in GC cells and tissues, and is related to the grade, pathological stage and poor prognosis of GC [86, 102]. The overexpression of CPT1a contributes to the proliferation, invasion and EMT process of GC cells, and activates FAO in GC cells by increasing the ratio of $NADP^+$/NADPH [86]. In addition, Wang et al. [102] found that

CPT1a enhanced the metastasis and invasion of cancer by binding to S100A10 of the calcium-binding cytoplasmic protein family and promoting its succinylation.

CPT1 and PC

Most PC deaths are caused by continued metastasis due to high resistance to current hormone therapy, a condition named castrated-resistant prostate cancer (CRPC) [103]. It is reported that androgen can increase the mRNA level of CPT1 [104]. Joshi et al. [105] found that CPT1a supported CRPC, in an androgen-dependent manner and also provided acetyl groups for histone acetylation to support CRPC. In PC LNCaP and PC3 cells, CPT1 promoting the oxidation of long-chain FAs also was beneficial to provide energy for PC cells, although glucose was a major source of energy [106]. Schlaepfer et al. [33] found that lipid oxidation decreased and led to apoptosis in PC LNCaP cell lines which knocked down CPT1a.

CPT1 and OC

It is reported that the increasing expression of CPT1a in OC, PC and other types of cancers play significant roles in contributing to cancer cells growth and development [50, 107]. Shao et al. [50] found that CPT1a had a high levels in most OC cell lines and ovarian serous carcinoma. An increasing CPT1a expression has a very close connection with poor prognosis in patients with OC [50]. CPT1a inactivation inhibits cells growth and ATP production, and they believed that this mechanism was mainly due to the induction of cell cycle by the cyclin-dependent kinase inhibitor $p21^{WAF1}$ (p21) [50]. The first is the inactivation of CPT1a, which can activate AMPK, p38 and JNK kinases, then stimulate the phosphorylation of forkhead box O (FoxO) and the up-regulation of p21, and finally block the cell cycle in G0/G1 [50].

CPT1 and HCC

Brown et al. [88] found that linoleic acid promoted transcriptional activator peroxisome proliferator-activated receptor α (PPAR-α) to up-regulate CPT gene, then induced $CD4^+$T cells apoptosis and promoted the progress of NAFLD into HCC. It has been proved that the pharmacological inhibition of CPT1 decreases the apoptosis of $CD4^+$T cells and benefits for HCC [88]. Lin et al. [94] found that overexpression of leucine-rich repetitive protein kinase 2 (LRRK2) in HepG2 cells can promote β-oxidation and provide energy for HepG2 through CPT1a. The mechanism may be that LRRK2 regulates CPT1a by activating AMPK and PPAR α [94]. Interestingly, Xu et al. [108] found that fatty degeneration in liver can be attenuated by continuous Ras activation while Ras promotes DNA damnification and development of liver cancer by CPT1a. Lliopoulos et al. [97] found that in HCC, miR-370 can directly down-regulate CPT1a, and promote adipogenesis by activating miR-122, thus promoting triglycerides accumulation in the liver. Interestingly, Impheng et al. [109] found that under the inhibitory influence of [6]-gingerol on the activity of FA synthesis, the increasing level of malonyl-CoA in turn inhibits CPT1 production, and finally promoted the apoptosis of HepG2 cells. [6]-gingerol is a major phenolic compound in the rhizome of ginger, which has the effect of anti-cancer [110].

CPT1 and leukemia

Chronic lymphoblastic leukemia (CLL) is the most common adult leukemia in western countries, which can be not cured at present [111]. A study has reported that CPT1 and CPT2 are highly expressed in CLL cells [112]. Inhibition of CPT by perhexiline led to decrease of phospholipids, an essential ingredient of mitochondrial membrane, and damaged the integrity of mitochondria, resulting in rapid depolarization and death of a large number of CLL cells [34]. It has been reported that the high expression of CPT1a indicates the adverse outcome of acute myeloid leukemia (AML) [113]. Recent studies have shown that CPT1a is extensively increased in leukemic cell lines, and targeting CPT1a has strong ability to resist to human leukemic cell lines and primary cells with diverse hematological diseases in vitro [34, 112-114]. In the models of Burkitt lymphoma, targeting CPT1a has shown beneficial impact, which can reduce the survival rate of cancer cells and inhibit tumor cells proliferation [115].

CPT1 and PaC

Wang et al. [41] has found that acylcarnitine decreased significantly and CPT1c activity decreased in aging human PaC PANC-1 cells. CPT1c knockout in PANC-1 cells led to abnormal mitochondrial function and abnormal energy metabolism, caused tomor cells senes-

cence, inhibited cells growth under metabolic stress, result in inhibiting the development of tumors in vivo [41].

CPT1 and thyroid carcinoma (TC)

Wang et al. [91] found that thyroid papillary carcinoma had a higher level of CPT1c than matched normal tissues. In addition, CPT1c promoted the survival of papillary TC cancer cells under hypoxia by transporting long-chain FAs to mitochondria for full oxidation and the complete process was mediated through AMPK signaling pathway [91].

CPT1 and nasopharyngeal carcinoma (NC)

Du et al. [92] found that the upregulation of CPT1a promoted the radiation tolerance of NC. Further studies revealed that PPAR coactivator-1α (PGC1α) formed a complex with CCAAT/CEBPB (a member of the CEBP transcription factor family), which integrates with the promoter of CPT1a to contribute to CPT1a transcription, followed by activating FAO to increase radiation tolerance. Hence they put forward the mechanism of PGC1α/CEBPB/CPT1A/FAO signal axis in NC [92].

CPT1 and BIC

The results of multi-omics integration analysis from Vantaku et al. [40] showed that FAO damage caused by the decreasing CPT1b gene expression had significant effects on the development of high-grade BIC. Moreover, the overexpression of CPT1b in high-grade BIC cells resulted in decreasing EMT in vitro and cell growth, EMT and proliferation in vivo, which obviously restrained tumor growth and development [40]. This suggests that increasing CPT1b expression in high-grade BIC may contribute to inhibiting tumor progression.

CPT1 and CC

Wang et al. [36] reported that CPT1a expression in the metastatic site was higher than that in the primary site in the clinical tissues of patients with colorectal cancer. Their results show that CPT1a-mediated FAO activation can induce colorectal cancer cells to resist apoptosis [36], which indicates that CPT1a serves a beneficial role in the treatment of metastatic colorectal cancer. Zaugg et al. [87] found that tumor cells has a high levels of CPT1c and change FA homeostasis under metabolic pressure, which could promote FAO, increase the production of ATP, and resist hypoxia. Cell experiments has demonstrated that the decreasing CPT1c expression greatly slows the growth of CC-derived tumors [87].

The role of CPT2 in FAO and different cancers

Studies have shown that CPT2 deficiency or dysfunction serves critical roles in many lipid metabolic diseases, such as diabetes, obesity, and NAFLD [42, 74, 116]. However, there are very few reports of CPT2 function in cancers. The abnormal function of CPT2 directly affects the carnitine transport of long-chain FAs through the mitochondrial inner membrane for β-oxidation [19, 21]. A study has shown that CPT2 mutated fibroblasts revealed the obvious reduction in FAO, adenosine triphosphate production and the decreasing mitochondrial membrane potential, which leads to fibroblasts apoptosis [26]. In addition, the heat-resistant phenotype of CPT2 can lead to the loss of ATP production under high heat conditions [117]. CPT2 deficiency is considered to be an inherited disease of mitochondrial FAO [77]. Related diseases include neonatal CPT2 deficiency, rhabdomyolysis, influenza-related encephalopathy and so on [75, 77]. Inactivation or mutation of CPT2 also has significant effects on the progression of cancer, such as HCC [70, 76].

CPT2 and HCC

Gu et al. [42] used rats to establish an in vivo model under the condition of lipid accumulation, and demonstrated that the low levels of CPT2 resulted in abnormal lipid accumulation in the liver, which led to mitochondrial damage, and finally led to the disturbance of energy metabolism, thus promoting the malignant transformation of hepatocytes. Fujiwara et al. [70] found a large accumulation of acylcarnitine types and a down-regulation of CPT2 in HCC tissue and serum of HFD-fed mice. The knockdown of CPT2 in HCC cells induced the suppression of FA β-oxidation and inhibited the activation of JNK mediated by Src, which caused them to avoid lipotoxicity [70]. The JNK has the role of promoting tumor in the occurrence of HCC [70, 118]. In addition, the in vitro studies from Lin et al. [76] has showed that knockout of CPT2 gene in HCC cells significantly enhanced the tumorigenicity and metastatic ability of HCC cells, and the low expression of CPT2 may promote adipogenesis of tumor cells

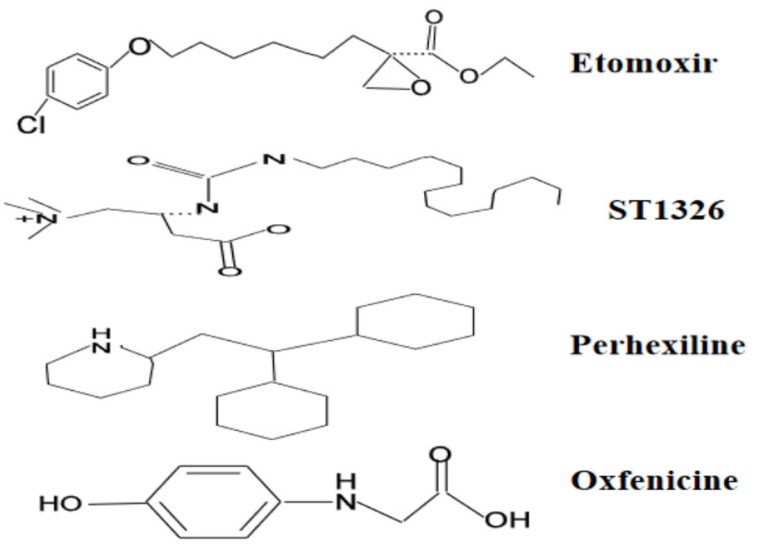

Figure 3. The chemical structure of four inhibitors.

through up-regulating the expression of stearoyl-CoA desaturase-1, a critical enzyme associated with monounsaturated FA synthesis. In addition, the down-regulated CPT2 augments the growth, migration, invasion and cisplatin resistance in HCC cells [76]. Interestingly, Liu et al. [119] has found that low levels of saturated palmitic acid FA can promote mitochondrial metabolism through CDK1-SIRT3-CPT2 cascade, which helps to protect hepatocytes from CCL_4-induced hepatotoxicity.

CPTs-related treatments in FAO and cancers

In view of the fact that CPT promotes FAs get into the mitochondrial matrix, the mitochondrial matrix serves an important role in β-oxidation to produce energy, and targeting CPT irreversibly inhibits the role of FAO, which has become a potential therapeutic target for many diseases, for example, cancers and other metabolic diseases [19, 22, 44, 82]. Some scholars have demonstrated that the process that targeting CPT1a to mediate FAO can enhance the sensitivity of several types of cancers therapy [94, 120, 121]. FAO inhibition may be a beneficial treatment for LC, CC and triple negative BC [36, 100]. In the models of Burkitt lymphoma, targeting CPT1a has shown beneficial impact, which can reduce the survival rate of cancer cells and inhibit tumor cells proliferation [115]. In animal models, the pharmacological effect of inhibiting mitochondrial long-chain FA input by inhibiting CPT1 has been demonstrated that the condition of a variety of diseases can be relieved, for instance, diabetes, psoriasis and myocardial infarction [122, 123]. A variety of evidence suggests that targeted CPTs are positive for cancers treatment [34, 114, 124, 125]. Besides, there are gene therapy [126-128] and immunotherapy [11] for CPTs, which provides a new direction for cancers treatment. Unfortunately, these methods are still under active exploration.

Treatments of targeted CPTs

Nowadays, there are only a few inhibitors targeting CPTs, such as etomoxir, ST1326 (teglicar), perhexiline, oxfenicine (**Figure 3**).

Etomoxir

Etomoxir (ethyl-2-[6-(4-chlorophenoxy)hexyl] oxirane-2-carboxylate) is a glycidyl acid derivative [129], which is metabolized and converted into corresponding CoA esters in vivo. Part of its oxidation ring binds to CPT1 covalently, acts directly on the active site of CPT1, and irreversibly inhibits CPT1a and CPT1b in myocardium [130]. It has long been applied to develop and cure type 2 diabetes and heart failure [131, 132]. Some studies have also reported that etomoxir promotes anti-proliferative effect by inhibiting CPT1a and CPT1b, and also increases the sensitivity of human metastatic BC [84], CC [36], leukemia [38], and NC [92, 125] to chemotherapy. However, it has been proved to have some serious side effects, so it is still in the stage of preclinical research [133]. A previous study has demonstrated that long-term use of etomoxir can lead to myocardial hypertrophy by promoting oxidative stress and activating NF-kB signaling pathways [133]. In PC, etomoxir can reactivate low levels of glycolysis [8].

ST1326 (Teglicar)

ST1326 ([R]-N-[tetradecylcarbamoyl]-aminocarnitine) is an unbreakable analogue of palmitoylcarnitine that is the CPT2 physiological substrate [134]. Rufer et al. [135] reported the complex crystal structure of rat CPT2 and ST1326. A study showed that ST1326 inhibited CPT1a in isolated rat mitochondria, which is more specific than CPT1b [134]. In addition, ST1326 caused a significant decrease in blood

glucose levels through oral administration to db/db mice [134], and was proven to cause anorexia effects after central administration and inhibit the production of endogenous glucose [136]. Conti et al. [137] also has proved that ST1326 selectively and reversibly inhibits CPT1a to reduce gluconeogenesis and improve glucose homeostasis. These characteristics are used to cure type 2 diabetes [134]. Furthermore, ST1326, a selective CPT1a inhibitor, shows strong cytotoxic activity [114]. By blocking FAO, it significantly delays or escapes the onset of lymphoma and has great potential in the treatment of leukemia [114]. At present, the inhibitor is still in the stage of preclinical experimental research [134-137].

Perhexiline

Perhexiline (2-(2, 2-dicyclohexylethyl) piperidine) was initially developed as an anti-angina drug in the 1970s [138]. Perhexiline can reduce FA metabolism by inhibiting CPT [34]. Despite its success, its use has been reduced because of little-known side effects, including neurotoxicity and liver toxicity, which appeared in a few patients [139]. In previous years, the roles of perhexilone and the molecular foundation in toxicity have been explained [34, 138, 140-142]. Ren et al. [140] reported that perhexiline ablated HER3 by promoting the internalization and degradation of HER3, and restrained the development of BC cells in vitro. Liu et al. [34] found that perhexiline inhibited the transport of CPT and FA to mitochondria, resulting in the decrease of cardiolipin, an important component of mitochondrial membrane, destroyed the integrity of mitochondria, and eventually led to rapid depolarization and the death of a large number of CLL cells. Brown et al. [88] found that liver-specific MYC transgenic mice were fed with methionine-choline-deficient diet feed and CPT was blocked with drug inhibitor perhexiline reduced $CD4^+$T cells apoptosis in the liver and inhibited the process of liver cancer formation. The Fyn is a kind cytoplasmic tyrosine kinase. Kant et al. [141] found that in gliomas, perhexiline did not inhibit FAO, but mediates Fyn kinase, showing anti-tumor activity. Several other reports have confirmed the antitumor activity of perhexiline [88, 143, 144]. Perhexiline has been completed phase 2 clinical trials in patients with chronic heart failure (NCT00841139), hypertrophic cardiomyopathy (NCT00500552) and diastolic heart failure (NCT00839228).

Oxfenicine

Oxfenicine (S-4-OH-phenyl-glycine) is considered to be a compound that stimulates the heart's use of carbohydrates, thereby reducing oxygen demand, especially in ischemic heart disease [145]. Keung et al. [146] found that inhibiting it can reduce diet-induced insulin resistance in ob/ob mice through inhibiting CPT1 activity. Sepa-Kishi et al. [147] found that oxfenicine treatment can reduce systemic fat oxidation, obesity, and improve insulin sensitivity in rats induced by high-fat diet. At present, there is no report of its research in cancer, and it is still in the state of preclinical research.

Other treatments related to CPTs

From a genetic point of view, some scholars have found that CPTs overexpression or low expression has an important impact on tumorigenesis and development [35, 41, 127]. Pucci et al. [35] found that silencing CPT1Av2 genes induced apoptosis in BC MCF-7 cells. Weber et al. [127] delivered a permanently active mutant form of human carnitine palmitoyltransferase 1A (hCPT1AM) in the liver of a mouse model of NAFLD and they found that liver hCPT1AM gene therapy NAFLD can reduce HFD-induced derangements. That may be good news for HCC patients. Wang et al. [41] found that in PANC-1 cells, knockdown of CPT1c genes led to mitochondrial dysfunction, leading to senescence-like growth inhibition and cell senescence, inhibiting cell survival under metabolic stress, and inhibiting tumorigenesis in vivo. In addition, another study found CPT2 silencing HepG2 cells facilitated cell proliferation, migration, and invasion [76]. Therefore, gene therapy for CPTs may be another way to treat cancers.

FAO mediated by CPTs also plays an important role in tumor immunity [11, 15]. It is reported that FAO contributes to IL-1β secretion in M2 macrophages and promotes macrophage-mediated tumor cell migration [15]. Myeloid-derived suppressor cells (MDSCs) can promote the proliferation and migration of malignant tumor cells and promote tumor growth by inhibiting T cell immunity [148]. Hossain et al. [11] found that FAO inhibitors combined with low-

dose chemotherapy (etomoxir with cyclophosphamide) could completely inhibit the immunosuppressive effect of T-MDSCs and induce a significant anti-tumor effect. In addition, Wong et al. [149] found that the specific loss of CPT1a of lymphatic endothelial cells impaired lymphoid development in transgenic mice. It is worth noting that blocking CPT1 can inhibit injury-induced lymphangiogenesis, which may suggest that inhibition of pathological lymphangiogenesis by reducing FAO may be a potential treatment in some diseases. For example, in cancer, excessive growth of lymphatic vessels promotes tumor cell metastasis, and inhibition of CPT1 can block its invasion and metastasis [150]. However, the method of immunosuppression combined with FAO in the treatment of cancer still needs to be further explored.

Conclusion and future

The metabolic ability of tumor cells has been paid more and more attention as a potential target for the treatment of cancers [30]. Some studies have emphasized the significance of FAs metabolism to cellular energy homeostasis through β-oxidative catabolism [1, 41, 72]. The CPT serves an indispensable role in the process [24]. Many studies have demonstrated that the abnormal expression of CPT is related to cancer development in BC, GC, PC, LC, HCC, OC and CC [33, 35, 36, 50, 89, 99, 105, 151]. CPT not only provides energy for the growth of tumor cells by activating FAO, but also interacts with other cellular signal pathways, related molecules or microRNA functionally, which has a direct or indirect effect on the pathogenesis of cancers [1, 80-82]. In addition, some inhibition of targeting CPT1 or CPT2 have shown a positive role in BC [100], leukemia [34], HCC [70] and NC [125]. The inhibitors of CPT have been developed, such as etomoxir [114-117], teglicar [118, 119], perhexiline [122-127], oxfenicine [128, 129].

The in-depth study of tumor metabolic pathway has opened up potential findings for the targeted therapy of malignant tumors. CPT-mediated FAO plays an important role in tumor growth, proliferation, metastasis, invasion and immune tolerance. Nowadays, there are relatively many studies on CPT1a and CPT1c, but few studies on CPT1c and CPT2 in cancers, and the mechanism of some pathways and signaling molecules with CPT in cancer is still unclear. Although several inhibitors have been studied, few can enter the clinical experimental stage. In addition to targeting CPTs inhibitors to treat tumors, there may also be CPT-related gene therapy or immunotherapy. CPTs are also indispensable at the junction of FAO, aerobic glycolysis and fatty acid synthesis, and there may be undiscovered media related to CPTs to coordinate the three biological processes. In view of the complexity and plasticity of cancer cell metabolism, inhibition of FAO binding glycolysis or glutamine decomposition may be a more effective strategy for cancer treatment. Drugs tolerance has always been a difficult problem in cancer treatment. In the future, we still need to explore the effect of CPTs on tumor cells drug tolerance and increase the clinical research of CPTs inhibitors.

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Disclosure of conflict of interest

None.

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