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Research Article

# Role of carnitine palmitoyl transferase in malignant tumors

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**Abstract** The progression of malignant tumors is often accompanied by abnormal energy consumption of tumor cells, which often triggers metabolic disturbances in energy supply pathways. In order to maintain its growth, proliferation and energy requirements, malignant tumors maintain metabolic homeostasis through metabolic reprogramming. Lipid metabolism plays an important role in the occurrence and development of various malignant tumors. Fatty acid oxidation (FAO), as an important part of lipid metabolism, provides energy and REDOX substances for tumor cells. Carnitine palmitoyl transferase (CPT), as a key enzyme of FAO, provides energy for the development and metastasis of tumor cells by promoting FAO, and also affects the occurrence and invasion of tumor cells through a variety of signal passage or cytokines. Targeting CPT has anti-tumor effect, so it is of great significance to analyze the effect of CPT in the prognosis and treatment of malignant tumors.

***Keywords:*** CPTs, Malignant tumors, Prognostic assessment, Reversing resistance, Immunotherapy

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Reprogramming of lipid metabolism is one of the top ten characteristics of tumor cells. Lipid metabolism includes lipid synthesis, uptake, decomposition and oxidative phosphorylation. Oxidative phosphorylation provides energy and REDOX substances for tumors. Therefore, Fatty acid oxidation (FAO) plays an important role in the survival, proliferation, metastasis and drug resistance of tumor cells. Many types of cancer show high activity of FAO, such as glioma, prostate cancer, ovarian cancer, etc. [1]. The FAO pathway is increasingly being viewed as a new potential target for cancer therapy. Carnitine palmitoyl transferase (CPT), a key enzyme of FAO, exists in the mitochondrial membrane and further affects the metabolic regulation and the tumor microenvironment of tumor cells and immune cells by affecting the process of fatty acyl-CoA entering the mitochondria. Thus, it affects the occurrence and development of tumors [1, 2]. In recent years, the research on CPTs in tumors has become a hot spot [1, 2], but there is a lack of relevant reviews on the research progress of CPTs in the prognosis evaluation, reversal of drug resistance and immunotherapy of malignant tumors. This article summarizes the role and mechanism of CPTs in evaluating the prognosis of malignant tumors, reversing drug resistance of malignant tumors, improving tumor microenvironment and improving the efficacy of immunotherapy, in order to provide reference for further research on CPTs as the target for tumor treatment.

## 1. Structure and function of CPTs

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CPTs is one of the key enzymes of FAO, it includes Carnitine palmitoyl transferase 1(CPT1) and Carnitine palmitoyl transferase 2(CPT2). CPT1 is located in the outer membrane of mitochondria and catalyzes the conversion of fatty acyl-CoA to fatty acylcarnitine. It can regulate the occurrence and development of tumors through a variety of signaling pathways. CPT1 includes three isoforms: Carnitine palmitoyl transferase 1A(CPT1A), Carnitine palmitoyl transferase 1B(CPT1A), carnitine palmitoyl transferase 1C(CPT1C), also known as liver type, muscle type, and brain type. The CPT1A gene is located on chromosome 11q13.1-q13.5 and consists of 773 amino acids, most of which are distributed in the liver. It is mainly responsible for transporting free fatty acids from cytoplasm to mitochondria for FAO [1, 2]. CPT1A can promote the growth of tumor cells by promoting FAO and activating histone deacetylase in the nucleus [1]. CPT1B gene is located on chromosome 22q13.31-q13.32, which consists of 772 amino acids and is mostly expressed in muscle tissues [1, 2]. Since CPT1A has two binding sites for malonyl-CoA, this leads to a stronger rate-limiting effect of CPT1A than CPT1B [3]. So far, most of the studies on CPT1B are in the aspects of eye movement frequency and body mass index (BMI), and the research reports on the correlation between CPT1B and tumors are relatively few. The CPT1C gene is located on chromosome 19q13.33 and consists of 798 amino acids. It is mostly expressed in the brain and is responsible for maintaining cellular homeostasis mainly by participating in fatty acid catabolism [1, 2, 4]. Different from CPT1A and CPT1B, a large number of studies have found that CPT1C is related to feeding behavior and energy consumption of animals, and can induce senescence of tumor cells by affecting the expression of c-Myc and cyclinD1 proteins [52]. CPT2 is close to the inner mitochondrial membrane and catalyzes the re-conversion of fatty acyl carnitine to fatty acyl-CoA. The CPT2 gene is located on chromosome 1p32 and consists of 658 amino acids and is widely expressed in vivo [1, 2]. Unlike CPT1 and CPT2 are single genes and multiple isoforms do not exist. Abnormal CPT2 function will directly affect the transport of carnitine in the mitochondrial inner membrane, which not only plays an important role in the occurrence and development of tumors, but also plays a key role in many lipid metabolic-related diseases, such as diabetes and obesity [1].

## 2. The role of CPTs in malignant tumors

### 2.1 The role of CPT1A in malignant tumors

#### 2.1.1 CPT1A can be used to evaluate the prognosis of malignant tumors

CPT1A is overexpressed in a variety of malignant tumors and is significantly correlated with tumor metastasis, TNM stage, histological grade and molecular subtype, which is expected to become a new prognostic indicator for tumors. Many studies have confirmed that CPT1A is highly expressed in a variety of cancers, supporting the proliferation, survival and metabolic adaptation of tumor cells, such as thyroid papillary carcinoma, nasopharyngeal carcinoma, esophageal cancer, lung cancer, gastric cancer, colorectal cancer, high-grade serous ovarian cancer, pancreatic cancer, prostate cancer, glioma, acute myeloid leukemia (AML), and so on, and is negatively correlated with overall survival [5]. It is an important cancer-promoting factor. In pancreatic cancer, CPT1A can promote the proliferation, migration and epithelial-mesenchymal transition process of tumor cells by interacting with quinone oxidoreductase 1 (NQO1) [6]. The expression of CPT1A is significantly increased in prostate cancer cells, which significantly affects the survival and proliferation of tumor

cells in the hypoxic area [7]. The overexpression of CPT1A promotes the differentiation of glioma stem cells, and then promotes the occurrence and development of glioblastoma, which is an important factor for tumor metastasis [8, 9]. The above studies show that CPT1A expression level is related to the occurrence, development and prognosis of a variety of malignant tumors, and it is expected to become an effective target for inhibiting tumor metastasis and improving prognosis.

CPT1A is overexpression in various malignant tumors and is associated with tumor stage, grade, and metastasis, thereby serving as a potential prognostic indicator and therapeutic target for tumors. However, some studies have demonstrated that CPT1A shows low expression in specific malignant tumors and is positively correlated with prognosis. In renal clear cell carcinoma (RCCC), CPT1A expression is lower compared to basic levels, which correlates with pathological grade, TNM stage, and lower disease-free survival [10-13]. The opposite conclusion of colorectal cancer in relevant studies may be caused by insufficient sample size [10-13]. For the divergence of CPT1A in breast cancer, we suspect that it may be caused by different breast cancer types. Relevant studies have shown that downregulation of CPT1A promotes the proliferation and migration of triple-negative breast cancer cells, but inhibits the proliferation and migration of non-triple-negative breast cancer cells [14]. Meanwhile, the expression of CPT1A in estrogen-receptor-positive tumors and cell lines is higher than that in estrogen-receptor-negative tumors and cell lines [15].

In conclusion, CPT1A has a certain correlation with the prognosis of a variety of malignant tumors, and it is expected to become a prognostic evaluation indicator of malignant tumors.

### 2.1.2 Targeting CPT1A can reverse drug resistance in malignant tumors

A major aspect of the survival of most tumor cells is drug resistance in cells, which is required for metastasis of malignant tumors. Radioresistant tumor cells showed significant enhancement of FAO [16]. The enhancement of FAO mediated by CPT1A can be considered as a marker of tumor cell resistance to radiotherapy and chemotherapy. Targeting CPT1A can increase the sensitivity of tumor cells to treatment, which is a new direction for the treatment of drug-resistant tumors. Relevant studies have shown that CPT1A overexpression in nasopharyngeal carcinoma and breast cancer improves the radioresistance of tumor cells by enhancing FAO, thereby improving the survival rate of tumor cells, which proves that CPT1A is a potential metabolic target in cancer radiotherapy [17, 18]. However, some studies have shown that low expression of CPT1A can make colorectal cancer cells radioresistant by accelerating the clearance of reactive oxygen species, and upregulation of CPT1A can reduce the damage repair ability and radiation resistance ability of colorectal cancer cells, making tumor cells more sensitive to radiation [19]. CPT1A inhibitors have drug-sensitization effect, and can be used in combination with antineoplastic drugs, such as sorafenib, platinum, venetoclax, etc., to improve the single drug resistance of antineoplastic drug and achieve higher anti-tumor effect. For example, CPT1A inhibitors have a synergistic effect on sorafenib [20, 21]. For liver cancer patients with elevated bilirubin, the sensitivity of sorafenib is reduced, which is due to the inhibition of the efficacy of sorafenib by increasing the expression of peroxisome proliferators-activated receptors α (PPARα) and CPT1A. Therefore, targeting PPARα-CPT1A axis can improve the efficacy of sorafenib in liver cancer [21]. Therefore, CPT1A inhibitor can

block the potential mechanism of bilirubin and sorafenib, and increase the sensitivity of liver cancer to sorafenib. CPT1A inhibitors have a higher inhibitory effect on proliferation of tumor cell when combined with platinum [22], can reverse the resistance of colorectal cancer to oxaliplatin, and can also enhance the sensitivity of high-grade serous ovarian cancer cells to platinum [23, 24]. The Bcl-2 inhibitor venetoclax is often used to treat AML in clinical practice, but drug resistance soon occurs after single drug treatment. Mao et al. found that CPT1A inhibitors and Bcl-2 inhibitors can synergistically induce apoptosis of AML cells, so venetoclax combined with CPT1A inhibitors may improve this situation in the clinic [25]. In conclusion, CPT1A is a potential therapeutic target for a variety of resistant and refractory malignancies, and evaluation of patients for CPT1A is warranted in the clinic. Inhibitors of CPT1A and FAO, represented by Etomoxir, are being explored as sensitizers for chemotherapy and radiotherapy to improve treatment outcomes and survival.

### 2.1.3 Targeting CPT1A can improve the tumor microenvironment and improve the efficacy of immunotherapy

CPT1A plays an important role in the tumor microenvironment and provides a new target for immunotherapy. CPT1A overexpression was negatively correlated with the abundance of tumor infiltrating lymphocytes (TIL), and the strongest correlation was observed with effector memory CD4 cells, Th1 cells, Tγδ cells, CD56bright natural killer (NK) cells, NK T cells, activated dendritic cells (DCs) and plasmacytoid DCs, suggesting that CPT1A overexpression can lead to disease progression and poor prognosis through the synergistic action of multiple immune pathways [26]. These results suggest that CPT1A can regulate the tumor immune microenvironment by inhibiting tumor infiltrating cells, thereby affecting the efficacy of immunotherapy and guiding individualized immunotherapy. Regulatory T cells (Treg) can make the body produce antigen tolerance to tumor cells, and cause tumor cells to escape. Therefore, Treg is also considered as a kind of immune cells that contribute to tumor survival and promote its growth. LU et al. believed that CPT1A can promote the malignant progression of RCCC by enhancing Treg infiltration and inducing an immunosuppressive microenvironment. Therefore, high CPT1A expression is associated with poor therapeutic effect, leading to poor prognosis of patients [27]. It has been found that CPT1A mediated FAO enhancement promotes CD47-mediated immune escape in glioblastoma. Therefore, targeting CPT1A can inhibit tumor growth while reducing the anti-phagocytic effect of CD47, indicating that CPT1A inhibitor combined with anti-CD47 antibody can synergistically eliminate the radioresistance and anti-phagocytosis of tumor cells, thereby improving the efficacy of radioimmunotherapy [28]. CPT1A inhibitors can also inhibit proliferation of tumor cell in AML and Burkitt lymphoma by blocking FAO [29]. Glycolysis can activate T cells, while CPT1A-mediated FAO can inhibit this process, thereby preventing T cells attack on the tumor, indicating that CPT1A can inhibit the immune system and anti-tumor immunity, and then promote the occurrence and development of tumors [30]. All these studies indicate that immune cells or stromal cells in the tumor microenvironment enhance CPT1A-mediated FAO, leading to tumor progression, metastasis and poor prognosis, suggesting that targeting CPT1A is a feasible strategy to improve the tumor microenvironment and improve the

efficacy of immunotherapy, which is conducive to individualized immunotherapy.

### 2.2 The role of CPT1B in malignant tumors

CPT1B is highly expressed in a variety of malignant tumors and is closely related to the occurrence and development of tumors. CPT1B is highly expressed in a variety of malignant tumors such as lung cancer, breast cancer, liver cancer, RCCC, and gastrointestinal tumors, and is associated with poor disease-free survival and overall survival [31-35]. At present, studies have also shown that high CPT1B expression is positively correlated with the prognosis of some malignant tumors, such as bladder cancer [36, 37]. However, for some malignant tumors, such as prostate cancer, scholars hold different views. Studies have shown that high expression of CPT1B inhibits the occurrence and development of prostate cancer [38]. However, Abudurexiti et al. showed that high CPT1B expression was negatively correlated with the prognosis of patients with castration-resistant prostate cancer [39]. The different views may be related to the different types of prostate cancer; androgen receptors are reduced in castration-resistant prostate cancer, and androgen receptors inhibit CPT1B transcription, which may be responsible for CPT1B overexpression in castration-resistant prostate cancer.

CPT1B can also affect the drug resistance of tumor cells. CPT1B is regulated by estrogen-related receptor γ (ERRγ) to enhance FAO in chemotherapy-resistant cells. CPT1B inhibitors can enhance the sensitivity of liver cancer cells to chemotherapy drugs such as doxorubicin, paclitaxel and vincristine by reducing the expression of ERRγ [33]. Targeting CPT1B can be used as a potential therapeutic strategy for castration-resistant and benzalutamide resistant prostate cancer [39]. These studies suggest that targeting CPT1B plays an important role in drug hyposensitivity and drug resistance malignant tumors and is expected to be a key target for improving the prognosis of such tumors.

### 2.3 The role of CPT1C in malignant tumors

CPT1C is highly expressed in a variety of malignant tumors, and predicts poor survival and short survival time, such as papillary thyroid carcinoma, breast cancer, gastric cancer, liver cancer, etc. [40-51]. Therefore, targeting CPT1C can also be a potential target to effectively inhibit tumor development and improve the prognosis of patients.

There are few studies on CPT1C and drug resistance. Some studies have found that CPT1C is associated with increased drug resistance to rapamycin, and CPT1C inhibitors can enhance the efficacy of anti-tumor drugs and play a sensitizing role [41].

Current studies have confirmed that CPT1C has a more significant effect on cell senescence than other CPT subtypes [52]. Under metabolic stress, upregulation of CPT1C enhances FAO and ATP production, meets the high energy demand of cancer cells, enables cancer cells to avoid death caused by glucose deprivation and hypoxia, protects cancer cells from lipotoxicity and senescence, and promotes cell survival and tumor growth [45, 53-57]. Therefore, CPT1C inhibitors are expected to be a new direction for cancer treatment by inducing cancer cell senescence.

### 2.4 The role of CPT2 in malignant tumors

CPT2 is highly expressed in some malignant tumors, and negatively correlated with the prognosis of patients, such as breast cancer and prostate cancer [13, 58-60]. However, some studies have also shown that CPT2 is a protective prognostic gene in malignant tumors such as colorectal cancer, ovarian cancer and RCCC, acting as a tumor suppressor, and is a

potential biomarker of malignant tumors with certain prognostic value [13, 61-68].

It is generally believed that CPT2 is lowly expressed in liver cancer tissues, which is related to tumor histological differentiation and venous invasion, and significantly enhances the tumorigenic activity and metastatic potential of liver cancer [69-72]. However, in 62 pairs of liver cancer and adjacent tissues, it was found that CPT2 was highly expressed in liver cancer cells and promoted cancer cell migration and invasion [73]. The differences in conclusions may be caused by insufficient sample size or experimental operation, which needs to be further verified. But it is certain that CPT2 has a certain role in the occurrence and development of malignant tumors.

CPT2 plays a role in the chemoresistance of malignant tumors. Relevant studies have shown that downregulation of CPT2 induces chemotherapy resistance of liver cancer to cisplatin and colorectal cancer to oxaliplatin, indicating that CPT2 has a positive effect on chemoresistant liver cancer and colorectal cancer [13, 68, 71]. In addition, downregulation of CPT2 leads to reduced fatty acid degradation in RCCC, which eventually leads to excessive lipid deposition, and lipid deposition is associated with tumor invasiveness, anti-angiogenic drug resistance and poor prognosis [13].

## 3. Summary and Prospect

The abnormal lipid metabolism of tumor cells has attracted more and more attention as a potential target for tumor treatment. FAO mediated by CPTs plays an important role in tumor growth, proliferation, metastasis, invasion and immune tolerance through various pathways and mechanisms, and then affects the survival rate of patients. Targeting CPTs can improve the drug resistance of tumor cells and enhance the anti-tumor immune response, thereby inhibiting tumor growth. It is a potential effective target for anti-tumor therapy. At present, some progress has been made in the related research of targeting CPTs for anti-tumor therapy. CPT1 inhibitors have been developed, the most common one is glycidic-acid, and the representative drug is Etomoxir. Etomoxir is an irreversible inhibitor and inhibits the activity of CPT1 by covalently binding to CPT1 [74]. Recent studies have shown that Etomoxir mainly affects the expression of CPT1A by inhibiting the enzyme activity, but there may still be "off-target" effects in this process [75, 76]. At present, studies have shown that Etomoxir has an inhibitory effect on the proliferation of a variety of malignant tumor cells. However, due to the hepatotoxicity in phase II clinical trials, relevant research has stalled, and further research is still needed [76]. Therefore, CPT1A inhibitors have a good therapeutic effect in the direction of anti-tumor, but "off-target" effects and side effects are still a big obstacle to their clinical application. Further study on the structure of CPT1A will help to improve drug specificity, avoid "off-target" effects and reduce side effects, which will provide safer and more effective drugs for clinical treatment. In addition to targeting CPTs inhibitors for tumor treatment, CPT-related gene therapy or immunotherapy may also be involved in the future. Drug tolerance has always been a difficult problem in cancer treatment. In the future, we still need to explore the effect of CPTs on tumor cell drug tolerance and increase the clinical research of CPTs inhibitors.

## Author Contributions

Shumin Cao: Collected articles and wrote articles; Yujing Chu：Collected articles；Jing Ai：Collected articles；Ming Zhang: Revised the article ; Shuangqing Chen：Collected articles； Jing Zhao: Proposed directions and revised the article.

## Participation Consent

All authors of this article participated and agreed to publish.

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## Conflict of Interests

There is no conflict of interest in this article.

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