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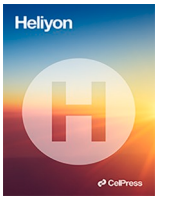

Review article

Dysfunction of the carnitine cycle in tumor progression

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ABSTRACT

The carnitine cycle is responsible for the transport of cytoplasmic fatty acids to the mitochondria for subsequent β-oxidation to maintain intracellular energy homeostasis. Recent studies have identified abnormalities in the carnitine cycle in various types of tumors; these abnormalities include the altered expression levels of carnitine cycle-related metabolic enzymes and transport proteins. Dysfunction of the carnitine cycle has been shown to influence tumorigenesis and progression by altering intracellular oxidative and inflammatory status or regulating tumor metabolic flexibility. Many therapeutic strategies targeting the carnitine cycle are actively being explored to modify the dysfunction of the carnitine cycle in patients with malignant tumors; such approaches include carnitine cycle-related enzyme inhibitors and exogenous carnitine supplementation. Therefore, here, we review the studies of carnitine in tumors, aiming to scientifically illustrate the dysfunction of the carnitine cycle in tumor progression and provide new ideas for further research.

1. Introduction

Carnitine is an amino acid-like compound belonging to the quaternary ammonium cation complex, which has two isomers: bioactive L-carnitine, also known as 3-hydroxy-4-N-trimethylaminobutyrate, and its enantiomeric isomer, dextro-carnitine [1]. L-carnitine is present in all mammalian species, and its most important biological function is the translocation of fatty acids into the mitochondria for subsequent β-oxidation, a process that leads to the esterification of carnitine to form acylcarnitine derivatives [2]. Hence, the endogenous carnitine pool consists of L-carnitine and various short-, medium- and long-chain acylcarnitines [1,2]. D-carnitine is only present in the synthesis of carnitine in vitro. This process interferes with the natural utilization of L-carnitine and prevents the oxidation of fatty acids and energy formation, thus causing symptoms of muscle weakness and cardiac arrhythmias that disappear with the use of L-carnitine [3]. Therefore, what we generally call carnitine is all L-carnitine and its related derivatives. Most carnitine in the human body is supplemented through the diet (especially red meat) and transported into cells via the ubiquitously expressed organic cation transporter protein New Family Member 2 (OCTN2)/Solute Carrier Family 22 Member 5 (SLC22A5). The remaining 25 % of carnitine is synthesized via de novo synthesis using lysine and methionine as raw materials [1,4,5].

Fatty acid oxidation (FAO) is an essential step in the lipid metabolism of organisms. The activation of intracellular fatty acids to

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acyl-coenzyme A(CoA) occurs in the cytoplasm, whereas its subsequent β-oxidation occurs in the mitochondrial matrix. The carnitine cycle serves as a specific shuttle system to transfer long-chain acyl-CoA from the cytoplasm to the mitochondrial matrix [1,6,7] (Fig. 1). Carnitine palmitoyltransferase I (CPTI), located on the outer mitochondrial membrane, converts acyl-CoA to acylcarnitine, which is then transported to the mitochondrial matrix by carnitine/acylcarnitine translocase (CACT) on the inner mitochondrial membrane [1,2,7]. Once acylcarnitine enters the mitochondrial matrix, free carnitine is released under the catalysis of CPTII, and the formed acyl-CoA undergoes fatty acid β oxidation to produce acetyl-CoA [1,2,7]. During this process, free carnitine can not only be transferred outside the mitochondria by CACT but can also be catalyzed with acyl-CoA by carnitine acetyltransferase (CRAT) to generate free CoA and acylcarnitine [4,6]. Consequently, it can regulate the ratio of acyl-CoA/CoA. Under normal conditions, the concentration of carnitine and acylcarnitine in the endogenous carnitine pool are relatively stable (a ratio of approximately 4), but their imbalance is associated with mitochondrial dysfunction [1,8]. In addition, free carnitine can support energy metabolism by regulating the ratio of free CoA to acyl-CoA in mitochondria, removing excessive or potentially toxic short- and medium-chain fatty acids from mitochondria, and thereby maintaining free CoA levels in mitochondria [1,9,10].

An imbalance in carnitine homeostasis can lead to many diseases. Patients often suffer from intracellular carnitine deficiency or excessive accumulation due to carnitine absorption, transport, or excretion disorders, leading to cardiomyopathy, lipid storage myopathy, fatty liver, and encephalopathy [11]. Recently, it has been found that an abnormal carnitine cycle also exists in tumor progression, including abnormal carnitine levels and carnitine cycle-related protein expression [11,12]. As the carnitine cycle plays an important role in mitochondrial fatty acid β-oxidation, its dysfunction is bound to alter the metabolic pattern of tumor cells, which will further affect the functional phenotype of tumors. Many studies have revealed the effect of carnitine cycle dysfunction on tumor phenotypes and their mechanisms, such as tumorgenesis, invasion, metastasis and chemotherapy resistance [7,12–15]. Here, we first review the existing studies to systematically analyze and characterize carnitine cycle dysfunction in tumor progression, and attempt to investigate its future research value.

2. Dysfunction of the carnitine cycle in tumor progression

The carnitine cycle involves various enzymes and transport proteins, including carnitine palmitoyltransferases (CPTs), CACT,

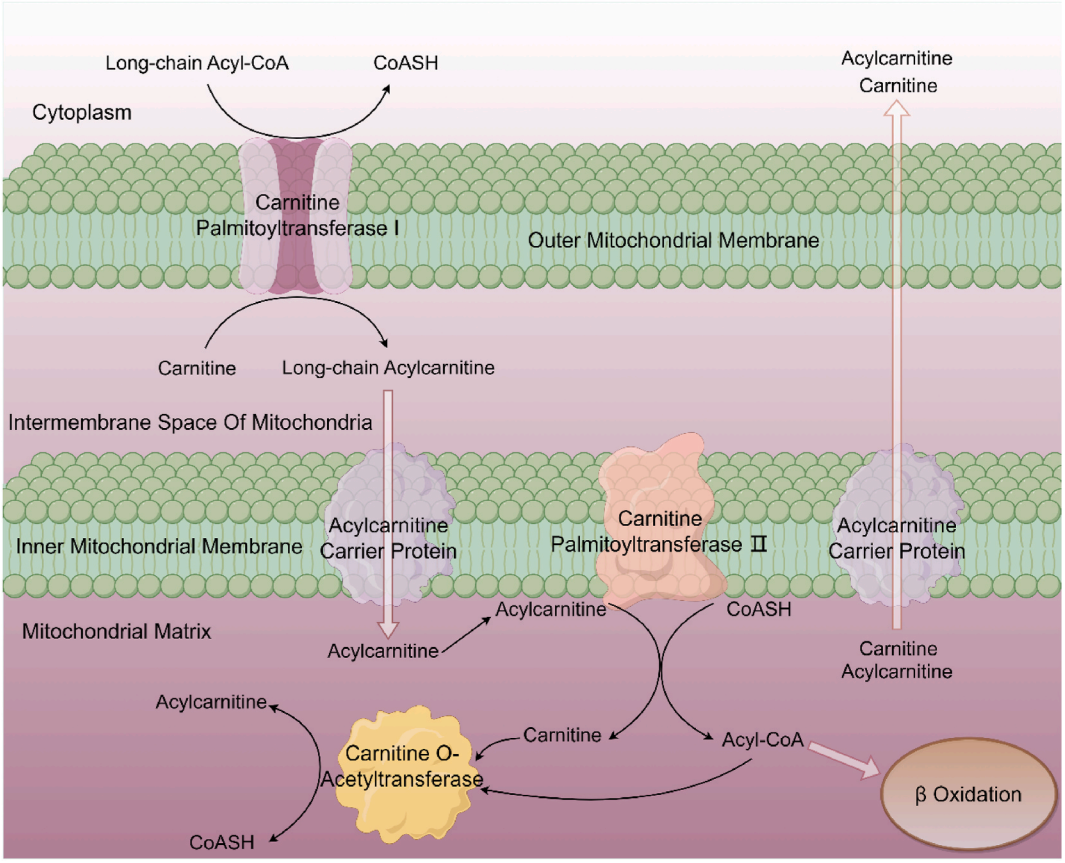

Fig. 1. The carnitine cycle assists long-chain acyl-CoA in entering mitochondria for β-oxidation (by Figdraw). CPTI converts acyl-CoA to acyl-carnitine, CACT exchanges acylcarnitine and free carnitine between the outer and inner mitochondrial membranes, and finally, CPTII converts acylcarnitine back to acyl-CoA for β-oxidation. CRAT in the matrix reconverts acyl-coenzyme A to acyl-carnitine.

CRATs, organic cation/carnitine transporter proteins (OCTNs), the membrane carnitine transporter protein CT2, and amino acid transporter $B^{0,+}$ ($ATB^{0,+}$). These proteins play critical roles in the carnitine cycle, and their aberrant expression and activity have been reported to participate in tumor progression (Tables 1 and 2). The carnitine level in serum and tumor tissue presents a gradual trend of change with tumor progression.

2.1. Enzymes and transporters in the carnitine cycle

2.1.1. CPT

CPT has two isoforms: CPTI and CPTII. CPTI has three isoforms, CPTIA, B, and C, whose distribution is tissue-specific [16]. CPTIA is the major isoform, and its expression is high in the intestine, liver, kidney, and lung [16]. CPTIB is predominant in skeletal muscle, heart, and adipose tissue, and CPTIC is mainly expressed in the brain [16,17]. Both CPTIA and CPTIB are located in the outer membrane of mitochondria, while CPTIC is located in the endoplasmic reticulum and outer mitochondrial membrane [16,18]. It has been shown that CPTI is overexpressed in various types of tumors, and patients with high CPTIA expression usually have a worse prognosis [19–22]. CPTI-mediated FAO can contribute to the formation of metabolic adaptations in tumors by increasing the production of ATP and NADPH [18,19,23,24], and to promote tumor cell proliferation by increasing nucleoside metabolism intermediates [25]. In addition, CPTI can remove palmitoyl-CoA from the cytoplasm and impede the production of C16 and C18-ceramides involved in the apoptotic pathway [26]. It has also been reported that the nuclear localization of CPTI is only present in tumor cells and that it can synergize with histone deacetylase 1 (HDAC1) to regulate tumor histone acetylation levels [27]. Although CPTI has a specific tissue distribution, targeted inhibition of all three isoforms attenuates tumor cell proliferation, chemoresistance, and neovascularization [19].

Compared with CPTI, CPTII plays opposite roles in different tumors. CPTII levels are significantly increased in recurrent breast cancer and chronic lymphocytic leukemia [28,29]. High CPTII expression induces radiation resistance in breast cancer stem cells with an associated poor prognosis [28], and knockdown of CPTII inhibits proliferation and metastasis in triple-negative breast cancer cells [30]. However, CPTII expression is frequently downregulated in colorectal cancer (CRC), hepatocellular carcinoma (HCC), and primary ovarian serous carcinomas; low CPTII expression is an independent prognostic factor for poorer overall survival [31–34]. Downregulation of CPTII expression can promote tumor cell proliferation, metastasis, and chemoresistance by inhibiting p53 expression, activating the ROS pathway, or enhancing stearoyl coenzyme A desaturase-1 (SCD-1)-mediated fatty acid biosynthesis [31–34]. Furthermore, studies have found that the downregulation of CPTII leads to the accumulation of acylcarnitine in HCC cells, which contributes to the formation of the lipid-rich tumor environment [35,36]. On the one hand, the knockdown of CPTII enhances HCC resistance to lipotoxicity by inhibiting steroid receptor coactivator (Src)-mediated activation of c-Jun amino-terminal protein kinase (JNK); on the other hand, accumulated oleoylcarnitine induces stemness in HCC cells through activation of signal transducer and activator of transcription 3 (STAT3) [35,36].

Table 1
Research overview of carnitine palmitoyltransferase system in tumors.

CPT isoform	Inhibitor	Tumor type	Dysfunction
CPTI	Etomoxir, Oxfenicine, ST1326, Perhexiline, Avocatin B	Lymphocytic/acute myeloid leukemia	High expression contributes to tumor proliferation and enhances chemotherapy resistance; inhibition by ST1326 induces dose- and time-dependent cell growth arrest, cell cycle modulation, and apoptosis; inhibition by Etomoxir has antitumor actions.
		Prostate cancer	Upregulated expression; inhibition by Etomoxir results in a significant decrease in viability.
		Glioblastoma	Upregulated expression; inhibition by Etomoxir impairs NADPH production and increases reactive oxygen species resulting in ATP depletion and cell death.
		Breast cancer	Upregulated expression; promotes tumor cell growth and progression; promote cancer cell stemness and chemoresistance; promotes histone acetylation in tumor cells; inhibition by perhexiline can sensitize drug-resistant breast cancer cells to chemotherapy.
		Ovarian cancer	Upregulated expression; high expression facilitates cell cycle progression in ovarian cancer; promotes cell proliferation and migration.
		Lung cancer	High expression promotes cell survival and tumor growth under conditions of metabolic stress; inhibition by Etomoxir attenuates chemoresistance of paclitaxel.
		Colorectal cancer	Upregulated expression; promotes proliferation and migration; CPTIA-dependent FAO promotes the acetylation and nuclear translocation of β-catenin.
		Gastric cancer	High expression promotes cell proliferation and metastasis; silencinge of CPTIC suppresses cell proliferation and induces cell cycle arrest.
CPTII	Perhexiline, Aminocarnitine	Breast cancer	Upregulated expression; high expression induces radiation resistance in breast cancer stem cells; knockdown of CPTII inhibits proliferation and metastasis in triple-negative breast cancer cells.
		Colorectal cancer	Downregulated expression; downregulation trigger stemness and oxaliplatin resistance; downregulation promotes proliferation and inhibits apoptosis through the p53 pathway.
		Hepatocellular carcinoma	Downregulated expression; downregulation enhances resistance to lipotoxicity and induces stemness in HCC cells; downregulation promotes tumorigenesis and chemoresistance to cisplatin.
		Ovarian cancer	Downregulated expression; downregulation promotes tumor growth and metastasis through inducing ROS/NF-κB pathway.

Table 2
Important carnitine transporters involved in tumors.

Carnitine related protein	Aliases	Substrate	Tumor type	Dysfunction
SLC22A4	OCTN1	Acetylcholine, Ergothioneine, Carnitine and acylcarnitine with low affinity, Anticancer drugs	Colorectal cancer, Acute myeloid leukemia	Transport of chemotherapeutic drugs such as camptothecin, cytarabine, floxuridine, and mitoxantrone.
SLC22A4	OCTN2	Carnitine and carnitine derivatives with the highest affinity, Anticancer drugs	Glioma, Epithelial ovarian cancer, Breast cancer, Colorectal cancer, Lung adenocarcinoma, Renal cancer, Pancreatic cancer	Upregulated expression; high expression increases carnitine uptake by tumor cells and promotes tumor cell proliferation; transport of chemotherapeutic drugs such as etoposide, oxaliplatin, and imatinib; inhibition by meldonium reduces tumor growth by enhancing sensitivity to exogenous damage.
SLC22A16	CT2	Spermidine, Carnitine, Anticancer drugs	Epithelial ovarian cancer, gastric cancer, Acute myeloid leukemia, Diffuse large cell lymphoma, Testicular cancer	Upregulated expression; knockdown of CT2 expression inhibits the growth and viability of acute myeloid leukemia cells; transport of chemotherapeutic drugs adriamycin, bleomycin, and cisplatin.
SLC6A14	$ATB^{0,+}$	Amino acids, Carnitine and propionylcarnitine with low affinity	Colorectal cancer, ER^+ breast cancer, Pancreatic cancer, Cervical cancer	Upregulation in solid tumors, used for drug delivery such as 5-fluorouracil.
SLC25A20	CACT	Carnitine, Acylcarnitine	Prostate cancer, Bladder cancer	Upregulation in androgen-dependent and nondependent prostate cancer cells; promoting histone acetylation in tumor cells indirectly.

2.1.2. CACT(SLC25A20) and CRAT

CACT and CRAT have been rarely studied in tumors, and their relationship with tumors needs to be clarified. Valentino et al. found that high expression of CACT and CRAT in androgen-dependent and nondependent prostate cancer (PCa) cells is fundamental for maintaining tumor mitochondrial FAO under heavy lipid load, which contributes to maintaining high metabolic flexibility in PCa [37]. In addition, acetylcarnitine which generated under the catalysis of CRAT can be transported out of the mitochondria by CACT. Then, it enters the nucleus, where it is converted to acetyl-CoA by intranuclear CRAT and becomes a source of acetyl groups for histone acetylation, thereby mediating epigenetic regulation of tumors [38–40].

2.1.3. OCTN1 (SLA22A4) and OCTN2 (SLC22A5)

There are three isoforms of OCTNs, including OCTN1 (SLA22A4), OCTN2 (SLC22A5), and OCTN3 (SLC22A21), which are expressed only in mice [41]. OCTN1, which is highly expressed in the kidney, mainly transports acetylcholine and ergothioneine, and it only transports free carnitine and acetylcarnitine with low affinity in a Na^+-dependent manner [42–45]. Therefore, OCTN1 is not a major carnitine transporter protein in vivo. However, previous studies have found that OCTN1 is highly expressed in some tumors and may contribute to tumor development in a noncarnitine cycle-dependent manner [14,46]. Interestingly, OCTN1 has also been reported to function as a transporter of some chemotherapeutic drugs (camptothecin, cytarabine, floxuridine, and mitoxantrone) and contributes to the enhancement of drug sensitivity in tumor cells [47–50].

OCTN2 is an essential carrier of carnitine transport that is widely present in the human body, and it has now been found to be expressed abnormally in various tumors [51–53]. However, the exact effect remains elusive. Wang et al. found that estrogen in estrogen receptor (ER)-positive breast cancer induced OCTN2 expression by binding to the estrogen response element (ERE), increasing carnitine uptake by tumor cells and promoting tumor cell proliferation [51]. Similarly, OCTN2 expression is upregulated in glioblastoma multiforme (GBM) and is higher in high-grade and recurrent GBM [52]. High OCTN2 expression negatively correlates with the overall survival of patients [52,54]. In contrast, inhibition of OCTN2/carnitine can reduce GBM cell survival by enhancing GBM sensitivity to exogenous damage (e.g., hypoxia, metabolic and cytotoxic stress) [52]. However, data in CANCERTOOL, developed by Cortazar et al. show that OCTN2 expression is significantly lower in colorectal cancer than in normal tissue [55,56]. Similarly, Scalise et al. found that OCTN2 expression is downregulated in epithelial tumor cell lines, which may be related to the hypermethylation status of the OCTN2 promoter region [53,57]. It has also been reported that chemotherapeutic drugs such as etoposide, oxaliplatin, and imatinib can be absorbed by cells via OCTN2 [58–60].In contrast, these chemotherapeutic drugs can inhibit the transcription of downstream OCTN2 by downregulating the expression of peroxisome proliferator-activated receptor gamma coactivator 1α (PGC-1α), thereby affecting the transport of carnitine [61].

2.1.4. CT2(SLC22A16)

The membrane carnitine transporter protein CT2 belongs to the SLC22 family. It has been subsequently categorized as the sixth member (OCT6) of the organic cation transporter (OCT) family of proteins, which primarily mediates the intra- and extra-cellular transport of carnitine and spermine [62]. The expression profile of CT2 in normal tissues is narrow and is mainly expressed in the testis and bone marrow [62,63]. Its mediated transport of carnitine may play an essential role in sperm maturation [62]. Previous

studies have found that CT2 is often overexpressed in epithelial ovarian cancer, gastric cancer, and acute myeloid leukemia cells, whereas the tissues of origin of these tumors usually do not express CT2 [14,64–66]. This implies that tumor cell development is closely related to an abnormal carnitine cycle. Zhao et al. found that CT2 expression was significantly upregulated in gastric cancer cells and that high expression of CT2 is a poor prognostic indicator of gastric cancer [66]. Similarly, the knockdown of CT2 expression inhibited the growth and viability of acute myeloid leukemia cells [64]. In recent years, it has been found that CT2 can also transport the chemotherapeutic drugs adriamycin, bleomycin, and cisplatin, enabling the accumulation of chemotherapeutic drugs in tumor cells [13]. Novak et al. found that CT2 was absent in 54 % of patients with diffuse large B-cell lymphoma (DLBCL) failing to achieve event-free survival failure at 24 months after diagnosis by whole-exome analysis, and CT2 may function as an adriamycin transporter protein in DLBCL cells [67]. In addition, overexpression of CT2 in leukemic Jurkat cells also significantly increased sensitivity to adriamycin [68]. NT1/D2 human testicular cancer cells, which highly express CT2, are extremely sensitive to bleomycin-A5 [69]. Upregulation of CT2 expression in lung cancer cells mediates the accumulation of cisplatin (CDDP) in the tumor cells, which enhances sensitivity to cisplatin [70]. Conversely, compared to their respective parental cells, both CT2 gene and protein expression were downregulated in cisplatin-resistant cells compared to their respective parents [70].

2.1.5. $ATB^{0,+}$(SLC6A14)

$ATB^{0,+}$/SLC6A14 is a Na^+/Cl^- -dependent cotransporter protein expressed primarily in lung and intestinal epithelia with broad substrate specificity [71]. $ATB^{0,+}$ can mediate the transport of neurotransmitters, carnitine, and all amino acids except aspartate and glutamate [72]. However, unlike OCTN2, $ATB^{0,+}$ can only transport carnitine and propionylcarnitine [73]. To date, $ATB^{0,+}$ has been found to be overexpressed in various tumors [74,75]. Although this may be more attributable to the high-capacity amino acid transport function of $ATB^{0,+}$, it does not exclude the contribution of its carnitine transport function to tumor FAO gain [13]. Current studies have considered $ATB^{0,+}$ a target for targeted drug delivery [76–78]. Kou et al. used carnitine-coupled nanoparticles targeting OCTN2 and $ATB^{0,+}$ to deliver 5-fluorouracil to tumor cells, and the results showed that the coupled drug had a stronger targeted killing effect [78].

2.2. Carnitine/acylcarnitine level

The relative balance of carnitine and acylcarnitine as substrates of the carnitine cycle is crucial for metabolism. Abnormal carnitine levels are frequently identified in tumors due to metabolic reprogramming, and numerous studies have found that abnormal carnitine levels in the serum or tumor tissue of patients may serve as tumor markers. For example, serum carnitine concentrations are significantly lower in patients with endometrial cancer than in healthy women, and carnitine levels in serum gradually decrease with tumor progression [79]. A large case-control study of endometrial cancer in Poland found that the levels of pivaloylcarnitine, octenoylcarnitine, and decatrioylcarnitine in serum were significantly lower in patients than in healthy individuals [80]. Serum samples from patients with prostate cancer were also found to have lower levels of decanoylcarnitine, octanoylcarnitine, and 5-cis-tetradecenoylcarnitine [81]. In addition, metabolomic analysis of hepatocellular carcinoma found increased levels of long-chain acylcarnitine (>C14) and reduced levels of short- and medium-chain acylcarnitine in HCC tissues compared to paracancerous or distal normal tissues [82]. In particular, acetylcarnitine was the only differentially abundant metabolite associated with tumor grade, and serum acetylcarnitine levels in patients with HCC were significantly and negatively correlated with γ-glutamyl transferase (GGT) levels and tumor grade [82]. However, using a spatial metabolomics strategy based on mass spectrometry imaging (MSI), Sun et al. found that the expression levels of carnitine and short-chain acylcarnitine (acetylcarnitine, propionylcarnitine, butyrylcarnitine, valeronylcarnitine, and hexanoylcarnitine) were significantly higher in human breast cancer tissues than in adjacent normal tissues, and butyrylcarnitine was statistically significant for differentiating tumors from normal tissue [83,84]. In addition, the spatial expression of carnitine and short-chain acylcarnitine in breast cancer tissues presented a downward gradient from the center region to the adjacent region [83]. This spatial distribution may be attributed to the inhibition of fatty acid β-oxidation in the central tumor region induced by severe hypoxia and oxidative stress, which in turn leads to carnitine accumulation [85].

3. Targeting the carnitine cycle in tumor therapy

As the role of the carnitine cycle in tumors has been increasingly revealed, targeting the carnitine cycle has been recognized as a promising strategy in tumor therapy.

3.1. Targeting enzymes and transporters of the carnitine cycle

As CPTI generally exerts protumorigenic effects, current studies related to inhibitors of the carnitine cycle have also focused on targeting the FAO rate-limiting enzyme, CPTI. To date, the known CPTI inhibitors include etomoxir, perhexiline, avocatin B, oxfenicine and ST1326, which can produce cytotoxicity by blocking the entry of fatty acids into mitochondria, inhibiting the fatty acid β-oxidation process, significantly reducing intracellular ATP and NADPH levels, and activating the mitochondrial apoptosis pathway [29,86–89] (Table 1). Etomoxir, an irreversible CPTIA and B inhibitor, has been used in the study and treatment of type 2 diabetes and heart failure [90,91]. Other studies have reported that etomoxir exerts antiproliferative and metastatic effects on tumors by inhibiting CPTIA and CPTIB and increasing the sensitivity of tumor cells to radiotherapy and chemotherapy [25,92–94]. However, it has been shown to have significant hepatotoxicity and cardiotoxicity and is still in the preclinical stage [95–97].

Perhexiline was initially developed in the 1970s as an antianginal drug that inhibited CPTI and II [29,98]. Although perhexiline is now approved as an angina treatment in clinical trials, its neurologic and hepatic toxicity is difficult to avoid [29,98]. Thus, its clinical

use is decreasing. Similarly, perhexiline has been reported to significantly inhibit tumor cell proliferation and survival by targeting CPT [29,99–102]. Interestingly, Kant et al. found in glioma that piperacillin exerts antitumor functions not by inhibiting FAO but by inhibiting the activation of tyrosine-protein kinase Fyn [103].

The side effects of etomoxir and perhexiline are mainly attributed to the disorder of cellular metabolism caused by the low selectivity of the drug. In contrast, ST1326, a novel reversible inhibitor developed in recent years, has been reported to be highly selective for CPTIA [104]. In mouse model of type II diabetes, full-dose long-term treatment with an oral formulation of ST1326 (teglicar) did not cause side effects such as cardiac hypertrophy and muscle insulin resistance as caused by etomoxir, and demonstrated excellent safety [105]. In tumors with high CPTIA expression, such as acute myeloid leukemia, ST1326 effectively inhibits FAO and induces cytotoxicity, suppressing tumor cell proliferation in a time-and dose-dependent manner [89]. Given the efficacy and safety of ST1326 in current trials, it is expected to be investigated in clinical trials and become a “new weapon” for tumor treatment. However, other reported inhibitors of CPTI, such as avocatin B and oxfenicine, have only been verified in vitro to induce acute myeloid leukemia cell and melanoma cell death, but whether they can be applied in clinical applications remains to be explored [87,89,106].

For carnitine-associated transporters, the OCTN2 inhibitor meldonium can be used to impede the growth of OCTN2 high expressing tumor cells [52]. In addition, tumor therapy can be optimized by drug delivery via the transporters. For example, it has been shown that carnitine-conjugated nanoparticles loading paclitaxel/5-fluorouracil can significantly improve drug efficacy in tumor cells with high OCTN2 and $ATB^{0,+}$ expression [78,107,108]. Moreover, as the transporters such as OCTN1, OCTN2, CT2, and $ATB^{0,+}$ exhibit the functionality in the uptake of chemotherapeutic drug, they are potential therapeutic targets to enhance chemosensitivity.

3.2. *Exogenous supplementation therapy with carnitine/acylcarnitine*

Numerous experiments have found that exogenous supplementation with L-carnitine inhibits tumorigenesis and progression in vivo/in vitro. In a mouse model of CRC, oral L-carnitine or acylcarnitine can inhibit colon cancer formation induced by intraperitoneal injection of 1,2-dimethylhydrazine (DMH)/pyrimethamine (AOM), while the combination of curcumin and acetylcarnitine completely inhibits the progression of advanced adenoma lesions (adenomas larger than 1.5 mm in size with submucosal invasion) [109,110]. Similarly, the combination of carnitine with drugs such as butyrate also induces apoptosis in CRC cells in vitro [111–113]. Acetylcarnitine has also been reported to inhibit PCa cell proliferation and induce PCa cell apoptosis in vivo/ex vivo [114]. In addition, acetylcarnitine hinders the production of pro-inflammatory cytokines (TNF-α and IFN-γ) and chemokines CCL2, CXCL12, and receptor CXCR4 and downregulates the expression of metalloproteinase (MMP-9), thus inhibiting the adhesion, migration, and invasive ability of PCa cells in vitro [114,115]. It also inhibits the proliferation and apoptosis of PCa cells in vivo/ex vivo by decreasing the production and release of intracellular pro-angiogenic factors [vascular endothelial growth factor (VEGF), CXCL8, CCL2, angiopoietin] in PCa cells, inhibiting the pro-angiogenic effects of the tumor [114,116]. Moreover, the vitro study of anti-cancer therapy in breast cancer stem cells has demonstrated that L-carnitine could potentially inhibit proliferation and induce apoptosis by decreasing the expression levels of p-JAK2, p-STAT3, leptin receptor, and components of the leptin pathway [117].

In a mouse model of HCC, oral L-carnitine supplementation reduced ROS production and mtDNA mutations by correcting mitochondrial dysfunction and delaying hepatocarcinogenesis [118]. Oral L-carnitine supplementation can also significantly reverse the increase in liver enzyme levels, thiobarbituric acid reactive substances (TBARS), and total nitrate/nitrite (NO_x) induced by intraperitoneal injection of diethylnitrosamine (DENA). It can also reverse the decrease in total carnitine levels and reduce glutathione (GSH), glutathione peroxidase (GSH-Px) and catalase (CAT) levels, thereby inhibiting precancerous lesions and preventing the occurrence of HCC. However, D-carnitine aggravates DENA-induced liver injury [119].Moreover, Huang et al. found that L-carnitine can directly inhibit HDACI/II activity by binding to the active site of HDAC, leading to the accumulation of histone acetylation in the promoter region of the cyclin-dependent kinase inhibitor p21 [120]. This, in turn, induces the expression of p21 in HCC cells and inhibits the proliferation of HCC cells in vivo/in vitro [120]. Similarly, L-carnitine can also enhance the sensitivity of tumor cells to apoptosis induced by tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) through the upregulation of the pro-apoptotic protein BCL2 associated X protein (Bax) [121]. Recently, Wang et al. found that cysteine-rich intestinal protein 1 (CRIP1) can downregulate the levels of L-carnitine and acetylcarnitine by inhibiting the expression of γ-butyl betaine hydroxylase (BBOX1), a key enzyme in the carnitine synthesis pathway [122]. This thereby reduces β-catenin acetylation levels, promoting β-catenin nuclear aggregation and activating the Wnt/β-catenin signaling pathway, ultimately enhancing HCC cell stemness [122].

However, a few studies have also found that L-carnitine/acylcarnitine supplementation promotes tumor development. Using a mouse model of liver cancer induced by diethylnitrosamine (DEN), Fujiwara et al. found that oral L-carnitine under normal feeding conditions cannot delay the development of HCC; instead, L-carnitine supplementation under high-fat diet feeding conditions promoted tumor development [36]. Further metabolomic analysis revealed that the levels of octadecanoylcarnitine and palmitoylcarnitine were significantly higher in induced HCC tissues than in normal liver tissues [36]. The accumulation of octadecanoylcarnitine can promote HCC development through the activation of STAT3, and this finding agrees with the finding by Yaligar et al. that acylcarnitine accumulation in the precancerous stages of HCC is a crucial feature of the early metabolic changes in HCC [123].

Although exogenous supplementation of carnitine and acylcarnitine has been found to inhibit tumor development, there are still many concerns that need to be addressed regarding the therapeutic strategy of exogenous supplementation of carnitine and acylcarnitine to modulate tumor FAO. 1. The differences in response to carnitine/acylcarnitine in different types of tumors may be related to heterogeneity and their different tumor microenvironments and stages. 2. The kinetics of the carnitine cycle in mice and humans are different, so more clinical studies are needed to confirm the findings obtained in animal models. 3. Because L-carnitine is not selective for normal and tumor cells and there are individual differences in the bioavailability of carnitine, the clinical benefits of carnitine use

remain to be investigated. When the carnitine cycle-related enzymes in the body are dysregulated, the clinical benefit achieved by carnitine/acylcarnitine alone may not be as expected, and sometimes the overdose of carnitine to achieve efficacy may aggravate the metabolic imbalance in the patient. Therefore, carnitine and acylcarnitine would be more feasible as adjuvant agents for relieving cachexia and chemotherapy-induced neurological and cardiac toxicity in tumor patients [124–126].

Significantly lower serum carnitine levels have been reported in patients with cachexia due to frequent metabolic disorders (reduced intake and increased metabolism) and drug treatment interfering with the absorption, synthesis, and excretion of carnitine [61,124]. Clinical research found that oral L-carnitine supplementation could improve tumor cachexia [127]. Studies have shown that L-carnitine may reduce chronic inflammation (increased levels of IL-6 and TNF-α) and oxidative stress (increased levels of ROS and reduced levels of GSHPx) in patients with advanced tumors by activating peroxisome activated receptor-γ (PPAR-γ), thereby improving symptoms of cachexia such as muscle wasting, fatigue and inflammatory/oxidative status [124,128]. In addition, carnitine supplementation may reduce the toxic side effects caused by chemotherapy. During cisplatin, vincristin or paclitaxel treatment, exogenous supplementation of L-carnitine can enhance neuronal responsiveness to nerve growth factor (NGF) by inhibiting lipid peroxidation in neuronal cells or by promoting histone acetylation as an acetyl donor, attenuating drug-induced peripheral neurotoxicity [125,129,130]. Moreover, acetylcarnitine does not affect the antitumor effects of chemotherapeutic agents such as cisplatin and vincristine [125,129,130]. Similarly, Saro suggests that L-carnitine supplementation may alleviate anthracycline-induced cardiotoxicity in pediatric tumor patients and reduce the probability of cardiovascular complications [126].

4. Conclusions and perspectives

Numerous experiments have found that an abnormal carnitine cycle is involved in tumor progression. Targeting the key enzymes and transporters of the carnitine cycle and supplementing carnitine for tumor treatment have gained much support through in vitro and animal experiments. However, the individual variations in metabolic phenotypes, tumor characteristics, and drug toxicity make it difficult for all tumor patients to benefit from this strategy. Therefore, future research should focus on the heterogeneity of tumor genes and metabolic phenotypes to screen out which patients could benefit from the regulators of the carnitine cycle.

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CRediT authorship contribution statement

Xiangjun Wang: Writing – original draft. **Chuanxin Yang:** Writing – original draft. **Chao Huang:** Writing – review & editing, Funding acquisition. **Wei Wang:** Writing – review & editing, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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