Journal of Translational Medicine

REVIEW

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Comprehensive review of the expanding roles of the carnitine pool in metabolic physiology: beyond fatty acid oxidation

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Abstract

Traditionally, the carnitine pool is closely related to fatty acid metabolism. However, with increasing research, the pleiotropic effects of the carnitine pool have gradually emerged. The purpose of this review is to comprehensively investigate of the emerging understanding of the pleiotropic role of the carnitine pool, carnitine/acylcarnitines are not only auxiliaries or metabolites of fatty acid oxidation, but also play more complex and diverse roles, including energy metabolism, mitochondrial homeostasis, epigenetic regulation, regulation of inflammation and the immune system, tumor biology, signal transduction, and neuroprotection. This review provides an overview of the complex network of carnitine synthesis, transport, shuttle, and regulation, carnitine/acylcarnitines have the potential to be used as communication molecules, biomarkers and therapeutic targets for multiple diseases, with profound effects on intercellular communication, metabolic interactions between organs and overall metabolic health. The purpose of this review is to comprehensively summarize the multidimensional biological effects of the carnitine pool beyond its traditional role in fatty acid oxidation and to summarize the systemic effects mediated by carnitine/acylcarnitine to provide new perspectives for pharmacological research and treatment innovation and new strategies for the prevention and treatment of a variety of diseases.

Keywords Carnitine, Acylcarnitine, Mitochondrial, Metabolism, Fatty acid oxidation, Carnitine transport

Introduction

The traditional view of cellular metabolism is that metabolic processes are passively adapted to meet the needs of the cell. However, modern research has shown that metabolites not only participate in metabolic reactions but are also important regulatory factors in the intracellular environment and intercellular communication [1]. The carnitine pool, comprising carnitine and its acyl derivatives, has been the subject of considerable interest because of its pivotal function in fatty acid oxidation (FAO). With the advent of omics technology, our understanding of the intricate roles of the carnitine pool in health and disease has become more profound [2]. The role of the carnitine pool has expanded from FAO to more biological processes [3, 4]. Carnitine and acylcarnitines are exchanged between different tissues as metabolic intermediates or signaling molecules, directly or indirectly affecting a variety of metabolic and biological pathways in almost all organs, and have broad impacts on interorgan communication and metabolic cooperation.

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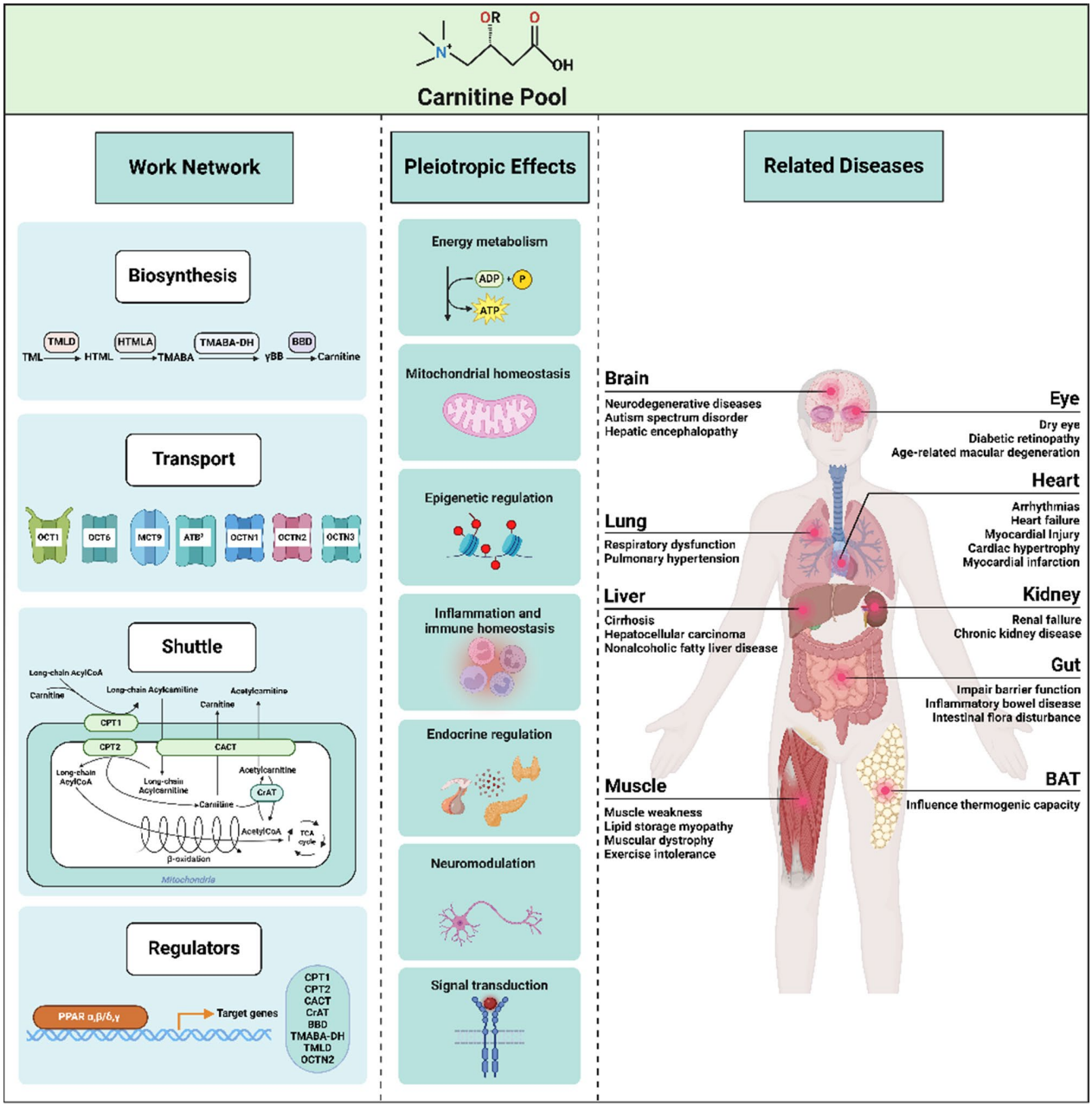
Graphical Abstract



The aim of this review is to provide a comprehensive overview of the multidimensional biological effects of the carnitine pool beyond FAO, and to explore its potential applications and impacts on intercellular communication, inter-organ metabolic interactions, and overall metabolic health. We focus on the roles of the carnitine pool in energy metabolism, mitochondrial homeostasis, epigenetic regulation, inflammation and immune homeostasis, endocrine regulation, neuromodulation, and signal transduction. By thoroughly investigating the systemic effects mediated by the carnitine pool, including its impacts on the liver, gut, kidney, muscle, heart, lung, and eye, we emphasize the importance of maintaining carnitine pool homeostasis for overall metabolic health and inter-organ metabolic cooperation. Additionally, we analyze its potential as multidisease biomarker, crosstalk mediator, and therapeutic target, providing new strategies and perspectives for drug research and the prevention and treatment of various diseases.

Methods

This review provides a comprehensive overview of the pleiotropic roles of the carnitine pool in metabolic physiology, especially its biological functions beyond FAO. We conducted an extensive literature search using multiple databases, including PubMed, Web of Science, Scopus, and Google Scholar. The search terms included "carnitine", "acylcarnitine", "metabolism", "inflammation", "neuroprotection", "mitochondrial", "epigenetic regulation" and "disease". There were no language or time restrictions on the search, but we focused on articles published in the past 20 years to ensure the relevance and timeliness of the information. We included original studies, review articles, and clinical trials that investigated the roles of the carnitine pool in various physiological and pathological states. These papers provided insights into the functions of carnitine and acylcarnitine in diverse biological processes. We excluded studies that were duplicates, had incomplete data, were less relevant to the topic, or focused solely on FAO. Two independent researchers screened the eligible literature and extracted data, focusing on the trends, biological effects, and mechanisms of action of carnitine/acylcarnitine under different physiological and pathological conditions. Each included study was critically evaluated for its methodological quality, relevance, and contribution to the field.

Pleiotropic effects of the carnitine pool

Carnitine can be combined with fatty acid chains of different lengths to derive a variety of acylcarnitines, which are amphiphilic because they contain hydrophilic quaternary ammonium groups and hydrophobic carbon chains [5], and acylcarnitines of different chain lengths have diverse chemical structure and metabolic pathways, making them widely involved in pathophysiology. These effects include energy metabolism, mitochondrial homeostasis, epigenetic regulation, endocrine regulation, inflammation and immune homeostasis, signal transduction, and neuromodulation (Fig. 1).

Energy metabolism

The carnitine pool plays a vital role in maintaining the body's energy balance and overall health. Carnitine finely regulates the metabolic pathway through fatty acid transport. The β-hydroxyl of carnitine is acylated so that acyl-coenzyme A (acyl-CoA), which cannot directly cross the inner mitochondrial membrane, can be transported into the mitochondrial matrix and then participate in β-oxidation to produce ATP. Incomplete FAO leads to the accumulation of even-chain acylcarnitines from C4 to C22 in the mitochondria, with a corresponding decrease in carnitine levels [6]. These acylcarnitines are then transported out of the mitochondria and released outside the cell to accumulate in the blood and urine. They are used as biomarkers for a variety of diseases.

The regulation of the carnitine pool also extends to carbohydrate metabolism, which helps the body maintain metabolic flexibility [7]. When FAO or glycolytic flux is increased, carnitine maintains the balance of intracellular metabolism by buffering excess acetyl-CoA to prevent its accumulation to harmful levels [8]. As acetyl-CoA is a universal breakdown product of metabolic substrates, acetylcarnitine becomes the most abundant acylcarnitine species in tissues and blood, acting as a regulator of cellular substrate utilization. This process, which ensures an adequate supply of free CoA, is essential for the oxidation of pyruvate and helps to coordinate pyruvate dehydrogenase activity with the rate of glycolysis, thereby maintaining the body's ability to switch between fat and carbohydrate as the main energy substrate [9].

In addition, the carnitine pool influences the metabolic process of branched-chain amino acids (BCAAs). Normally, BCAAs (e.g., valine, leucine and isoleucine) can be converted to their corresponding branched-chain keto acids that in turn can be converted to branched-chain CoA, which can also bind carnitine to form branched-chain acylcarnitines (BCACs), such as propionylcarnitine (C3-carnitine), succinylcarnitine (C4DC-carnitine) and isovalerylcarnitine (isoC5-carnitine), which are involved in the energy production process of cells [10]. However, excessive BCACs produced by the breakdown of branched-chain amino acids can interfere with normal mitochondrial function and cause energy metabolism disorders [11].

Mitochondrial homeostasis

Carnitine pool homeostasis plays an important role in maintaining mitochondrial function and integrity [12, 13]. Carnitine can effectively inhibit mitochondria-dependent apoptosis by regulating the balance of Bcl-2/Bax, inhibiting the mitochondrial permeability transition (MPT), and reducing mitochondrial membrane damage and the release of apoptosis-related factors [14, 15]. Acetylcarnitine can also improve mitochondrial biosynthesis, quality control and dynamics by increasing the levels of peroxisome proliferator-activated receptor γ coactivator 1α (PGC-1α) and mitochondrial DNA (mtDNA) [16]; increasing the expression of mitofusin 1 (MFN1) and mitofusin 2 (MFN2); and decreasing the expression of dynamin-related protein 1 (Drp1) and mitochondrial fission protein 1 (Fis1) [17].

Mitochondria are the major source of reactive oxygen species (ROS) in cells. If the scavenging capacity of the antioxidant system is insufficient, the accumulation of ROS further damages mitochondria, creating a vicious cycle. Carnitine and acetylcarnitine, which are potent antioxidants [18], can scavenge ROS and increase the

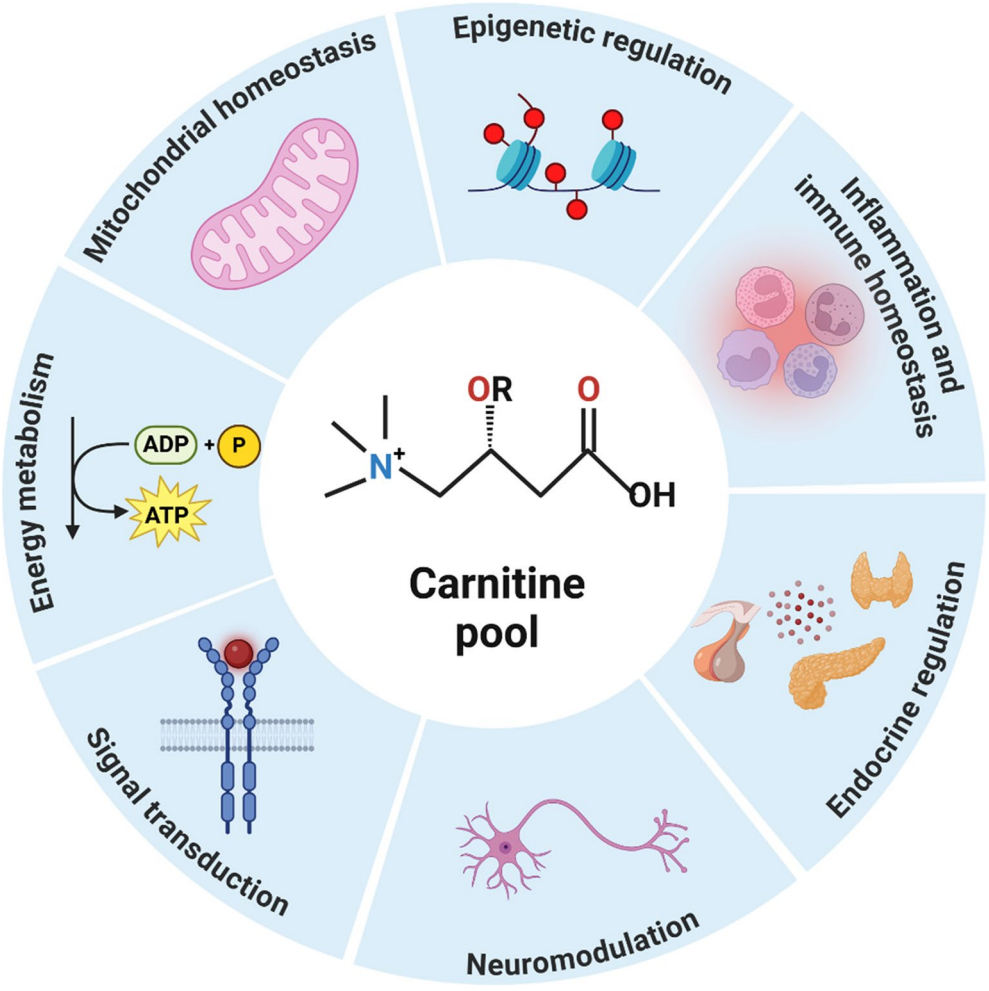


Fig. 1 Major physiological roles mediated by carnitine pool. The role of carnitine pool composed of carnitine and acylcarnitines has extended from fatty acid oxidation to more biological processes. Carnitine and acylcarnitines are not only participants in metabolic reactions, but also important regulators of intracellular environment and body homeostasis. Created with BioRender.com

levels of antioxidant enzymes such as superoxide dismutase (SOD) and catalase (CAT) [19]. However, when the level of long-chain acylcarnitines (LCACs) is abnormally elevated, not only is it a signal of mitochondrial dysfunction but its high concentration can also aggravate mitochondrial damage and further deteriorate mitochondrial function [20, 21]. Reducing the harmful accumulation of LCACs helps to improve mitochondrial function [22]. In the fatty acid pathway, the accumulation of LCACs is thought to be a major factor in ROS production. By inhibiting oxidative phosphorylation (OXPHOS), which induces mitochondrial hyperpolarization and subsequently stimulates ROS production [23], the oxidation of palmitoylcarnitine (C16-carnitine) produces more ROS in mitochondria than carbohydrates [24]. The hydrophobic tail of LCACs can be inserted into the membrane and may trigger the nonspecific activation of signaling pathways in the inner mitochondrial membrane to modulate its function, providing new insights into the unique mechanism of action of acylcarnitines in mitochondrial homeostasis [25].

The carnitine pool also affects the communication between mitochondria and other subcellular organelles. Carnitine affects the metabolic interaction between mitochondria and peroxisomes by participating in the acyl transfer between organelles [26, 27]. Peroxisomal β-oxidation is incomplete and is responsible for the oxidation of very long-chain fatty acids (VLCFAs) and branched-chain fatty acids (BCFAs) that are incompatible with mitochondrial enzymes to produce some shorter acyl-CoAs [28]. Carnitine then binds to VLCFAs to form the corresponding acylcarnitines, allowing them to leave the peroxisome and eventually enter the mitochondria for complete β-oxidation [29]. Carnitine-mediated acyl transfer not only ensures efficient fatty acid utilization and energy production in mitochondria and peroxisomes but also prevents the toxic accumulation of VLCFAs in cells. The accumulation of LCACs during mitochondrial

FAO disorders can inhibit the activity of PPARα/PGC1α, destroy the regeneration of peroxisomes, lead to increases in BCAA and ROS levels, and activate the nuclear factor erythroid 2-related factor 2 (Nrf2) pathway. Moreover, increased levels of LCACs may also induce endoplasmic reticulum (ER) stress and accelerate the progression of cell damage [30]. LCACs also affect Ca^{2+} homeostasis between the mitochondria and the ER. In cardiac cells, the physical proximity between mitochondria and the sarcoplasmic reticulum (SR, a specific type of ER in heart and skeletal muscle cells) allows the exchange of Ca^{2+} in local microdomains, providing rapid Ca^{2+} buffering. However, C16-carnitine disrupts this interaction, resulting in inefficient uptake of Ca^{2+} released from the SR by mitochondria, thereby exacerbating intracellular calcium overload [31]. The carnitine pool also influences mitochondrial–nuclear crosstalk. Carnitine has a trophic genomic effect, inducing the protein activity and mRNA expression of a variety of nuclear receptors, directly regulating nuclear receptor signaling to affect downstream targets of cell metabolism [32]. However, during high-fat diet (HFD) feeding, obesity and insulin resistance, the accumulation of medium-chain and long-chain acylcarnitines due to incomplete β-oxidation may negatively regulate the expression of nuclear-encoded mitochondrial genes, further reducing mitochondrial number and function and creating a vicious metabolic cycle [33].

Epigenetic regulation

The role of the carnitine pool in regulating epigenetic processes helps to reveal the deep link between cellular metabolism and epigenetic regulation. Carnitine/acetylcarnitine play active roles in histone acetylation [34]. Carnitine has been shown to be an endogenous histone deacetylase inhibitor capable of regulating the acetylation status of histones [35]. The increased FAO driven by carnitine leads to an increase in intracellular acetyl-CoA levels, which can be transferred to the nucleus for acetylation of histone H3K27, thereby activating GATA3 gene expression and promoting the differentiation of triple-negative breast cancer cells to the luminal cell state [36]. Notably, acetylcarnitine can act as an acetyl donor [37], supporting the acetylation process of cells through the shuttle mechanism of acetylcarnitine in the absence of conventional acetyl-CoA synthetase enzymes such as ATP-citrate lyase (ACLY) and acyl-CoA synthetase short chain 2 (ACSS2) [38]. Decreasing the level of acetylcarnitine can reduce the acetylation of β-catenin and promote its nuclear accumulation, leading to excessive activation of the Wnt/β-catenin signaling pathway [39]. Acetylcarnitine also has potential regulatory effects on pain perception and emotion regulation by increasing the level of acetylated H3K27 bound to the *Grm2* promoter through the epigenetic regulation of the type 2 metabotropic glutamate (mGlu2) receptor, as well as the acetylation of the NF-κB p65 subunit by increasing the transcription of the *Grm2* gene [40, 41]. The evidence indicates that acetylcarnitine may also play a beneficial role in the metabolism and functional recovery of aged hearts by increasing the acetylation of mitochondrial proteins [42].

Acylcarnitines also affect epigenetic regulation in various ways. In Erbin-deficient platelets, increased mitochondrial OXPHOS leads to the transfer of more acylcarnitine to B cells. Acylcarnitine subsequently increases the activity of mitochondrial electron transport chain complexes and mitochondrial OXPHOS by promoting the acetylation of H3K27. In addition, acylcarnitine accelerates the degradation of the PD1 protein by promoting the acetylation of the E3 ubiquitin ligase FBXO38, revealing not only the mediating role of acylcarnitine in mitochondrial communication between platelets and B cells but also its epigenetic regulatory role in regulating mitochondrial function and PD1 degradation [43]. In NOZ cells, acylcarnitine upregulates m6A methylation levels in a dose-dependent manner by decreasing the expression of ALKBH5 and increasing the level of METTL3, thereby stabilizing lncBCL2L11 expression [44]. Acylcarnitine also plays a role in the pathological development of nonsteroidal anti-inflammatory drug-exacerbated respiratory disease (N-ERD) by affecting the DNA methylation pattern of macrophages and directing macrophage function in a proinflammatory direction [45]. In addition, C16-carnitine has been shown to regulate the growth, differentiation and nerve regeneration of nerve cells by affecting the palmitoylation of the GAP-43 protein [46]. These findings highlight the important role of the carnitine pool as a bridge between cellular metabolism and epigenetic regulation and open the possibility of developing novel therapeutic strategies targeting specific metabolic and epigenetic targets.

Inflammation and immune homeostasis

The carnitine pool plays a role in the maintenance of inflammation and immune homeostasis. Carnitine has been shown to be an endogenous substance with anti-inflammatory properties [47], as it inhibits the activity of NF-κB and other core transcription factors involved in the inflammatory response and effectively reduces the levels of proinflammatory cytokines (e.g., IL-1β, IL-6, and TNF-α) [48, 49]. Carnitine can also exert anti-inflammatory effects by inhibiting the polarization of M1 macrophages and reducing the activity of Th17 cells and other proinflammatory cell populations [50, 51]. Similarly, acetylcarnitine can also increase the proportion of Treg cells in the colon, reduce the proportions of Th17 cells and macrophages, and regulate immune homeostasis [52]. Notably, carnitine increases the arachidonic acid-induced production of PGE1 and PGE2 in macrophages, whereas

in T and B cells, carnitine reduces the secretion of these prostaglandins. This specific regulation of immune cell function suggests that carnitine may act as a fine immune regulator [53].

In contrast, LCACs are thought to have the potential to activate inflammation, activating the NF-κB luciferase reporter gene in RAW 264.7 cells in an acyl chain length- and concentration-dependent manner, as well as the phosphorylation of JNK and ERK [54, 55]. The number of senescent $CD8^+$ T cells and their production of proinflammatory cytokines (e.g., IFN-γ and TNF-α) are positively correlated with acylcarnitine levels in the peripheral blood of patients with Graves' disease [56]. Lauroylcarnitine (C12-carnitine) can inhibit AMPK and secrete proinflammatory cytokines to promote the polarization of bone marrow-derived macrophages to the pro-inflammatory M1 phenotype [57]. C16-carnitine can induce IL-6 secretion and gene expression in PC3 cells [58]. Notably, acylcarnitine from renal cancer may act to reduce the inflammatory response, providing a mechanism by which these cells are able to evade immune surveillance [59]. During *Salmonella Typhimurium* infection, C16-carnitine localizes to regions of immune cell destruction, and C16-carnitine acts as a local immunoregulatory molecule that significantly interferes with host immune homeostasis by affecting the number and function of specific immune cell populations, such as T cells and B cells, suggesting that the accumulation of LCACs is part of the pathogen immune evasion strategy [60]. In addition, recent studies have shown that pentadecanoylcarnitine (C15-carnitine) has a wide range of anti-inflammatory activities in a variety of diseases and has pleiotropic activities related to supporting physical and mental health, which also differs from the general knowledge of LCACs [61]. Therefore, the inflammatory regulatory activity of LCACs should be treated with caution, and the immunomodulatory role of the carnitine pool requires further investigation in a wider range of immune cells and immune responses to fully understand its impact on immune regulation.

The carnitine pool plays an important role in cancer biology, which is not only closely related to the metabolic reprogramming of cancer cells [62, 63], but also involved in the crosstalk between immune cells and the tumor microenvironment, affecting the immune escape mechanism of tumors. In the dynamic interaction between immune effector cells and tumor cells, carnitine can confer resistance to immune cell killing to tumor cells through carnitine palmitoyltransferase 1 A (CPT1A)-mediated FAO [64]. Carnitine secreted by TAMs activates CPT1A/c-Myc positive feedback loop, enhances the antioxidant capacity of cells through the Nrf2/GPX4 pathway, and limits the production of polyunsaturated fatty acids by downregulating the expression of ACSL4. The inhibition of ferroptosis in lung cancer stem cells and the activation of $CD8^+$ T cells revealed the role of carnitine in tumor immune escape in the tumor microenvironment [65]. The accumulation of LCACs in tumor tissues has been shown to alter the lipid uptake and metabolism of infiltrating T cells, which in turn affects T cell states such as cell division, apoptosis, and cell senescence. In hepatocellular carcinoma (HCC), LCACs are effectively loaded into the mitochondria of lymphocytes, resulting in the inhibition of invariant natural killer T (iNKT) cell expansion and the promotion of their senescence while simultaneously facilitating tumor evasion of immune surveillance [66]. In gallbladder cancer tissues, the accumulation of acylcarnitine not only provides an additional energy source for tumor cells, but also promotes tumor cell proliferation and migration by activating the phosphorylation of JNK. Acylcarnitine stabilizes the expression of lncBCL2L11 through the m6A modification and participates in the positive feedback loop of tumor cell invasiveness, which provides a powerful driving force for the malignant progression and metastasis of gallbladder cancer [44]. Notably, different tumor cells respond differently to acylcarnitine; HepG2 cells showed an approximately 8% increase in survival after 48 h of exposure to C16-carnitine, whereas HT29 and HCT 116 cells exhibited reduced survival [67]. In colorectal cancer cells, C16-carnitine can produce cytotoxic effects on them by deplete glutathione [68]. Taken together, these findings suggest that carnitine pool homeostasis is closely related to inflammatory and immune homeostasis, tumor development, and immune escape, providing new perspectives and potential targets for the treatment of inflammatory diseases and cancer.

Endocrine regulation

The carnitine pool plays a generalist role in the endocrine system, maintaining the stability of the internal environment by regulating the secretion and metabolic behavior of hormones in a finely tuned manner. The carnitine pool influences insulin sensitivity within the endocrine system through direct or indirect mechanisms [69]. Carnitine has the capacity to regulate the level of insulin-like growth factor (IGF) and influence the synthesis and secretion of insulin, thereby increasing insulin sensitivity [70]. Acetylcarnitine has been reported to function as a secretagogue of insulin, whereas the accumulation of stearoylcarnitine (C18-carnitine) in β cells has been shown to impair insulin synthesis [71]. The majority of scholars concur that elevated levels of LCACs are associated with insulin resistance and that their accumulation can be employed as a biomarker of insulin resistance [72]. Reducing the content of LCACs is an effective strategy to improve insulin sensitivity [73], and low acylcarnitine accumulation is conducive to improving insulin signaling

and enhancing glucose uptake [74]. However, skeletal muscle-specific carnitine palmitoyltransferase 2 (CPT2)-deficient mice accumulate large amounts of acylcarnitine in muscle and plasma and still preserve insulin sensitivity [75], highlighting the role of acylcarnitine only as an indicator of FAO rather than as a direct mediator of insulin resistance [76]. The effect of acylcarnitine on insulin sensitivity is also related to the saturation of acylcarnitine, with myotubes incubated with C16-carnitine exhibiting reduced insulin sensitization, whereas the accumulation of oleoylcarnitine (C18:1-carnitine) and linoleoylcarnitine (C18:2-carnitine) increases insulin sensitization [77]. Based on these studies, the relationship between insulin resistance and the carnitine pool remains elusive, and more studies are needed in the future for detailed elucidation.

Carnitine also functions as an endogenous thyroid hormone nuclear uptake inhibitor that can impede the nuclear transfer of triiodothyronine (T3) and thyroxine (T4), thereby inhibiting the biological activity of thyroid hormones [78]. Decreased carnitine levels may contribute to the development of thyroid myopathy [79], and carnitine therapy can effectively reduce muscle function damage caused by hyperthyroidism. Furthermore, alterations in plasma acylcarnitine concentrations are linked to the reductions in muscle mass and strength associated with Graves' disease. Acylcarnitine can be employed as a potential biomarker to assess recovery from thyrotoxic myopathy [56]. Notably, thyroid hormones may facilitate augmented carnitine synthesis in the liver by increasing γ-butyrobetaine hydroxylase (BBD) activity and gene expression, which may constitute a feedback regulatory loop between thyroid hormones and carnitine [80]. In addition, carnitine can also activate glucocorticoid receptor α (GRα) and regulate glucocorticoid- responsive genes through this mechanism, playing a role in glucocorticoid regulation [81], and reducing glucocorticoid-induced muscle atrophy in patients with pemphigus [82].

The carnitine pool also influences the neuroendocrine system. Carnitine/acetylcarnitine have been shown to contribute to the improvement of functional hypothalamic amenorrhea caused by hypogonadotropin through the regulation of the hypothalamic–pituitary–gonadal axis [83], which affects gonadotropin production [84, 85]. Carnitine/acetylcarnitine also have potentially positive effects on hormonal and metabolic parameters in patients with reproductive dysfunction, such as polycystic ovary syndrome [86, 87], and these effects may involve a series of complex signal transduction pathways to maintain the homeostasis of the endocrine system [88]. Carnitine metabolism in the hypothalamus plays a role in the fine regulation of the endocrine feedback mechanism by interacting with metabolic hormones (e.g., ghrelin, leptin and insulin) [89].

Through these mechanisms, the carnitine pool affects multiple aspects of the endocrine system, including hormone synthesis, secretion, and signal transduction. Thus, the carnitine pool plays a key role in maintaining endocrine homeostasis and metabolic health and provides a new therapeutic strategy for the treatment of some reproductive and metabolic diseases. However, the interaction between the carnitine pool and the endocrine system is complex, and more studies are needed to understand the specific mechanisms involved.

Neuromodulation

Although FAO is not a major pathway in brain bioenergetics, carnitine still accumulates in the brain, and in neurons isolated from the adult brain, about 80% of total carnitine remains in free form, while about 10–15% is present as acetylcarnitine and about 10% as LCACs [90]. Carnitine is not only synthesized in the brain [91], but also can be taken up from the circulating blood by specific transporters and transported out of the brain when needed [92, 93]. Carnitine has been demonstrated to exert beneficial effects on the structure and development of white matter in the brain [94, 95]. The concentration and composition of carnitine reserves in the blood, cerebrospinal fluid, and brain are associated with the development of neurological disorders and the modulation of brain functions. The neuroprotective effects of carnitine have revealed its potential therapeutic value in the treatment of neurological diseases such as autism spectrum disorder, depression, and Alzheimer's disease [96, 97]. Carnitine can improve neurotoxicity induced by a variety of chemicals [98], and improve the imbalance of amino acid metabolism in human astrocytes and prevent ammonia-induced cytotoxicity [99]. Carnitine has been reported to exert a beneficial effect on synaptic plasticity through a range of mechanisms, including its antioxidant and anti-inflammatory effects, as well as its capacity to regulate the expression of synaptic plasticity-related biomarkers [100–102]. The primary cilia of nerve cells can sense and respond to the changes of the local extracellular environment. Carnitine can promote primary ciliogenesis in SH-SY5Y cells and have a positive effect on neuronal function [103]. Carnitine can also reverse the harmful neuroinflammatory effects caused by activated microglia, which are resident immune effector cells in the central nervous system [104].

Acetylcarnitine has greater bioavailability than carnitine and has been shown to contribute to improvements in cognitive function by providing acetyl groups to promote the synthesis of acetylcholine [105]. Acetylcarnitine also induces antinociception through central cholinergic mechanisms involving M1 muscarinic receptors [106]. Furthermore, acetylcarnitine has been demonstrated to facilitate the release of neurotransmitters

(e.g., norepinephrine, serotonin, dopamine, and gamma-aminobutyric acid). This process is crucial for the transmission of information between neurons and between neurons and other cells [107]. Acetylcarnitine has been shown to upregulate the expression of neurotrophins, including brain-derived neurotrophic factor and nerve growth factor. It has been reported to promote the survival, differentiation and synapse formation of nerve cells [108, 109]. Acetylcarnitine has been found to cause some changes in gene expression. Acetylcarnitine can up-regulate the expression of voltage-dependent anion channel gene in rat brain, which plays an important role in synaptic plasticity [110]. Acetylcarnitine also rapidly induces mGlu2 receptor expression through epigenetic mechanisms, resulting in antidepressant and analgesic effects [40, 106]. Acetylcarnitine is able to directly interfere with the key pathogenesis of Alzheimer's disease, the β-amyloid cascade, enhancing α-secretase activity and affecting the release of non-amyloid metabolites [111]. Furthermore, C18:1-carnitine has been demonstrated to function as an efficacious noncompetitive inhibitor of GlyT2, which has the potential to serve as an analgesic by regulating the transport of glycine in the central nervous system (CNS) and influencing the concentration of this pivotal inhibitory neurotransmitter [112]. Acylcarnitines have also been shown to be involved in the phospholipid and fatty acid turnover of the nerve membrane, affecting its fluidity and membrane protein activity [113].

The regulation of carnitine pool homeostasis is particularly important in the context of pathological conditions. Studies have revealed that LCAC colocalizes with resident microglia/macrophages at the edge of spinal cord injury (SCI), indicating its potential involvement in the pathophysiology of SCI progression [114]. The accumulation of LCACs can affect the metabolic support of neurons by astrocytes. Astrocytes release free fatty acids (FFAs) from lipid droplets, and the released fatty acids enter the mitochondria and bind to carnitine to form LCACs, the accumulation of which leads to mitochondrial dysfunction in astrocytes and exacerbates neuronal damage [115]. Acylcarnitine is released from abnormal mitochondria in peripheral glial cells to affect surrounding axons, resulting in the destruction of axonal membrane properties and the induction of axonal degeneration, which has been shown to be neurotoxic [116]. Recent studies have shown that C16-carnitine induces mitochondrial dysfunction and leads to calcium overload by increasing mitochondrial fission in SH-SY5Y cells. This calcium overload activates Tau kinases, such as GSK-3β and CDK5, thereby promoting Tau phosphorylation and exacerbating the pathological process of Alzheimer's disease [117].

Other aspects

Carnitine is widely involved in Ca^{2+} signaling in a variety of biological processes [118]. Carnitine promotes the influx of Ca^{2+} from the extracellular environment through the depolarization of L-type Ca^{2+} channels, providing an impetus for the initial activation of intracellular calcium signaling. In addition, carnitine also depletes mitochondrial and ER Ca^{2+} storage by activating phospholipase C, further increasing the intracellular Ca^{2+} concentration. The use of the Ca^{2+}-sensitive receptor (CaSR) inhibitor NPS-2143 can block the carnitine-induced increase in the cytoplasmic Ca^{2+} concentration, indicating that carnitine-induced Ca^{2+} mobilization is mediated by the activation of CaSR [119].

Acylcarnitine also functions as a regulator of numerous key enzymes and ion channels, influencing ion handling mechanisms, including the flux of Na^{+}, Ca^{2+}, and K^{+} [120]. Under physiological conditions, LCACs have the capacity to regulate the current amplitude and kinetics of hERG channels in the heart, which have important effects on arrhythmia [121]. C16-carnitine exhibits complex dual-regulatory characteristics. At low concentrations, C16-carnitine activates the Ca^{2+}-ATPase of the cardiac SR, increases Ca^{2+} binding, and promotes the binding of Na, K-ATPase to [^{3}H]ouabain, which may enhance myocardial Ca^{2+} regulation. However, as the concentration increases, C16-carnitine changes from an activator to an inhibitor, inhibiting the activity of these key enzymes and their binding to [^{3}H]ouabain. This regulatory mechanism may stem from its detergent-like effect, which affects the structure and function of the cell membrane [122]. Furthermore, C16-carnitine may influence the functionality of vascular endothelial cells by interacting with the endothelial cell differentiation gene-1 receptor, resulting in the accumulation of Ca^{2+} within the cells [123].

Furthermore, carnitine/acylcarnitine exert pleiotropic effects by interacting with the intracellular signal transduction network and participating in the regulation of a multitude of pivotal cellular physiological processes. For example, carnitine has been observed to block MAPK signaling and regulate apoptosis, oxidative stress and inflammation in a dose-dependent manner [124]. Carnitine has been shown to mitigate myocardial ischemia-reperfusion injury (IRI) resulting from oxidative stress by activating the Nrf2/HO-1 signaling pathway [125]. Acetylcarnitine exerts antiangiogenic and anti-inflammatory effects by targeting key signaling pathways, including the VEGF/VEGFR2, NF-κB, and CXCL12/CXCR4 pathways [126, 127]. C16-carnitine affects the insulin signaling pathway by activating PTP1B and reducing the phosphorylation of InsR Tyr1151 and Akt Ser473, thereby playing a role in the occurrence of insulin resistance [128]. The functions of carnitine/acylcarnitine in signaling may differ according to the cell type and physiological

state. A comprehensive overview of the specific signaling regulatory pathways is presented in Table 1; Fig. 2.

In summary, the carnitine pool is involved in a variety of biological pathways, and maintaining the homeostasis of the carnitine pool helps to enhance the coordination of cell functions so that cells can respond more effectively to changes in the internal and external environments and enhance the adaptability of the body to environmental changes. Understanding the diversity of carnitine pool functions is highly important for revealing the molecular mechanism of diseases and developing new treatment strategies.

The exquisite network of carnitine biosynthesis, transport, shuttle and regulation

Carnitine biosynthesis pathway

The endogenous carnitine synthesis pathway is carried out at multiple locations in the cell, including the cytoplasm, mitochondria and lysosomes. Synthesis includes the following steps: I. First, proteins containing N-methylated lysine residues are degraded by lysosomes or proteasomes to release 6-N-trimethyllysine (TML), in which lysine provides the carbon backbone and nitrogen atom of carnitine, whereas methionine provides the methyl group. II. TML is then hydroxylated by 6-N-trimethyllysine dioxygenase (TMLD), which is located in the mitochondrial matrix, to form 3-hydroxy-6-N-trimethyllysine (HTML). III. Subsequently, HTML is transported to the cytosol and cleaved to glycine and 4-N-trimethylaminobutyraldehyde (TMABA) by 3-hydroxy-6-N-trimethyllysine aldolase (HTMLA). 4-N-trimethylaminobutyraldehyde dehydrogenase (TMABA-DH) then catalyzes TMABA dehydrogenation to generate γ-butyrobetaine (γBB). IV. Finally, γ-butyrobetaine dioxygenase (BBD) catalyzes the hydroxylation of γBB to produce carnitine [158]. In addition, niacin, vitamin C, vitamin B6 and Fe^{2+} are also required for the synthesis of carnitine. Notably, recent studies have shown that both humans and mice have lost the gene encoding enzyme with efficient HTMLA activity. In humans, the HTMLA activity is partially compensated by serine hydroxymethyl transferase (SHMT) 1 and 2, while in mice, threonine aldolase (Tha1) is the primary source of HTMLA activity, but this gene is absent in humans [159].The liver and kidney are considered the primary organs involved in carnitine synthesis because of their considerable BBD activity. Brain tissue also synthesizes small amounts of carnitine. Other tissues, such as the myocardium and skeletal muscle, have no or very low BBD activity and are highly dependent on the uptake of carnitine from the blood [160]. This dependence highlights the importance of carnitine transport and homeostasis between different organs for intercellular communication and overall metabolic health.

Carnitine transport system

The transport efficiency and distribution of carnitine and its derivatives are affected by the specificities of different transporters, which vary in their expression levels and patterns in various tissues. OCTN2 (*SLC22A5*) is not only a Na^+-independent organic cation transporter but also a Na^+-dependent and high-affinity carnitine transporter, which is widely distributed in various tissues such as kidney, intestine, placenta, breast, liver, heart, testis, skeletal muscle and blood–brain barrier [161]. The amine and carboxylic acid groups of carnitine are the key groups for OCTN2 to recognize it, and the hydroxyl group of carnitine is esterified by acyl derivatives and does not hinder the recognition effect of OCTN2, indicating that OCTN2 has high substrate diversity and adaptability and is able to process a variety of acylcarnitines [162]. Among the known carnitine transporters, OCTN2 has the highest affinity for carnitine [163]. OCTN2 not only mediates the absorption of dietary carnitine in the intestine, providing exogenous carnineit to the body, but also is responsible for the renal reabsorption of carnitine, reducing its loss in urine. Moreover, OCTN2 mediates the tissue distribution of carnitine, ensuring that these tissues receive sufficient carnitine to maintain their normal functions [164]. Defects in the *OCTN2* gene cause primary carnitine deficiency, further emphasizing the strategic position of OCTN2 in maintaining carnitine homeostasis [165]. In addition, OCTN2 protein was detected in exosomes released from HEK293 cells [166], indicating that carnitine and its derivatives may be transported between cells through exosomes, a finding that provides new insights into the role of carnitine and its transporters in exosomes and their functions in intercellular communication and pathological processes.

In addition to OCTN2, other transporters are also involved in the transmembrane transport of carnitine. OCTN1 (*SLC22A4*), the first member of the OCTN subfamily, is widely expressed in various tissues, including bone marrow, heart, kidney, liver, intestine, muscle, placenta, and the nervous system [167]. As a polyspecific transporter, OCTN1 is capable of transporting a variety of organic cations and zwitterions (e.g., tetraethylammonium, acetylcholine, and ergothioneine) and is also involved in the transport of certain drugs. However, despite its broad substrate specificity, OCTN1 has relatively low transport efficiency for carnitine and plays a limited role in carnitine transport [168, 169]. OCTN3 (*Slc22a9*) is also involved in carnitine transport and is highly expressed in the mouse testis [170]. The Km value of OCTN3 is higher than that of OCTN2, and the function of carnitine transport is relatively minor [171]. Moreover, the expression of OCTN3 has only been reported in mice and rats [172]. $ATB^{0,+}$ (*SLC6A14*) is a Na^+ and Cl^--dependent amino acid transporter widely

Table 1 Molecular mechanisms of carnitine and its derivatives in regulating diseases

Carnitine forms	In vitro	In vivo	Signaling pathways	Effector molecules	Effects	Diseases	References
Carnitine	NA	Letrozole-induced female SD rats	Nrf2, Cyt c and caspase-3 signaling	Cyt c↓, caspase-3↓, MDA↓, Nrf2↑, GSH↑, CAT↑	Alleviates hepatorenal oxidative stress and apoptotic.	Letrozole-induced hepatorenal toxicity	[14]
Acetylcarnitine	Hypoxic-induced primary hippocampal neurons	Hypobaric hypoxia simulated SD rats	ERK1/2-Nrf2	caspase-3↓, NADP/NADPH↓, PGC-1α↑, NRF1↑, Nrf2 in nuclear↑, TFAM↑, Ca^{2+} uniporter↑, p-LKB1↑, p-AMPK↑, mtDNA↑	Reduce neuronal apoptosis and mitochondrial dysfunction, promote mitochondrial biosynthesis, alleviate excitotoxicity, and improve bioenergetic status of hippocampal neurons.	Neurodegenerative diseases	[16]
Acetylcarnitine	NA	Propionic acid-induced male Wistar rats	ALDH1A1-RA-RARα signaling	NF-κB↓, TNF-α↓, IL-6↓, Bax↓, caspase-3↓, MDA↓, ALDH1A1↑, RARα↑, Bcl-2↑, GSH↑, SOD↑, CAT↑	Improve brain tissue damage, oxidative stress, inflammatory response and apoptosis.	Autism spectrum disorder	[19]
Carnitine	NA	Monoiodoacetate-induced knee osteoarthritis model in SD rats	miRNA-373/P2×7/NLRP3/NF-κB pathway	IL-1β↓, IL-18↓, IL-6↓, TNF-α↓, P2×7R↓, NLRP3↓, NF-κB↓, cleaved caspase-1↓, procaspase-1↑, miRNA-373↑, IκB↑	Reduce osteoarthritis knee size and reestablishing motor coordination and joint mobility.	Osteoarthritis	[49]
Carnitine	LPS-induced RAW 264.7, RANKL-induced bone marrow-derived macrophages	Ovariectomy-induced bone loss mouse model in C57BL/6J mice	Nrf2/Keap1 pathway, MAPK and NF-κB pathway	iNOS↓, NFATc1↓, c-Fos↓, CTSK↓, MMP9↓, IL-1β↓, TNF↓, IL-6↓, TXNIP↓, NLRP3↓, RANKL↓, TRAP↓, p-ERK↓, p-JNK↓, p-P38 MAPK↓, p-NF-κB↓, Nrf2↑, HO-1↑, CAT↑, SOD1↑, GSR↑, IL-10↑, IκB-α↑, Arg-1↑	Improve oxidative stress, inhibit M1 macrophage polarization and osteoclast differentiation	Osteoporosis	[51]
Acetylcarnitine	TNF-α-induced cell inflammation	Dextran sodium sulfate-induced male C57BL/6J mice	CADM2/TLR-MYD88 pathway	IL-1β↓, IL-2↓, IL-6↓, IL-12B↓, INF-γ↓, NLRP3↓, NF-κB↓, TNF-α↓, IL-8↓, MyD88↓, Th17↓, CADM2↑, IL-10↑, Treg↑	Improve gut inflammation and immune homeostasis.	Inflammatory bowel disease	[52]
Carnitine	NA	Carbendazim-induced Adult male Swiss albino rats	p38 MAPK pathways	TNF-α↓, IL-6↓, iNOS↓, NF-κB↓, p38 MAPK↓, MDA↓, StAR↑, FABP9↑, Testosterone↑, LH↑, FSH↑, inhibin B↑, T3↑, GSH↑, GSH-Px↑, SOD↑, IL-10↑	Relieve endocrine disruption, inflammation burst and oxidative stress.	Reproductive toxicity	[88]
Carnitine	NA	Ligation of the bilateral common carotid arteries-induced chronic hypoperfusion in male Wistar rats	PTEN/Akt/mTOR signaling pathway	p-PTEN↓, HNE↓, 8-OHDG↓, p-Akt↑, p-mTOR↑, pNFH↑, MBP↑, CPT1A↑, CPT2↑	Improve mitochondrial membrane dysfunction, reduce oxidative stress, increase axonal plasticity and myelination.	Chronic cerebral hypoperfusion causes white-matter lesions	[100]
Carnitine	LPS-induced H9c2 cells	NA	MAPK signaling	TNF-α↓, IL-6↓, IL-1β↓, p-ERK↓, p-JNK↓, Bax↓, MDA↓, LDH↓, ROS↓, Bcl-2↑, SOD↑, GSH↑, mtDNA↑, ATP↑	Inhibit inflammation, apoptosis, and oxidative stress, and improve mitochondrial function.	Sepsis-induced cardiomyopathy	[124]

Table 1 (continued)

Carnitine forms	In vitro	In vivo	Signaling pathways	Effector molecules	Effects	Diseases	References
Carnitine	H9c2 cell hypoxia-reoxygenation model	Ligation the left anterior descending coronary artery-induced IRI in SD rats	Nrf2/HO-1 signaling pathway	caspase-3↓, caspase-8↓, Bax↓, MDA↓, CK↓, LDH↓, SOD1↑, SOD2↑, Bcl-2↑, Nrf2↑, HO-1↑, Na^{+}-K^{+}-ATPase↑, Ca^{2+}-Mg^{2+}-ATPase↑	Reduce oxidative stress and apoptosis of myocardial cells.	Myocardial IRI	[125]
Acetylcarnitine	ox-LDL-induced RAW264.7	HFD feed $ApoE^{-/-}$ mice induced arteriosclerosis model	TLR4/NF-κB pathway	TNF-α↓, IL-1β↓, TLR4↓, MyD88↓, NF-κB↓	Reduce lipid accumulation and inflammation in foam cells.	Atherosclerosis	[129]
Carnitine	NA	Supplemented with carnitine in male SD rats	IGF-1/PI3K/Akt signaling pathway	MuRF1↓, ubiquitin-protein conjugates↓, IGF-1↑, p-Akt↑, p-mTOR↑, p-FoxO1↑	Reduce muscle fibrin degradation.	NA	[130]
Carnitine	TNF-α-induced myotube atrophy in C2C12 cells	Subcutaneously transplanting CT26 cells into the left flanks of the BALB/c nude mice	Akt/FOXO3a/MaFbx and p70S6K pathways	IL-1↓, IL-6↓, MuRF-1↓, MaFbx↓, p-FOXO3a↑, p-Akt↑, p-p70S6K↑	Protect muscle cells and reduces inflammation related to cancer cachexia.	Muscle wasting of cancer cachexia	[131]
Carnitine	NA	Ligation of left anterior descending artery-induced Myocardial Infarction in ICR mice	Bax/Bcl-2 signal pathway	IL-1β↓, IL-6↓, TNF-α↓, Bax/Bcl-2↓, α-SMA↓, AST↓, LDH↓, NT-proBNP↓, cTnT↓	Reduce myocardial injury and inflammatory factors, and improve left ventricular function.	Myocardial Infarction	[132]
Carnitine	Palmitate-treated primary atrial cardiomyocyte cell	HFD-induced obesity-mediated atrial fibrillation in C57BL/6J mice	AMPK/PGC1α signaling	p-NF-κB↓, PFKM↓, TNF-α↓, IL-6↓, IL-18↓, IL-1β↓, Cx43↓, TGF-β↓, α-SMA↓, Smad3↓, collagen I↓, collagen III↓, MDA↓, p-AMPK↑, PGC1α↑, CPT1B↑, Nrf2↑, SOD2↑, p-Akt↑, GLUT4↑, PKM2↑, PDK4↑, FABP-pm↑,	Promote FAO, reduces atrial fat toxicity, and alleviate obesity mediated atrial fibrillation and structural remodeling.	Atrial fibrillation	[133]
Carnitine	NA	Imatinib-induced Wistar albino rats	PDGF/PPARγ/MAPK pathways	IL-6↓, TNF-α↓, α-SMA↓, MAPK↓, CTGF↓, Bax↓, MDA↓, NO↓, PPAR-γ↑, Bcl-2↑, SOD↑, GSH↑	Reduce inflammation, oxidative stress and improve apoptosis.	Imatinib-induced cardiotoxicity	[134]
Carnitine	NA	γ-radiation-induced C57Bl/6j mice	p38 MAPK/Nrf2 signaling	Bax↓, cleaved-caspase 3↓, HO1↑, NQO1↑, p-p38 MAPK↑, p-Nrf2↑	Inhibit ROS production and apoptosis in heart.	Radiation-induced heart damage	[135]
Carnitine	Hypoxia-indued cardiomyocytes of mice	Ligation the left anterior descending coronary artery-induced IRI model in C57Bl/6j mice	PI3K/Akt signaling pathway	p-Akt↑, p-PI3K↑, Bcl-2/Bax↑	Improve cardiac function and reduce myocardial apoptosis.	Myocardial IRI	[136]

Table 1 (continued)

Carnitine forms	In vitro	In vivo	Signaling pathways	Effector molecules	Effects	Diseases	References
Carnitine	NA	Potassium dichromate-induced Wister albino male rats	Nrf2/HO-1 signaling pathway	TGF-β↓, MDA↓, Nrf2↑, Keap1↑, HO-1↑, Akt↑, NQO1↑, GCLM↑, GSH↑	Reduce the number of goblet cells, inhibited the mucus formation in bronchioles and interstitial inflammatory infiltrate, alleviate alveolar wall damage and vascular congestion.	Acute lung injury	[137]
Carnitine	TGF-β1-induced NRK-52E cells	L-NG-nitroarginine ethyl-ester-induced hypertensive Wistar rats	PPARγ signaling pathway	TGF-β1↓, CTGF↓, Nox2↓, Nox4↓, collagen I↓, collagen III↓, IL-6↓, IL-1β↓, PPARγ↑, IL-10↑	Reduces renal fibrosis, oxidative stress and inflammation.	Hypertension-associated kidney fibrosis	[138]
Carnitine	NA	Methotrexate-induced male SD rats	SIRT1/PGC-1α/Nrf2/HO-1 axis	TNF-α↓, IL-6↓, Bax↓, caspase-3↓, MDA↓, SIRT1↑, PGC-1α↑, Nrf2↑, HO-1↑, Bcl-2↑, SOD↑	Improve renal pathological changes, reduce renal oxidative stress, inflammation and apoptosis.	Methotrexate-induced nephrotoxicity	[139]
Carnitine	Tacrolimus-induced HK-2 cells	Tacrolimus-induced SD rats	PI3K/Akt/PTEN signaling	cleaved caspase-3↓, TGF-β1↓, βig-h3↓, MCP-1↓, TLR2↓, IL-18↓, IL-1β↓, NLRP3↓, Nox2↓, 8-OHdG↓, Drp1↓, LC3B-II/LC3B-I↓, Beclin-1↓, p-PI3K↓, p-Akt↓, PTEN↑, Bcl-2/Bax↑, MnSOD↑, TOMM20↑, NDUFA10↑, SDHA↑, OPA1(L)↑, OPA1(S)↑	Reduced renal inflammation, fibrosis and oxidative stress, improved mitochondrial dysfunction and programmed cell death.	Chronic tacrolimus nephropathy	[140]
18:0-carnitine	18:0-carnitine treatment with primary hepatocytes	Triptolide-induced Male C57BL/6J mice	Notch-Nrf2 signaling pathway	ALT↓, AST↓, *Nrf2*, *Gpx1*, *Gpx4*, *Gsta4*, *Notch1*, *Notch2*, *Notch3*, and *Nrarp* mRNA↑	Protect the liver, improve liver function, and improve acylcarnitine metabolism.	Triptolide-induced liver injury	[141]
Carnitine	Carnitine treatment with C2C12 cells	NA	IGF-1/Akt/p70S6 pathway	MyoD↑, Myogenin↑, MyHC↑, IGF-1R↑, p-Akt↑, p-p70S6↑, SOD2↑	Enhance myotube formation, support muscle regeneration, and improve antioxidant capacity.	Sarcopenia and muscle atrophy	[142]
Carnitine	LPS-induced primary rat fibroblast-like synoviocytes	anterior cruciate ligament-induced knee osteoarthritis in male SD rats	AMPK-ACC-CPT1 signaling pathway	Cyt c↓, TRPA1↓, IL-1β↓, IL-6↓, TNF-α↓, IL-8↓, MDA↓, TRPA1↓, p-AMPK↑, p-ACC↑, CPT1A↑, IL-10↑, SOD↑	Improve mitochondrial function and reduce lipid accumulation, inhibit inflammatory response.	Knee osteoarthritis	[143]
Carnitine	Carnitine treated with primary rat trophoblast cells	NA	IGF-1 signaling pathway	IGF-1↑, IGF-1R↑, p-Akt↑, p-mTOR↑, p-ERK↑, SNAT1↑, SNAT2↑	protect placenta trophoblast cells against apoptosis and increased their proliferation.	NA	[144]
Carnitine	H_2O_2-induced human lens epithelial cells	MA	MAPK signaling	cleaved caspase-3↓, COX-2↓, IL-1β↓, IL-6↓, IL-8↓, Vimentin↓, α-SMA↓, p-p38 MAPK↓, p-ERK↓, PCNA↑, CDK2↑, CDK4↑, AQP1↑, FOXO1↑, PRDX4↑, CAT↑	Inhibit oxidative damage, prevents inflammation, apoptosis and epithelial-mesenchymal transition, and promote cell proliferation.	Cataracts	[145]

Table 1 (continued)

Carnitine forms	In vitro	In vivo	Signaling pathways	Effector molecules	Effects	Diseases	References
Carnitine	NA	UVA-induced skin tissue injury in male Wistar rats	p38 MAPK/c-Fos signaling	TNF-α↓, IL-6↓, IL-1β↓, 8-oxo-dG↓, CPDs↓, caspase-3↓, p38 MAPK↓, p-c-Fos↓, TBARS↓, PCNA↑, GSH↑	Downregulate oxidative stress, oxidative stress sensitive signaling cascade, and inflammatory response.	Skin tissue injury	[146]
Carnitine	NA	Colon-26 tumor-bearing BALB/c mice	PPARγ signaling	NF-κB↓, Cox-2↓, PGE2↓, CRP↓, TNF-α↓, IL-6↓, MDA↓, PPARα↑, PPARγ↑, SOD↑, GSH-Px↑	Ameliorate liver inflammation and serum pro-inflammatory markers in cancer cachexia.	Liver inflammation in cancer cachexia	[147]
Carnitine	NA	Methotrexate-induced male SD rats	Notch1/Hes-1 signaling	Notch1↓, Hes-1↓, TNF-α↓, IL-6↓, IL-1β↓, MDA↓, SOD↑, CAT↑	Reduce oxidative stress and inflammation, improve liver injury.	Methotrexate-induced hepatotoxicity	[148]
Carnitine	Calcium oxalate monohydrate adhesion crystals to Madin Darby canine kidney cells	NA	Akt/GSK-3β/Snail signaling	Vimentin↓, p-Akt↓, p-GSK3β↓, Snail↓, E-cadherin↑	Inhibit cell dedifferentiation and resist calcium oxalate monohydrate adhesion crystals adhesion.	Urolithiasis	[149]
Carnitine	NA	Aged (>18 months old) male Wistar rats	JNK/p53 pathway	p21↓, p16↓, p53↓, p-JNK↓, IL-6↓, IL-1β↓, TGF-β1↓, TNF-α↓, Adiponectin↓, Leptin↓, IGF↓, MCP-1↓, MMP-3↓, p-IRS1↓, CD3↓, CD4↓, CD68↓, Foxp3↓, IRS1↑, p-Akt↑	Reduce senescence-associated secretory phenotype factors express, alleviate chronic inflammation and insulin resistance.	Adipose tissue dysfunction of aging.	[150]
Acetylcarnitine	Primary hippocampal cells exposed to hypoxia (3% O_2)	NA	ERK1/2 signaling	caspase-3↓, Cyt c↓, p-Bcl-2↓, ROS↓, GSSG↓, NGF↑, TrkA↑, p-ERK1/2↑, p-Elk-1↑, GSH↑	Stabilize mitochondrial membrane, restore cholinergic transmission, and prevent apoptosis.	Hypoxic stress and associated neurodegenerative diseases	[151]
Acetylcarnitine	NA	Chronic unpredictable mild stress-induced ICR mice	PI3K/Akt/BDNF/VGF signaling pathway	p-Akt↑, BDNF↑, VGF↑	Reduce immobility time in forced swimming test and reverse depressive like behavior.	Depression	[152]
Carnitine	NA	Potassium dichromate-induced Wister albino male rats	AMPK/Akt/NF-κβ signaling pathway	TNF-α↓, IL-6↓, NF-κB↓, MDA↓, Akt↑, AMPK↑, GSH↑	Anti-inflammatory, anti-oxidation, improve cognitive impairment.	Acute brain injury	[153]
Carnitine	Carnitine-induced adipose tissue-derived mesenchymal stem cells	NA	Wnt/β-catenin and PKA pathway	NGF↑, BDNF↑, nestin↑, β-catenin↑, DKK1↑, LRP5↑, Wnt1↑, Wnt3a↑, PKA↑	Promote adipose tissue-derived mesenchymal stem cells neurogenic differentiation.	Neurodegenerative diseases	[154]
Acetylcarnitine	NA	LPS-induced depression in SD male rats	PPAR-γ / NF-κB/NLRP3 pathway	p-NF-κB↓, NLRP3↓, COX2↓, TNF-α↓, TBARS↓, PPARγ↑, GSH↑, GST↑, CAT↑	Neuroprotective, anti-inflammatory and anti-oxidative	Depression	[155]
Acetylcarnitine	NA	LPS-induced neuroinflammation in male Wistar rats	TLR4/NF-κB pathways	TLR4↓, NF-κB↓, TNF-α↓, ROS↓, MDA↓, LC3-II/LC3-I↑, becline-1↑	Restore autophagy activity, inhibit oxidative stress and anti-inflammation.	Neurodegenerative diseases	[156]

Table 1 (continued)

Carnitine forms	In vitro	In vivo	Signaling pathways	Effector molecules	Effects	Diseases	References
Carnitine	NA	Radiation-induced acute lung injury in Wistar albino rats	AMPK/SIRT1/TGF-1β pathway	AMPK↑, SIRT1↑, caspase-3↓, TNF-α↓, TGF-1β↓	Reduce inflammation and oxidative stress.	Radiation-induced acute lung injury	[157]

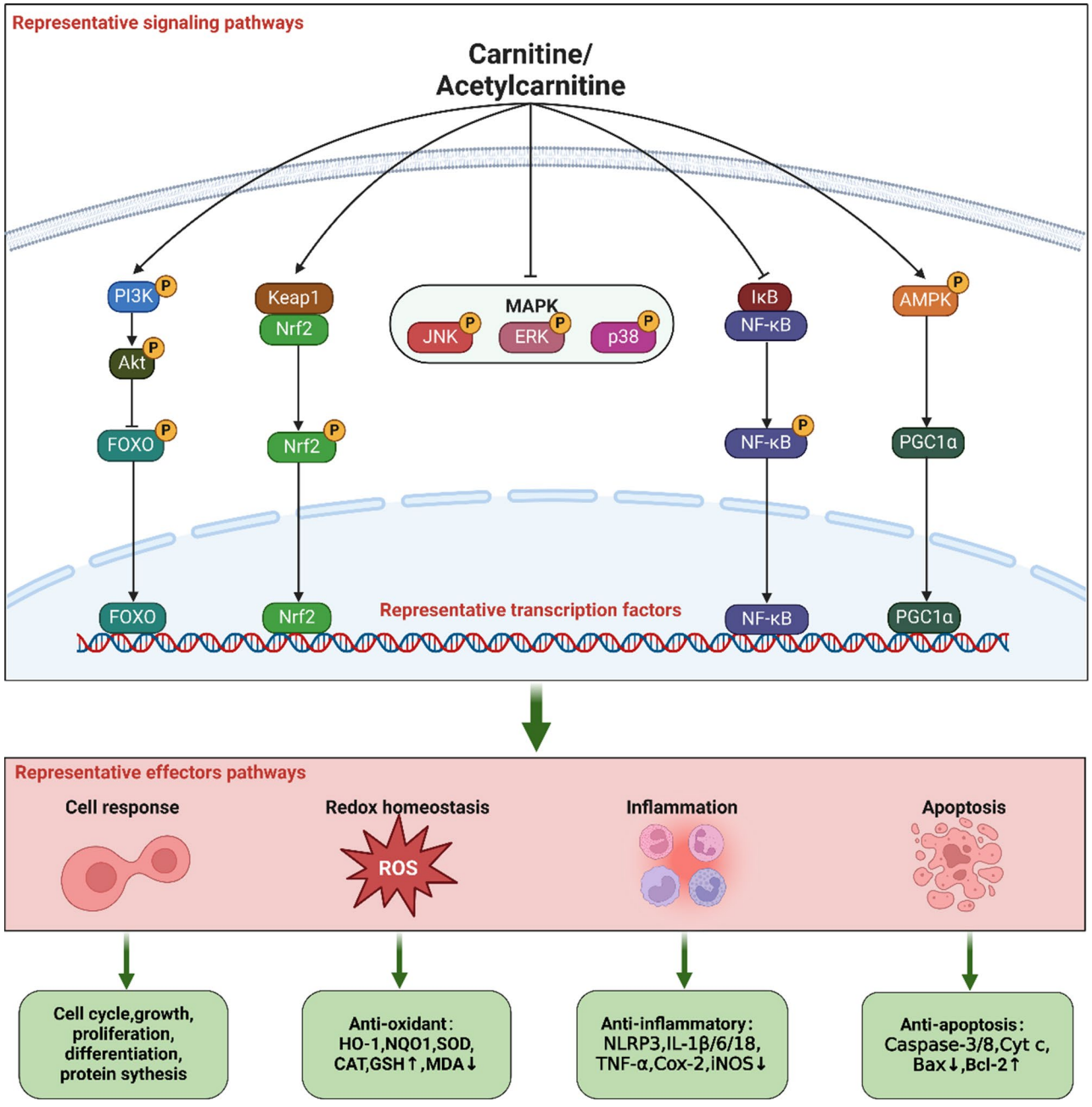


Fig. 2 Representative signaling pathways regulated by carnitine/acetylcarnitine. Carnitine and acetylcarnitine, as the focus of current research, have been found to interact with intracellular signaling transduction networks. By regulating PI3K/Akt, Nrf2, NF-κB, AMPK and other signaling pathways, they widely affect a variety of physiological processes such as cell differentiation, protein synthesis, inflammatory response, oxidative stress, and programmed cell death. They play an indispensable role in maintaining the normal physiological activities of cells and responding to environmental changes. Created with BioRender.com

distributed in lung, trachea, salivary gland, breast, stomach, eye, hippocampus, intestine, blood–brain barrier and other tissues. It is mainly responsible for transporting neutral and basic amino acids, but not acidic amino acids (e.g., aspartic acid and glutamate). $ATB^{0,+}$ is also involved in neurotransmitter transport. $ATB^{0,+}$ is able to transport carnitine with low affinity when OCTN2 activity is limited [173]. $ATB^{0,+}$ has also been shown to mediate the intestinal absorption of butyrylcarnitine (C4-carnitine) [174]. OCT6 (*SLC22A16*) is mainly highly expressed in the testis and is a high-affinity carnitine transporter, which can also transport a variety of substrates (e.g., tetraethylammonium, spermidine and doxorubicin) [175]. OCT6 mediates the secretion of carnitine from the epididymal epithelium into the lumen and to participate in sperm maturation [176]. MCT9 (*SLC16A9*) is expressed in kidney, adrenal gland and intestine, and its main function is to transport monocarboxylic acids. Studies have shown that MCT9 has been characterized as a carnitine efflux transporter, which is involved in the transport of carnitine from the inside to the outside of the cell [177]. OCT1 (*SLC22A1*) is a polyspecific, pH- and Na^+ -independent bidirectional transporter. In humans, OCT1 is mainly expressed in the sinusoid membrane of hepatocytes, whereas in rodents, OCT1 is strongly expressed in the basolateral membrane of renal proximal tubule cells. In addition to being involved in the transport of endogenous (e.g., neurotransmitters) and exogenous (e.g., drugs) substances [178], it also receives carnitine transport [179, 180]. Notably, OCT1 acts not only as an uptake transporter of isoC4-carnitine but also as an efflux transporter in mice. However, OCT1 acts neither as an uptake transporter nor as an efflux transporter for isoC4-carnitine in humans [181]. The absence of OCTN3 in humans, together with the OCT1 functional difference between humans and rodents, is a critical issue that limits the use of mice as a model.

Carnitine/acylcarnitines are activated molecules that can be transported throughout the body. The synergistic actions of these solute carrier family members constitute a complex carnitine regulatory network that participates in the absorption and distribution of carnitine through diverse transport mechanisms and affinities. They are the basis for the precise regulation of carnitine transport between different tissues and different subcellular compartments within the cell, maintaining the balance of the carnitine pool. A deep understanding of the molecular mechanisms that regulate the expression and function of carnitine transporters opens new prospects for the treatment of a variety of diseases. For example, carnitine-modified drugs can effectively target OCTN2 transporters to improve drug bioavailability [182, 183].

Carnitine shuttle system

Carnitine acts as an ideal carrier for mobile acyl groups, transporting fatty acids to mitochondria for consumption through an efficient shuttle system. The steps of the carnitine shuttle process are as follows: I. Long-chain fatty acids (LCFAs) cannot directly cross the mitochondrial membrane because of their high polarity and are activated to long-chain acyl-CoA by acyl-CoA synthetase (ACS). II. Long-chain acyl-CoA then binds to free carnitine in the mitochondrial outer membrane under the catalysis of carnitine palmitoyl transferase 1 (CPT1) to form LCACs. III. Subsequently, LCACs are transported to the mitochondrial matrix by the carnitine acylcarnitine translocase (CACT, *SLC25A20*), which is located in the mitochondrial inner membrane. IV. Ultimately, CPT2 on the inner mitochondrial membrane converts LCACs to free carnitine and long-chain acyl-CoA. Free carnitine is returned to the cytoplasm via CACT in preparation for the subsequent cycle, while long-chain acyl-CoA enters β-oxidation and ultimately produces acetyl-CoA for oxidative phosphorylation. This ordered shuttle system ensures the normal concentration and metabolic balance of carnitine within the cell [184, 185]. Notably, the direct oxidation of medium-chain fatty acids (MCFAs) is still a controversial issue. The traditional view holds that MCFAs are oxidized independently of carnitine [186]. Another study suggests that the liver can oxidize FFAs with 6 to 14 carbons independently of carnitine, while the kidneys can oxidize FFAs with 6 to 10 carbons independently of carnitine, but not those with 12 or 14 carbons. However, the heart and skeletal muscle are unable to oxidize FFAs of any chain length independently of carnitine. This indicates that the ability of MCFAs to be oxidized independently of carnitine is tissue-specific. Moreover, there is still no consensus on the specific chain length range of MCFAs. Currently, the lower limit of the carbon chain length of MCFAs is generally considered to be between 6 and 8 carbons, while the upper limit is between 10 and 14 carbons. This variation in definition also adds to the complexity of research on the metabolic characteristics of MCFAs [187].

The carnitine acyltransferase system is diverse according to the structural specificity of the acyl group and its subcellular localization. As the rate-limiting enzyme in the oxidation of LCFAs, CPT1 has three isoenzymes, CPT1A, CPT1B and CPT1C, which exhibit significantly different kinetic and regulatory properties. CPT1A is the most ubiquitously expressed isoform and is expressed mainly in the liver, whereas CPT1B is the muscle isoform and is highly expressed in the heart, skeletal muscle and brown adipose tissue. CPT1A has a higher affinity for its substrate carnitine and a lower affinity for the physiological inhibitor malonyl-CoA than does the muscle isoform. CPT1C is localized in the CNS, is a neuron-specific

isoform, is expressed in the ER rather than the mitochondria, and has carnitine palmitoyltransferase activity [188]. Carnitine acetyltransferase (CrAT) can act as "safety valve" to catalyze the reversible transfer of acetyl groups between acetyl-CoA and acetylcarnitine, promoting the combination of excess acyl groups with carnitine, increasing the membrane permeability of these products and thus removing them from the mitochondria, allowing acylcarnitine to be formed in the mitochondrial matrix and exported to the plasma [7]. Carnitine octanoyltransferase (CrOT) is predominantly found in peroxisomes and plays a key role in the transfer of medium-chain acyl groups from the peroxisomes to the cytoplasm and mitochondria for further degradation [27].

PPARs as master regulators of carnitine homeostasis

Genes regulated by peroxisome proliferator-activated receptor α (PPARα) are involved in many biological processes such as fatty acid catabolism, ketogenesis and gluconeogenesis, and also play a key role in the regulation of carnitine homeostasis [189]. Inhibition of PPARα leads to serum acylcarnitine accumulation [190], whereas hepatic PPARα activation induced by energy deprivation or fibrates is associated with an increase in the carnitine concentration and a decrease in serum acylcarnitine accumulation [191, 192]. PPARα is able to upregulate the expression of almost all genes involved in the carnitine shuttle mechanism (e.g., CPT1, CPT2, CACT and CrAT) [193, 194]. In addition, PPARα also plays a regulatory role in carnitine synthesis by upregulating the carnitine synthases TMLD, TMABA-DH and BBD. PPARα is also involved in carnitine transport and uptake processes, and treatment with its activator increases the transcript levels of OCTN2 and OCTN3 [195, 196]. Activation of the other two isoforms, PPARβ/δ and PPARγ, also contributes to the maintenance of carnitine homeostasis [197, 198]. Thus, PPAR may act as an upstream "gate" to regulate carnitine homeostasis.

Carnitine pool homeostasis is also regulated by a number of factors, including diet, exercise, stress and disease state. Under exercise or stress conditions, the demand for carnitine increases. The body adopts a series of regulatory measures to adapt to this change, such as promoting the synthesis process of carnitine and increasing the activity or expression level of carnitine synthases to increase the production of endogenous carnitine. Improving the efficiency of carnitine absorption and utilization is also possible by improving the mechanism of carnitine transport, such as increasing the expression or activity of carnitine transporters [199, 200]. Through these integrated regulatory measures, the body is able to maintain carnitine pool homeostasis under different physiological and environmental conditions (Fig. 3).

The carnitine pool as multidisease biomarker, crosstalk mediator, and therapeutic target

The differences in the composition and levels of the carnitine pool in different organs reflect their unique metabolic states and health conditions, carnitine/acylcarnitine have the potential to serve as biomarkers for the occurrence and development of a variety of diseases. Carnitine/acylcarnitine can reach almost all organs of the body to regulate metabolic functions and actively participate in communication and metabolic interactions between organs. The balance of the carnitine pool is essential for maintaining organ function and is a promising target for the intervention and treatment of diseases.

Liver

Carnitine plays a key role in maintaining liver function. Carnitine deficiency impairs a variety of metabolic processes in the liver, including lipid metabolism, gluconeogenesis, ketogenesis, albumin biosynthesis, and ammonia detoxification in the urea cycle [201], and carnitine/acetylcarnitine supplementation can ameliorate a variety of liver diseases [202, 203]. In patients with severe liver disease, portal blood bypassing the liver leads to increased levels of ammonia and other toxic substances in the blood, which can lead to complications such as brain damage, sarcopenia and muscle spasticity [204]. Carnitine/acetylcarnitine also show great potential for improving complications in patients with liver disease because of their abilities to reduce ammonia toxicity [205–207].

The disorder of acylcarnitine metabolism is related to the stage of liver disease, and with the deterioration of the disease, the disorder of acylcarnitine metabolism becomes more obvious [208]. During the development of nonalcoholic fatty liver disease (NAFLD), disorders of the carnitine pool are considered important drivers, in which the LCAC profile changes significantly with the progression of NAFLD and provides key clues for revealing the complex pathogenesis of NAFLD [209, 210]. In addition, the accumulation of acylcarnitine in the pathological state of the liver leads to insulin resistance, which further aggravates the development of liver diseases and results in a vicious cycle [211]. In HCC driven by obesity and nonalcoholic steatohepatitis, the downregulation of CPT2 leads to the accumulation of acylcarnitines, among which C18:1-carnitine enhances spheroid formation by HCC cells through STAT3 activation, indicating that the accumulation of acylcarnitine can promote the development of liver cancer [212].

The liver is a key organ for endogenous carnitine synthesis and metabolism, and carnitine homeostasis in the liver has a major effect on carnitine levels in other tissues throughout the body [213, 214]. In the *TMLHE* gene knockout mouse model, the carnitine biosynthetic pathway is inhibited due to the loss of TMLD activity in the

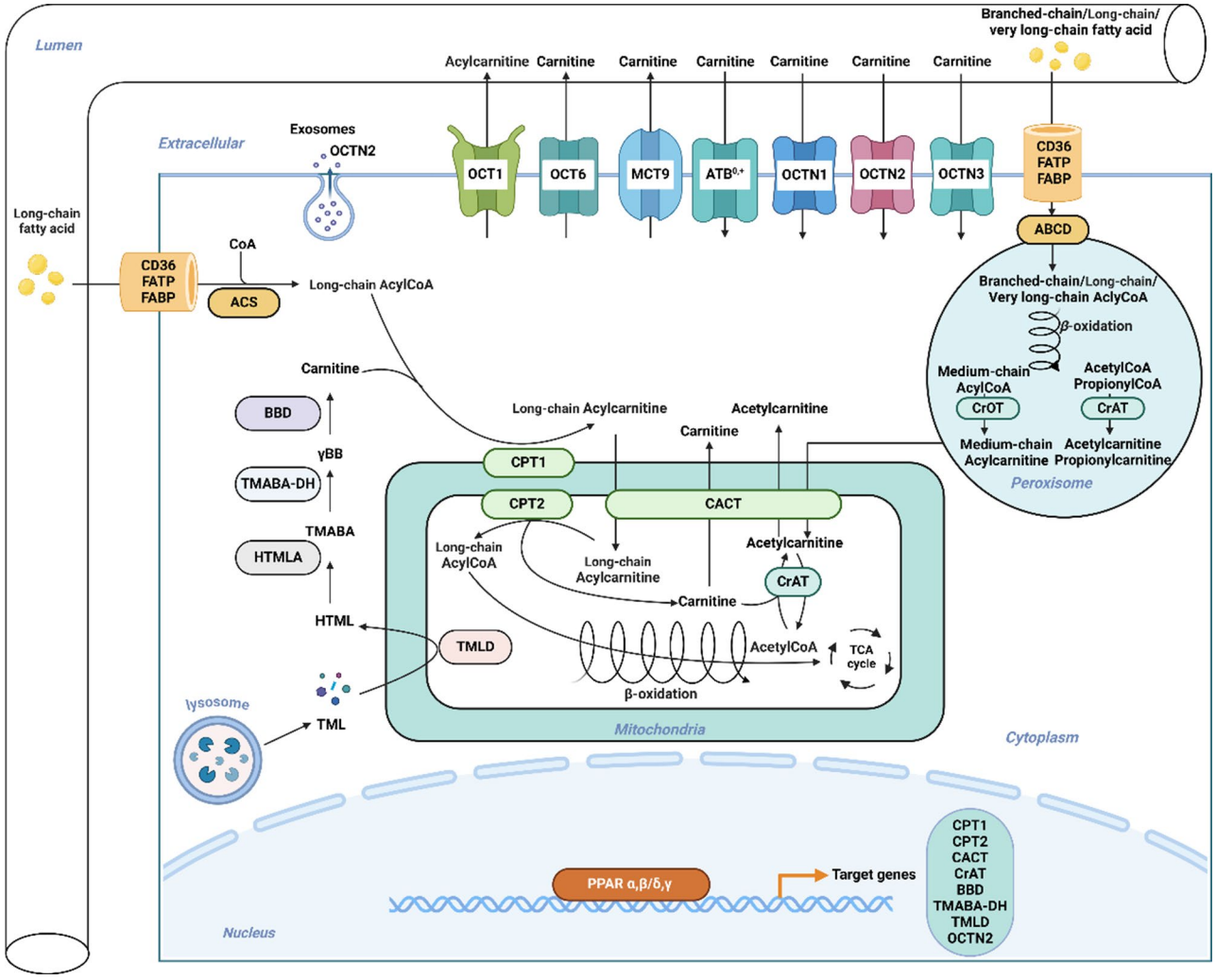


Fig. 3 Overview of the synthesis, transport, shuttle and regulation about carnitine. The carnitine pool homeostasis is a finely regulated process involving a variety of enzymes and transporters, which is essential for cellular energy metabolism and overall health. Lysine and methionine provide the carbon skeleton and methyl of carnitine, respectively, and undergo a series of enzymatic reactions to ultimately form carnitine. Notably, both humans and mice have lost the gene encoding enzyme with efficient HTMLA activity. In humans, this activity is partially compensated by SHMT1 and SHMT2, while in mice, Tha1 is the primary source of HTMLA activity, but this gene is absent in humans. Specific solute carrier family members are responsible for the absorption, distribution, and excretion of carnitine. In addition, OCTN2 was detected in exosomes, suggesting that carnitine may be transported between cells through exosomes. The carnitine shuttle system is a key pathway for transporting fatty acids to mitochondria for oxidation, involving carnitine binding to fatty acids, acylcarnitine transport and carnitine recycling. PPARs play an important role in the regulation of carnitine homeostasis and affect the balance of carnitine metabolism by regulating genes related to carnitine synthesis, shuttle and transport. Created with BioRender.com

liver, affecting the availability of carnitine in the heart, significantly reducing the rate of synthesis of LCACs, and contributing to the protection of mitochondrial function after myocardial IRI [215]. Extensive and close interactions exist between the liver and the intestine. Carnitine/acylcarnitine synthesized by the liver enters the intestine through bile secretion, which is crucial for the health of the intestinal flora [216]. The secondary intestinal flora imbalance in patients with liver cirrhosis may also be related to acylcarnitine [217]. In addition, liver-derived acylcarnitine can also be taken up by intestinal epithelial cells and used for mitochondrial oxidative metabolism, providing additional energy for intestinal cells [218].

Acylcarnitine is more stable and less reactive than acyl-CoA and is an ideal form for storing activated acyl groups that can be transferred to CoA and provide a direct source of energy via FAO. Liver-derived acylcarnitine can serve as an energy substrate, particularly during prolonged exercise or fasting. Brown adipose tissue (BAT), heart muscle and skeletal muscle can use it as an energy source. Acylcarnitine has been shown to mediate white adipose tissue (WAT)–liver–BAT crosstalk [219]. In response to cold conditions and excessive food intake, WAT lipolysis promotes acylcarnitine production in the liver. BAT increases energy consumption by using acylcarnitine produced by the liver as a heat-producing fuel.

This process not only helps maintain body temperature and resist cold but also reduces the risk of obesity [220, 221]. Studies have shown that inhibiting liver-derived acylcarnitine production leads to a decrease in body temperature, highlighting the importance of acylcarnitine in regulating body temperature [222]. Acylcarnitine also acts as a metabolic messenger to coordinate metabolic cooperation between the liver and muscle. During exercise, the muscle signals its energy requirements to the liver by changing the concentration of acylcarnitine in the blood, and the liver adjusts its metabolic activity to increase the synthesis and release of energy substances [223, 224], support muscle contraction and meet the energy demands of exercise [225, 226]. This mechanism of metabolic crosstalk has deepened our understanding of the role of acylcarnitine as a metabolic messenger for intertissue communication and revealed its critical role in coordinating energy metabolism.

Under pathological conditions, the excessive accumulation of liver-derived carnitine/acylcarnitine can also trigger a series of adverse events. Excess carnitine released by hepatocytes prevents hepatitis B surface antigen (HBsAg) clearance through immunosuppression. Moreover, it plays an immune negative regulatory role in chronic hepatitis B virus (HBA) infection by preventing the formation of germinal centers (GCs), reducing the antiviral activity of GC-related immune cells and enhancing the function of immunosuppressive cells [227]. The liver's contribution to blood acylcarnitine levels is also closely related to the risk of cardiovascular events. Polystyrene nanoplastics (PS-NPs) lead to the accumulation of LCACs by inhibiting hepatic CPT2. These LCACs enhance the ability of RAW264.7 cells to phagocytose lipids by upregulating macrophage receptor with collagenous structure (MARCO), thereby aggravating the accumulation of intracellular lipids, which promotes the formation of foam cells and accelerates the development of atherosclerosis [228]. Notably, another study reported that C16-carnitine can directly interact with plasma enzymes and tissue plasminogen activator (tPA) to exert antithrombotic effects by increasing the activities of these enzymes [229], implying that LCAC has a complex dual role in cardiovascular health.

Therefore, carnitine pool not only affects liver metabolism, but also affects the communication and metabolic cooperation between the liver and multiple organs. Liver-derived acylcarnitine can be used as a signal molecule for inter-tissue communication to coordinate energy metabolism, highlighting the role of the liver as a "metabolic center", and unveiling the new insight of the liver-organ axis.

Gut

Changes in the intestinal carnitine profile reflect the diversity and composition of the intestinal microbiota, which has potential application value in the diagnosis and monitoring of intestinal diseases. The gut is the main organ where food-derived carnitine is absorbed. Gut microbes can use carnitine and acylcarnitine as carbon sources, nitrogen sources, osmotic protectants or electron acceptors, but the gut microbiota cannot synthesize carnitine itself, and the mitochondrial function of acylcarnitine produced by carnitine palmitoyltransferase has not been observed in prokaryotes [230]. This finding implies the importance of the carnitine pool for gut microbes. Gut microbes consume acylcarnitines in a category-specific pattern, suggesting that the metabolic requirements and utilization efficiency of these compounds vary among bacterial species [231]. Some intestinal diseases, such as inflammatory bowel disease (IBD) or irritable bowel syndrome, can change the composition of the intestinal microbiota and affect the homeostasis of the intestinal carnitine pool. In individuals with IBD, proinflammatory cytokines downregulate OCTN2 through the PPARγ/RXRα pathway, resulting in reduced carnitine uptake by intestinal epithelial cells that leads to the dysfunction of intestinal regeneration and repair and further deterioration of IBD [232]. Appropriate supplementation with carnitine can regulate the composition of the intestinal flora and improve the imbalance of the intestinal flora [233, 234]. The immunosuppressive properties of carnitine also help eliminate intestinal inflammation [235]. Acylcarnitine also helps promote intestinal peristalsis, which has been shown to be significantly positively correlated with the defecation frequency and can relieve constipation symptoms [236]. However, acylcarnitine was shown to reduce the levels of specific claudin proteins and alter the barrier function of tight junctions in Caco-2 cell monolayers and is should be cautiously considered for people who already have intestinal barrier problems [237].

The intestinal carnitine pool plays an important role in the communication system of the gut–organ axis, and it can directly affect remote organs by remodeling intestinal carnitine metabolism. For example, *Bifidobacterium animalis* F1-7 can upregulate acetylcarnitine levels in the gut, thereby downregulating the TLR4/NF-κB pathway and reducing lipid accumulation and inflammation in foam cells, leading to a reduction in atherosclerotic plaque accumulation [129]. *Lactobacillus reuteri* can increase the content of C16-carnitine in the intestine, thereby effectively activating the Nrf2/HO-1 signaling pathway to resist hepatic IRI [238]. Gut microbes can also convert 2-methylbutyric acid (2MBA) to 2-methylbutyrylcarnitine (2-MBC). This BCAC increases the activation of cytoplasmic phospholipase A2 (cPLA2) by binding to

integrin α2β1 in platelets and promoting platelet hyperresponsiveness, thus promoting thrombosis [239].

Gut microbes can also metabolize carnitine into a variety of undesirable intermediates that affect host health [240]. The metabolism of carnitine by the intestinal flora and its impact on cardiovascular health has become a research hotspot. The long-term intake of red meat significantly increases the levels of the carnitine metabolites trimethylamine (TMA) and trimethylamine-N-oxide (TMAO), leading to endothelial dysfunction and adverse cardiovascular events [241]. In posterior segments of the gut (e.g., the cecum and proximal large intestine), gut microbes directly cleave the C–N bond of carnitine to release TMA, which subsequently enters the liver through the portal circulation, is converted to TMAO by hepatic flavin monooxygenases (FMOs) [242, 243], and eventually enters the blood circulation [244]. However, in the anterior segment of the intestine (e.g., jejunum and ileum), carnitine is first converted to γBB and then further metabolized to TMA in the cecum [245]. Crotonobetaine has also been identified as a carnitine-derived gut microbial metabolite that participates in the formation of TMAO and affects the development of atherosclerosis [246]. Notably, at physiological concentrations, TMAO can enhance the integrity of the blood–brain barrier through the tight junction regulator annexin A1, limit the reactivity of astrocytes and microglia, and protect the cognitive function of mice from inflammatory challenges. However, its precursor TMA has a negative effect on blood–brain barrier function [247]. Increased TMAO levels caused by high carnitine intake also impair liver function, highlighting the complex and fine regulatory role of carnitine in gut–liver communication [248, 249].

Gut microbes and their metabolites also influence carnitine homeostasis in remote organs. Intestinal microorganisms metabolize TML into trimethyl-5-aminovaleric acid (TMAVA), which can competitively inhibit the binding of γ-BB to BBD, thereby inhibiting carnitine biosynthesis and FAO in the liver, promoting steatosis and aggravating fatty liver [250]. TMAVA also inhibits carnitine metabolism by simultaneously inhibiting carnitine synthesis and uptake in cardiac tissue, accelerating the development of cardiac hypertrophy [251]. Carnitine analogs produced by the gut microbiota can colocalize with carnitine in the white matter of the brain and inhibit carnitine-mediated FAO in cell culture models of mouse CNS white matter, affecting the host's nervous system, which provides a new perspective for understanding the complexity of the gut–brain axis [252]. In addition, in a pig model, *Lactobacillus reuteri* XL0930 in the gut microbiota reduced muscle carnitine levels and promoted fatty acid deposition by downregulating SLC22A5 in muscle tissue [253].

Kidney

The kidney finely regulates the systemic carnitine pool through its reabsorption and excretion functions. In the renal tubules, more than 90% of carnitine is efficiently reabsorbed, and this transport process is dependent on OCTN2, which is localized in the renal brush border membrane. Renal OCTN2 expression and activity increase when the carnitine concentration is reduced in the plasma and/or glomerular filtrate, whereas OCTN2 mRNA expression levels remain unchanged in the gut, liver, or skeletal muscle [254], highlighting the central role of the kidney in maintaining carnitine homeostasis. In contrast, when the concentration of carnitine in the plasma increases and the filtration load of carnitine increases, the kidney rapidly increases the rate of carnitine excretion and reduces its reabsorption efficiency to prevent the excessive accumulation of carnitine in the body. This regulatory mechanism is a dynamic adaptive change that ensures the stability of carnitine levels [184]. Clinically, in patients with renal failure, acute kidney injury, dialysis and other pathological states of renal function deterioration, renal reabsorption function is impaired, resulting in a significantly lower serum free carnitine concentration than that in healthy people [255], and the metabolic profile of acylcarnitine also changes significantly [256]. Abnormal acylcarnitine profiles in urine can also be used as biomarkers for a variety of kidney diseases [257, 258]. In addition, the pleiotropic physiological effects of carnitine (e.g., antioxidant, anti-inflammatory and antiapoptotic effects) are particularly important for the protection against kidney diseases, especially drug-induced nephrotoxicity [259].

The reabsorption of carnitine by the kidney affects the carnitine availability in other organs and maintains the metabolic balance between the kidney and other organs. The downregulation of OCTN2 activity and protein expression in the kidney reduces the reabsorption of carnitine in the kidney, leading to a decrease in carnitine availability in the liver and causing hepatic lipid metabolism disorders [260]. Disorders of renal carnitine metabolism may also have a negative effect on cardiac function. In hemodialysis patients, due to reduced renal clearance, carnitine depletion and acylcarnitine accumulation become significant, resulting in an abnormal increase in the ratio of acylcarnitine to free carnitine in plasma, which in turn inhibits cardiac fatty acid metabolism [261]. In patients with chronic kidney disease, reduced reabsorption of carnitine can affect the availability of carnitine in muscles, leading to skeletal muscle atrophy and decreased exercise endurance [262]. Disorders in renal carnitine metabolism may affect red blood cells, leading to anemia. Studies have shown that carnitine supplementation may ameliorate anemia through the following mechanisms: increasing the fluidity and stability of the

red blood cell membrane, improving the flexibility and osmotic resistance of red blood cells, prolonging the lifespan of red blood cells; affecting erythrocyte membrane phospholipid fatty acid metabolism, repairing oxidative damage to membrane phospholipids, reducing hemolysis; preventing sphingomyelin breakdown, inhibiting caspase-3 activation, reducing cell death, and increasing erythrocyte survival [263, 264]. Renal carnitine loss may also affect the morphology and function of red blood cells and reduce the oxygen carrying and releasing capacity of red blood cells, thereby reducing tissue oxygen supply (including the kidney), and tissue hypoxia activates hypoxia-inducible factor 1α (HIF-1α), which in turn reduces OCTN2 expression through the HIF-1α-PPARα signaling pathway. This further aggravates the loss of carnitine and forms a negative feedback loop [265].

Muscle

Although muscle cannot synthesize carnitine, it stores more than 95% of the carnitine in the body. The availability of carnitine in muscle plays a central role in regulating muscle fuel metabolism [266, 267]. Carnitine supplementation has a positive effect on enhancing skeletal muscle strength, accelerating fatigue recovery and optimizing contraction characteristics [268, 269]. It can improve physical performance in healthy individuals and expedite the recovery of physical function, thereby providing strong support for rehabilitation and training [270]. Carnitine supplementation also inhibits the expression of ubiquitin–proteasome system genes in skeletal muscle and reduces damage to the muscle mass under catabolic conditions [130, 131]. However, muscle uptake of carnitine from the blood is a long process and is not highly sensitive to additional carnitine uptake [271], indicating that muscle cells have a certain degree of saturation of carnitine uptake and that additional intake has a limited effect on muscle carnitine levels when the energy demand is low or when the metabolic status is stable. This result suggests that the actual needs and possible effects of individuals should be evaluated when considering carnitine supplements. However, insulin can stimulate carnitine transport to skeletal muscle [272], which is associated with the upregulation of OCTN2 transcript levels [273].

The availability of carnitine in skeletal muscle appears to influence the fuel choice during exercise [274]. During low-intensity aerobic exercise, the body prefers to use fatty acids as the main energy source, and an adequate supply of carnitine can promote FAO and support prolonged exercise [275]. However, during high-intensity exercise, the rapid demand for energy causes carbohydrates to become the main energy substrate. This shift reduces the contribution of FAO to the total energy expenditure. During this process, acetyl-CoA produced by the pyruvate dehydrogenase (PDC) complex in muscle exceeds the processing capacity of the tricarboxylic acid (TCA) cycle. Carnitine plays a buffering role by absorbing excessive acetyl groups in the PDC reaction and promoting more efficient matching of carbohydrate oxidation, rather than simply enhancing exercise performance by increasing the fat oxidation rate. The decrease in free carnitine availability caused by the increase in carbohydrate flux is a key mechanism for the decrease in the fat oxidation rate [276, 277]. Muscle carnitine efflux may be more important than its uptake during exercise. Skeletal muscle can release medium-chain acylcarnitines (MCACs) into the circulation to remove acyl-CoA, which can be detrimental to cellular function, particularly when the supply of energy substrates exceeds the oxidative capacity of the TCA cycle. Skeletal muscle is considered a major source of MCACs released into the circulation [278, 279], and these acylcarnitines have been shown to play a key role in exercise-induced cross-tissue metabolic crosstalk [280].

Acylcarnitine may also act as a fatigue or tiredness signal in the muscle–somatosensory–CNS communication system. In vitro, C16-carnitine has been found to activate specific subsets of neurons in the dorsal root ganglia (DRGs) of muscles that play a key role in sensing muscle fatigue or exertion and are involved in transmitting these sensory signals to the CNS, indicating that C16-carnitine acts as a signaling molecule for muscle afferent nerves [281]. The neuromuscular junction (NMJ) is the point of contact between neurons and muscle cells that allows neural signals to be transmitted to the muscle, triggering muscle contraction. After aging or nerve compression, increased acetylcarnitine levels exert a beneficial effect on the NMJ [282]. Carnitine supplementation has also been shown to reduce neuromuscular fatigue caused by KAATSU training [283]. Therefore, carnitine/acylcarnitine not only play roles in muscle energy metabolism but also participate in the whole-body energy balance and fatigue perception by affecting neuromuscular signaling, underscoring the potential importance of carnitine in exercise physiology, exercise recovery and performance improvement.

Heart

The heart is an organ with high energy demand, and FAO is an important source of cardiac energy. Since the heart cannot produce carnitine [284], it relies on uptake from the circulation [285], which explains the cause of cardiomyopathy in patients with primary carnitine deficiency. Carnitine therapy has been developed as a strategy for the prevention and treatment of cardiac disease [286]. Carnitine can help the heart adapt to the disease environment via metabolic reprogramming by regulating changes in oxidative metabolism, glycolysis and ATP production in the damaged myocardium [287]. When oxygen

availability is limited, glucose is the most metabolically efficient fuel, and during myocardial ischemia, the ratio of acetyl-CoA/CoA in mitochondria increases, leading to the activation of pyruvate dehydrogenase (PDH) kinase, which in turn phosphorylates PDH to inhibit its activity. By promoting the conversion of acetyl-CoA to acetylcarnitine, carnitine reduces the ratio of acetyl-CoA/CoA, thereby reducing the activity of PDH kinase and restoring the activity of PDH, allowing more pyruvate to enter the mitochondria for oxidation to produce energy [288]. Carnitine has shown potential in counteracting and ameliorating drug-induced cardiotoxicity. For example, doxorubicin (DOX) has cardiac side effects that lead to irreversible dilated cardiomyopathy and congestive heart failure, and acetylcarnitine has been shown to prevent cardiac functional and structural damage caused by DOX-induced oxidative stress [289]. In addition, carnitine is involved in the repair and regeneration of the heart, especially after cardiac injury, by promoting cardiomyocyte metabolism and reducing apoptosis to support the recovery of cardiac tissue. For example, reducing left ventricular remodeling is associated with hyperuricemia [290]. Carnitine may also regulate Bax/Bcl-2 signaling [132], AMPK/PGC1α signaling [133], MAPK signaling [134, 135], PI3K/Akt signaling [136] and other signaling pathways to play a protective role in the heart.

Excessive carnitine/acylcarnitine levels have been associated with the pathogenesis of various cardiomyopathies. In a zebrafish model, compared with C3-carnitine, C18-carnitine and C18:1-carnitine can induce the inhibition of OXPHOS, interfere with the energy supply of cardiomyocytes, and lead to a significant impairment of cardiac systolic function, which manifests as a decreased heart rate and reduced shortening of the atrial and ventricular fractions [21]. The accumulation of acylcarnitines in the myocardium is thought to be responsible for impaired myocardial regeneration after myocardial infarction. The accumulation of LCACs promotes mitochondrial failure by producing ROS [291], which block mitochondrial β-oxidation by inhibiting redox-sensitive Slc25a20. This process further aggravates the vicious cycle of LCAC accumulation [292]. For example, C16-carnitine (10 μM) may impair mitochondrial function in rat ventricular myocytes by accelerating ROS production and increasing the probability of mitochondrial permeability transition pore (mPTP) opening, whereas low concentrations (1 and 5 μM) of C16-carnitine lightly hyperpolarize the ΔΨm but do not open the mPTP [293]. LCACs also perturb Ca^{2+} homeostasis in the cytoplasm and have been shown to disrupt myocardial contractility and electrophysiology, thereby inducing cardiomyopathy and arrhythmias [294]. The deposition of acylcarnitine also disrupts the function of the Na^{+}-K^{+}-ATP pump and affects the action potentials, polarization, hyperpolarization, and depolarization cycles of the myocardial cell membrane, which further affects the electrophysiological stability of the heart [295]. Changes in the contents of carnitine and acylcarnitine are highly important for determining cardiac mitochondrial energy metabolic patterns. In different physiological or pathological states, cells may choose the most appropriate metabolic pathway according to the content of LCACs to produce energy most effectively to meet the energy demand of the heart [296]. Especially under ischemia–reperfusion conditions, reducing the level of acylcarnitine has a significant effect on the energy metabolism of the heart and the maturity and proliferation of cardiomyocytes because reducing the utilization of fatty acids and increasing the reliance on glucose oxidation as an energy source can promote the recovery of myocardial function at a lower rate of oxygen consumption. These findings provide new mechanisms and therapeutic strategies for cardiac regeneration [297]. The inhibition of OCTN2 to reduce the carnitine and LCAC contents has also been shown to be an effective strategy to protect the heart from IRI [298]. Similarly, long-term treatment with the carnitine inhibitor meldonium can induce adaptive cardioprotective effects by altering energy metabolic pathways [299]. In summary, carnitine plays a multifaceted role in cardiac energy metabolism and protection, but its level needs to be finely regulated to avoid potential cardiac damage. Since the heart has no capacity to synthesize carnitine, the homeostasis of the blood carnitine pool is crucial for the heart.

Lung

Although the lung is not generally regarded as the main site of lipid metabolism, carnitine metabolism has also been increasingly implicated in respiratory diseases [300]. Studies have reported OCTN2 expression in respiratory epithelial cells and alveolar macrophages, which is especially high in the upper lung region [301], and OCTN2-mediated carnitine uptake plays an important role in maintaining respiratory cilia beating and airway mucociliary clearance function, helping to remove excess mucus and potentially harmful substances from the airway [302]. Carnitine is also involved in the process of surfactant synthesis, which helps to regulate the tension of the alveoli and prevent their collapse. It is also able to promote the production of pulmonary surfactant through its phospholipid repair activity. In the treatment of neonatal respiratory distress syndrome, the application of carnitine has the potential to reduce the need for surfactant, shorten the duration of mechanical ventilation, and reduce the incidence of bronchopulmonary dysplasia [303]. Acylcarnitines that accumulate through disordered carnitine metabolism directly inhibit the surface activity of pulmonary surfactants and are considered risk

factors for increased lung injury due to a "second hit", such as respiratory tract infection, sepsis, or inhalation of toxins, in patients with dysregulated FAO [304, 305]. In patients with N-ERD, the accumulation of acylcarnitine aggravates the proinflammatory metabolism and epigenetic reprogramming of macrophages. This disorder of acylcarnitine metabolism promotes a continuous inflammatory response and thus plays a key role in the pathological process of N-ERD [45].

The importance and potential efficacy of carnitine in the treatment of lung diseases is gradually being recognized [306, 307]. In cultured pulmonary endothelial cells in vitro, carnitine can effectively reduce the apoptosis, damage to migration and obstruction of angiogenesis caused by hyperoxia, resulting in improvements in endothelial cell dysfunction and persistent lung injury under hyperoxic conditions [308]. In addition, carnitine inhibits mucus secretion and interstitial inflammatory cell infiltration in the bronchiolar inflammatory response by participating in the Nrf2/HO-1 signaling pathway and alleviates structural damage to the alveolar wall and congestion of lung tissue vessels caused by heavy metal salts [137]. In a lipopolysaccharide-induced acute lung injury model, carnitine regulates mitochondrial function and controls the inflammatory response of lung macrophages [309]. In a model of lung injury induced by amethopterin, carnitine has shown therapeutic potential by reducing the activities of P53 and CD68 while increasing the activity of Bcl-2 [310]. Disruption of carnitine homeostasis is also associated with pulmonary vascular endothelial dysfunction, and carnitine supplementation can alleviate this endothelial dysfunction by restoring nitric oxide signaling and reducing reactive oxygen species production [311]. Modulation of carnitine metabolism may improve lung health and treat certain lung diseases, suggesting that our understanding of lung function and disease mechanisms may need to be updated and expanded.

Eye

The role of carnitine homeostasis in a variety of eye diseases has gradually attracted the attention of researchers. Carnitine is abundant in eye tissues. Animal studies have shown that the highest concentrations of carnitine are present in the iris, ciliary body and choroid retina [312]. Carnitine and acetylcarnitine can be taken up into ocular tissues from the circulation to support the function of ocular tissues such as the retina [313–315]. Alterations in acylcarnitine metabolism in the retina and retinal pigment epithelium/choroid tissue, especially decreased concentrations of short-chain or medium-chain odd-numbered acylcarnitine, may play a key role in accelerating the development of choroidal neovascularization and age-related macular degeneration [316]. In patients with diabetic retinopathy, abnormal carnitine metabolism may exacerbate oxidative stress and inflammation in the retina and promote the development of the disease [317]. Given the important role of the carnitine pool in numerous metabolic functions, changes in its levels may serve as powerful biomarkers for the early identification or prediction of pathological states related to visual impairment.

The multiple beneficial effects of carnitine provide potential targets for the treatment of related eye diseases. Carnitine has a protective effect on glaucoma-induced retinal ganglion cells injury by reducing the expression of typical markers of cell stress, such as glial fibrillary acidic protein (GFAP), inducible nitric oxide synthase (iNOS), ubiquitin and caspase-3, and reducing the level of the lipid peroxidation product malondialdehyde (MDA) [318]. Carnitine can protect human retinal pigment epithelial (RPE) cells from oxidative damage induced by H_2O_2 [319]. Carnitine also has osmoprotective properties, which can inhibit the activation of transient receptor potential vanilloid type 1 (TRPV1) and protect corneal and conjunctival cells from hyperosmotic stress in dry eye [320]. Understanding the role of carnitine in eye diseases will facilitate the development of targeted drugs. PMX500FI, a synthetic carnitine-conjugated α-lipoic acid derivative, can cross the blood–retinal barrier and improve mitochondrial function [321]. Intraperitoneal injection of PMX500FI not only significantly reduced cell apoptosis in the photoreceptor layer of a mouse retinal detachment model and alleviated the inflammatory response accompanied by retinal detachment but also broadly protected the thickness of the outer nuclear layer, thereby maintaining the structural integrity and functional efficacy of the retina [322]. However, research on the role of carnitine in eye diseases is still in its preliminary stage, and more experimental and clinical studies are needed to explore its potential and mechanism in the treatment of eye diseases in depth.

As a metabolic component in organisms, the multifaceted role of the carnitine pool in physiology and pathology has gradually received increasing attention. It can not only indicate the occurrence and progression of diseases but also mediate interorgan crosstalk. Strategies designed to regulate the carnitine pool have shown great potential and prospects in the treatment of metabolic diseases, cardiovascular diseases and neurodegenerative diseases. Through the precise regulation of carnitine levels, new treatments can be developed for these complex diseases, and more effective interventions can be provided for patients (Fig. 4).

Conclusion and prospects

The carnitine pool is crucial for maintaining the health and function of the body, and its importance is becoming increasingly prominent with in-depth research. In the

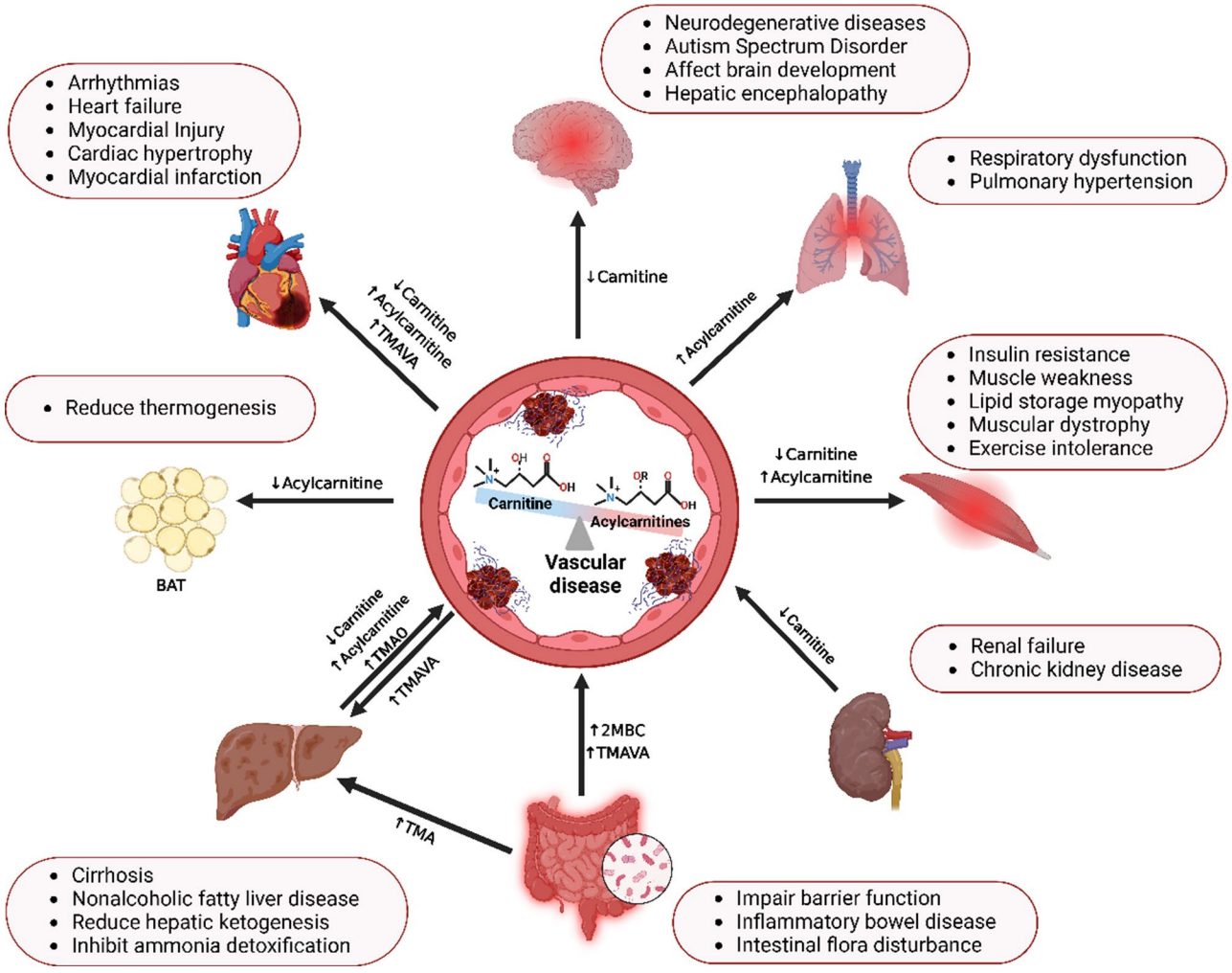


Fig. 4 Diseases associated with the carnitine pool disorders. Carnitine/acylcarnitines are found in almost every part of our body. The composition and level differences of the carnitine pool in different organs accurately reflect the unique metabolic characteristics and health status of each organ, showing great potential as disease biomarkers. Carnitine/acylcarnitines are also important mediators of organ crosstalk, coordinating energy metabolism and responding to different physiological needs. The delicate balance of the carnitine pool is essential for maintaining healthy organ function, and it is a promising target for future intervention and treatment of various diseases. Created with BioRender.com

past, research on the carnitine pool focused mainly on FAO, but it has now expanded to many biological fields, including energy metabolism, mitochondrial homeostasis, epigenetic regulation, inflammatory and immune homeostasis, endocrine regulation, cell signaling, neuroprotection, and tumor biology. Although mass spectrometry has revealed the diversity of acylcarnitines, research still focuses on a few specific acylcarnitines, suggesting that many acylcarnitines have not been fully explored. Future research needs to explore the complex mechanisms of action of these acylcarnitines and their roles in diseases, which will not only enrich our understanding of their biological functions but also may provide molecular targets for new therapeutic strategies.

The homeostasis of the carnitine pool is a dynamic metabolic process involving synthesis, uptake, reabsorption, and excretion, as well as the synergistic actions of multiple organs and metabolic pathways. As the main carnitine-synthesizing organ, the liver can convert lysine and methionine to carnitine through its efficient BBD activity. The kidney plays an important role in carnitine recycling by reducing the loss of carnitine through its reabsorption and ensuring the effective utilization of carnitine. The importance of maintaining the metabolic health of the carnitine pool is emphasized by the high demand for carnitine in tissues that cannot synthesize carnitine, such as the myocardium and skeletal muscle. Carnitine and acylcarnitine can also be used as metabolic messengers to participate in the communication between tissues and coordinate energy metabolism between tissues. The heart, skeletal muscle, and adipose tissues have an increased demand for carnitine during strenuous exercise or metabolic stress, at which point the liver and kidney adjust carnitine synthesis and reabsorption

accordingly in response to the changing demands of these tissues. This finely regulated crosstalk ensures a balance between the supply and demand of carnitine in different physiological and pathological states, thus supporting the health and function of the whole organism. Therefore, perturbations in the homeostasis of the carnitine pool may reflect disorders in the metabolism of the whole body. The mechanism by which it responds to signals from interorgan communication contributes to our deeper understanding of the complexity of metabolic diseases and provides insights into the development of new therapeutic strategies.

Although some progress has been made in understanding the biological functions and potential mechanisms of the carnitine metabolism pool, their complexity and differences in pharmacology and pathophysiology still need to be further explored and understood. The dynamic changes in the carnitine pool under physiological and pathological conditions are extremely complex, and existing research may not yet have fully revealed the complete picture. This complexity is not only reflected in the composition and concentration changes of the carnitine pool but also involves the functional diversity of carnitine in different tissues and cell types. Moreover, there may be significant gender and individual differences in carnitine metabolism, which may have important implications for its functions in physiological and pathological processes. The absence of OCTN3 in humans, along with functional differences in OCT1 between humans and rodents, suggests that there are differences in the physiological and metabolic characteristics of carnitine across species. This may limit the generalizability of certain research conclusions and highlights the need for caution in addressing species-specific effects on carnitine transport in cross-species studies. Regarding the specific chain length range of MCACs, there is no consensus in the academic community. This inconsistency in definition further complicates the study of the metabolic characteristics of MCACs. Notably, the pleiotropic effects of C15-carnitine in various diseases are significantly different from the traditionally recognized harmful effects of LCACs. This discrepancy suggests that the conventional view that LCACs are generally harmful may not be universally applicable to all types of LCACs. In addition, while carnitine supplementation may be beneficial in some cases, excessive intake may bring potential side effects. Therefore, it is necessary to carefully evaluate the safety and efficacy of carnitine supplements.

Future research should focus on further elucidating the multidimensional mechanisms of the carnitine pool in the regulation of intercellular communication and metabolic processes and exploring its important role in maintaining the physiological balance and coping with pathological conditions. To explore the specific expression patterns of carnitine metabolism pool in different cell types and tissues, and to analyze how these patterns respond sensitively to the fluctuations in physiological and pathological signals. To reveal the expression profile and functional evolution of the carnitine pool in different disease states, and how these changes profoundly affect the disease process, the effect of treatment, and the response of patients to treatment. Using advanced molecular biology and systems biology tools, such as proteomics, metabolomics and computational modeling, to comprehensively analyze the role of the carnitine pool in the regulation of the cellular metabolic network, providing new perspectives and strategies for the prevention, diagnosis and treatment of diseases.

Abbreviations

FAO	Fatty Acid Oxidation
acyl-CoA	acyl-Coenzyme A
BCAA	Branched-Chain Amino Acid
BCAC	Branched-Chain Acylcarnitine
LCAC	Long-Chain Acylcarnitine
OXPHOS	Oxidative Phosphorylation
BCFA	Branched-Chain Fatty Acid
VLCFA	Very Long-Chain Fatty Acid
C16-Carnitine	palmitoylcarnitine
CPT1A	Carnitine Palmitoyltransferase 1 A
TML	6-N-trimethyllysine
TMLD	6-N-trimethyllysine dioxygenase
HTML	3-hydroxy-6-N-trimethyllysine
TMABA	4-N-trimethylaminobutyraldehyde
HTMLA	3-hydroxy-6-N-trimethyllysine aldolase
TMABA DH	4-N-trimethylaminobutyraldehyde Dehydrogenase
γBB	γ-Butyrobetaine
BBD	γ-Butyrobetaine Dioxygenase
OCTN	Organic Cation Transporter Novel
CrAT	Carnitine Acetyltransferase
CrOT	Carnitine Octanoyltransferase
TMA	Trimethylamine
TMAO	Trimethylamine-N-oxide
TMAVA	Trimethyl-5-Aminovaleric Acid
PDC	Pyruvate Dehydrogenase
IRI	Ischemia-Reperfusion injury
AKT	Protein Kinase B
PI3K	Phosphatidylinositol-3-Kinase
AMPK	AMP-Activated Protein Kinase
JNK	c-Jun N-terminal Kinase
mTOR	mechanistic Target Of Rapamycin
MAPK	Mitogen-Activated Protein Kinase
NF-κB	Nuclear Factor κB
Nrf2	the Nuclear factor E2-related factor 2
TNF-α	Tumor Necrosis Factorα
CAT	Catalase
COX-2	Cyclooxygenase-2
ERK	Extracellular signal-Regulated Kinase
ROS	Oxygen Species
MDA	Malondialdehyde
SOD	Superoxide Dismutase
MyD88	Myeloid Differentiation factor 88
ER	Endoplasmic Reticulum
PGC-1α	Peroxidase proliferator-activated receptor γ coactivator-1α
PPAR	Peroxisome Proliferator-Activated Receptor
GST	Glutathione-S-Transferase
GSH	Reduced Glutathione
GSH-Px	Glutathione peroxidase
GSSG	Oxidized Glutathione
TBARS	Thiobarbituric Acid Reactive Substances

NLRP3	NOD-Like Receptor Thermal Protein Domain Associated Protein 3
COX2	Cyclooxygenase-2
Cyt c	Cytochrome c
HO-1	Heme Oxygenase-1
FOXO	Forkhead box O
IGF-1	Insulin like Growth Factor-1
BDNF	Brain-Derived Neurotrophic Factor
NGF	Nerve Growth Factor
NQO1	NAD(P)H Quinone Oxidoreductase 1

Acknowledgements
We thank BioRender for providing drawing support and AJE for English language editing.

Author contributions
FX: Investigation, Writing– original draft. ZZ: Writing– review & editing. JX: Methodology. SX: Visualization, Software. CY: Visualization, Software. DL: Conceptualization. BX: Conceptualization, Supervision. LL: Project administration, Funding acquisition.

Funding
This work was supported by the National Natural Science Foundation of China (8247143079), The Discipline Construction Project of Hunan University of Chinese Medicine (Z2023JBGS05), the Key Project of Education Bureau of Hunan Province (23A0293), the Hunan Province Science and Technology Innovation Leading Talent Project (2021RC4034), the Key Project at Central Government Level: the ability establishment of sustainable use for valuable Chinese medicine resources (2060302).

Data availability
Not applicable.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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Received: 9 November 2024 / Accepted: 1 March 2025
Published online: 14 March 2025

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