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Review

Metabolic interactions between peroxisomes and mitochondria with a special focus on acylcarnitine metabolism

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ABSTRACT

Carnitine plays an essential role in mitochondrial fatty acid β-oxidation as a part of a cycle that transfers long-chain fatty acids across the mitochondrial membrane and involves two carnitine palmitoyltransferases (CPT1 and CPT2). Two distinct carnitine acyltransferases, carnitine octanoyltransferase (COT) and carnitine acetyltransferase (CAT), are peroxisomal enzymes, which indicates that carnitine is not only important for mitochondrial, but also for peroxisomal metabolism. It has been demonstrated that after peroxisomal metabolism, specific intermediates can be exported as acylcarnitines for subsequent and final mitochondrial metabolism. There is also evidence that peroxisomes are able to degrade fatty acids that are typically handled by mitochondria possibly after transport as acylcarnitines. Here we review the biochemistry and physiological functions of metabolite exchange between peroxisomes and mitochondria with a special focus on acylcarnitines.

1. Introduction

Carnitine is a substrate for the carnitine acyltransferases, which catalyze the transesterification of an acyl-CoA to an acylcarnitine with free carnitine and free CoA as the respective co-substrate and co-product. Three types of carnitine acyltransferases are defined based on their substrate specificity; carnitine palmitoyltransferase (CPT), carnitine octanoyltransferase (COT), and carnitine acetyltransferase (CAT). Carnitine is most well-known for its essential function in mitochondrial long-chain fatty acid β-oxidation (FAO) in which it enables the translocation of fatty acid intermediates from the cytosol to the mitochondria via the carnitine cycle [1]. CPT1 and CPT2 function in the carnitine cycle. CPT1 is an integral outer mitochondrial membrane protein that converts a long-chain acyl-CoA into an acylcarnitine. The acylcarnitine is subsequently transported into the mitochondria via a specific translocase (carnitine-acylcarnitine translocase, CACT, SLC25A20). CPT2, a peripheral inner mitochondrial membrane protein, then reconverts the acylcarnitine into an acyl-CoA, which is the substrate for mitochondrial long-chain FAO (Fig. 1). The acyltransferase reaction is reversible, and therefore the net flux through the enzyme will depend on the concentration of substrates and products. The role of the carnitine cycle in mitochondrial long-chain FAO has been reviewed elsewhere [2–4]. Other less well known roles of carnitine include the detoxification of a wide variety of acyl-CoA esters that may accumulate in specific inborn errors of metabolism [5–7], mediating the mobility of acyl-CoA esters between cells, tissues and body fluids [8], and mediating the mobility of acyl-CoA esters between peroxisomes and mitochondria. The latter role is the topic of this review.

2. The peroxisomal carnitine acyltransferases

Both COT and CAT are peroxisomal enzymes. This finding that carnitine acyltransferases localize to the peroxisome basically established that carnitine is not only important for mitochondrial metabolism, but also for peroxisomal metabolism [9]. The CAT protein, but not COT, localizes also to the mitochondria, because the gene can encode a protein with a mitochondrial targeting sequence and/or peroxisomal targeting sequence 1. Alternative splicing in the 5′ region leads to mRNAs with different start codons, which likely affects subcellular localization [10–12]. A cytosolic localization in heart was recently suggested as well [13]. Human *CRAT* is ubiquitously expressed, but higher levels are observed in liver, skeletal muscle and testis [14]. Subcellular expression levels of CAT have not been systematically studied. CAT accepts various short-chain acyl-CoAs as substrate including acetyl-

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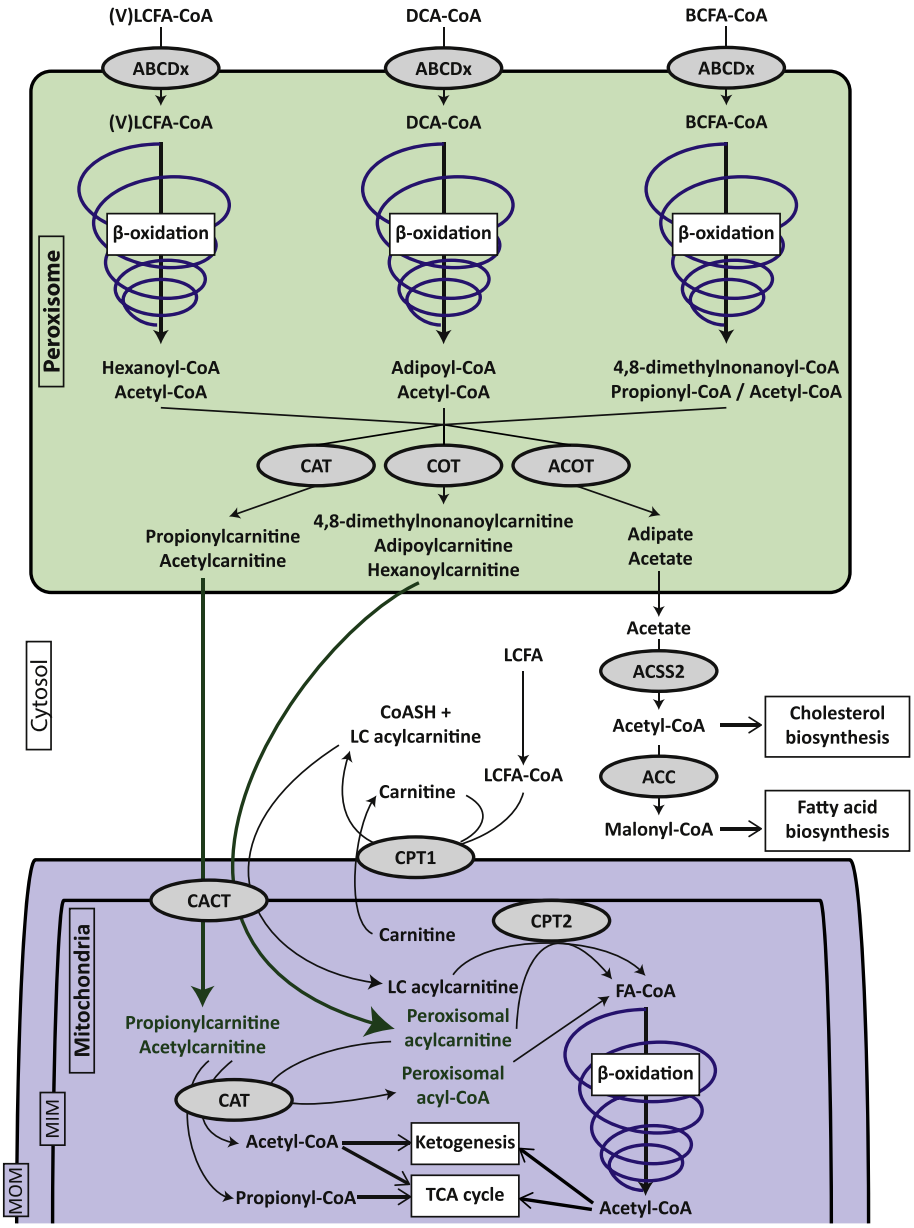

Fig. 1. Schematic representation of acylcarnitine metabolism and transport from peroxisomes to mitochondria. The figure is focused on the substrates and products of peroxisomal fatty acid β-oxidation, but only the most abundant end-products are indicated. Details of the pathways and the individual enzyme steps are omitted. ABCD transporters are half-transporters and function as homodimers or heterodimers. For the simplicity of the figure, they have been represented as monomers. Abbreviations: ABCDx, members of the peroxisomal ABC transporter family; ACC, acetyl-CoA carboxylase; ACSS, short-chain acyl-CoA synthetase; ACOT, acyl-CoA thioesterases; BCFA, branched-chain fatty acid; CACT, carnitine acylcarnitine translocase (SLC25A20); CPT1, carnitine palmitoyltransferase 1; CPT2; carnitine palmitoyltransferase 2; DCA, dicarboxylic acid; LCFA, long-chain fatty acid; MIM, mitochondrial inner membrane; MOM, mitochondrial outer membrane; VLCFA, very long-chain fatty acid.

CoA, propionyl-CoA and butyryl-CoA [7]. *CROT* is also ubiquitously expressed with highest levels in thyroid [14]. COT has a peroxisomal targeting sequence 1 [15] and localizes exclusively to the peroxisome [16]. When compared to CAT, COT prefers acyl-CoAs or acylcarnitines with carbon chain lengths of 6, 8 and 10 atoms [16–18]. COT has also been demonstrated to accept 4,8-dimethylnonanoyl-CoA, a product of the peroxisomal oxidation of branched-chain fatty acids (BCFAs) [19]. More detailed studies on the substrate specificity of COT focusing on peroxisomal FAO intermediates such as dicarboxylyl-CoAs have not been reported yet.

3. The role of peroxisomal carnitine acyltransferases

Whereas mitochondria are thought to handle the bulk of dietary fatty acids such as palmitate and oleic acid, peroxisomes accept a more diverse spectrum of carboxylic acids including very long-chain fatty acids (VLCFAs), dicarboxylic acids (DCAs), BCFAs and bile acids (Fig. 1). In order to be able to degrade these substrates, peroxisomes have two sets of FAO enzymes, a topic reviewed elsewhere [20,21]. In contrast to mitochondrial FAO, peroxisomal FAO does not completely degrade most substrates and based on substrate specificities of isolated peroxisomes and the individual enzymes, medium-chain products with 6 carbons are thought to be the final products [22,23]. In addition, peroxisomes do not have metabolic pathways to use acetyl-CoA, one of the major end products of FAO. Therefore, peroxisomes do not only need mechanisms to import the substrates of FAO, but also export its products [24]. Acylcarnitines theoretically could mediate both processes. However, given that CAT and COT handle short- and medium-chain acyl-CoAs, it is most likely that acylcarnitines are mainly used to export the FAO intermediates out of the peroxisome. Although there is some evidence that peroxisomes can also accept acylcarnitines as substrates for import [25], the current consensus is that peroxisomes import acyl-CoA esters. This process is mediated by peroxisomal ABC transporters (ABCD1, 2 and 3 in humans) that have intrinsic thioesterase activity leaving a free acid in the peroxisome that must be reactivated before it can undergo peroxisomal FAO [26,27]. Other studies suggest that in human cells, VLCFA-CoA esters are transported into peroxisomes by ABCD1 independently of additional synthetase activity [28]. Specific peroxisomal transporters for acylcarnitines have not been described, and it is thought that these metabolites cross the peroxisomal

membrane through unspecific channels such as PXMP2 [29].

Acylcarnitines are not the only possible products of peroxisomal FAO. Alternatively, acyl-CoA products can undergo enzymatic hydrolysis by acyl-CoA thioesterases (ACOTs) that generate a free carboxylate that can cross the peroxisomal membrane (Fig. 1). It has been hypothesized that the carnitine acyltransferases and ACOTs provide complementary systems for transport of metabolites across the peroxisomal membrane [11]. This was based on the observation that in mouse tissues, the expression patterns of these genes was very different [11]. The tissue expression pattern of the human peroxisomal ACOTs (*ACOT4* and *ACOT8*), however, is relatively ubiquitous and as such comparable to *CRAT* and *CROT* [14]. *ACOT4* expression is somewhat higher in liver and kidney of both humans and mice [14,30], but this is a commonly observed expression pattern for many peroxisomal enzymes. Expression of CAT, COT and ACOT4 is upregulated by hypolipidemic drugs such as Wy-14,643, an agonist of peroxisome proliferator-activated receptor (PPAR) α [16,30]. Therefore, as based on tissue expression patterns, there is currently no clear evidence that the role of peroxisomal carnitine acyltransferases diverges between tissues. The availability of peroxisomal substrates, however, is expected to differ between tissues, most notably the generation of DCAs, which is restricted to liver and kidney.

The metabolic fate of peroxisomal acylcarnitines and free carboxylates is likely different. Whereas further acylcarnitine metabolism is expected to be restricted to mitochondria, carboxylates, in particular acetate, can also be metabolized within the cytosol. In the cytosol, acetate can be reconverted into acetyl-CoA by acetyl-CoA synthetase (ACSS2). The expression of this enzyme is regulated by Sterol Regulatory Element-Binding Proteins (SREBPs), consistent with a role in lipid biosynthesis. Importantly, it is known that the acetyl-CoA formed by peroxisomal FAO can enter the cytosolic pool of acetyl-CoA and is used for cholesterol biosynthesis in rat hepatocytes [31] and malonyl-CoA synthesis in rat heart [32]. The tissue-specific fates of peroxisomal FAO products and the regulation of their production is clearly a topic that deserves more investigation.

4. Transfer of acylcarnitines from peroxisomes to mitochondria

The best studied example of metabolic crosstalk between peroxisomes and mitochondria is the oxidation of the BCFAs phytanic and pristanic acid [33–35] (Fig. 1). Using fibroblasts from patients with defects in the carnitine cycle, Jakobs and Wanders first showed that propionyl-CoA, a product of peroxisomal FAO of pristanic acid, is shuttled from the peroxisome to the mitochondria for complete oxidation [33]. Verhoeven et al. used control and patient fibroblasts with defects in different peroxisomal proteins and enzymes or the carnitine cycle, and analyzed acylcarnitines after loading with phytanic and pristanic acid [34,35]. They demonstrated that phytanic acid first undergoes peroxisomal α-oxidation followed by 3 cycles of peroxisomal FAO [34]. The resulting product 4,8-dimethylnonanoyl-CoA is transferred to the mitochondria as a carnitine ester (C11:0) using the carnitine shuttle and then undergoes at least one additional FAO cycle to yield 2,6-dimethylheptanoyl-CoA as one of the final mitochondrial products that is exported as a carnitine ester (C9:0) [35]. 2,6-Dimethylheptanoyl-CoA is a specific substrate for the mitochondrial long-chain acyl-CoA dehydrogenase (LCAD) [36]. The relatively poor metabolism of 2,6-dimethylheptanoyl-CoA in human fibroblasts is likely related to the poor expression of LCAD in most human cells and tissues [37].

A similar transfer of substrates must occur in the metabolism of other peroxisomal substrates. VLCFA oxidation yields multiple acetyl-CoAs as well as a medium-chain acyl-CoA, all of which require further oxidation in mitochondria or cytosolic metabolism (Fig. 1). There is good evidence that peroxisomes are crucial for the metabolism of DCAs, as mitochondria are unable to handle these substrates [38–45]. The oxidation of DCAs yields acetyl-CoA units, but also a dicarboxylyl-CoA that can have different fates depending on its carbon chain length (Fig. 1). Suberyl-CoA and adipoyl-CoA can be converted into suberic and adipic acid, respectively, which may be considered dead end metabolites, because they are excreted in urine. Low levels of carnitine esters of these metabolites are detected in plasma of which the physiological significance is unknown. Peroxisomal FAO of DCAs can also yield succinyl-CoA [46,47]. Peroxisomal succinyl-CoA can be shuttled to the mitochondria as succinate or succinylcarnitine, and then serve as an anaplerotic substrate in the TCA cycle [30,48]. Many aspects of the transfer of metabolites from peroxisomes to mitochondria have not been fully elucidated. This is likely due to the inherent difficulties of studying the origin and fate of intracellular metabolites. Studies with stable isotopes in genetically modified model organisms, as well as patient-derived cell lines, are therefore expected to yield novel insights.

5. Transfer of mitochondrial metabolites to peroxisomes

From a biochemical perspective, the transfer of mitochondrial acylcarnitines to peroxisomes is more difficult to explain since peroxisomes need mitochondria to adequately finish the metabolism of these molecules. Recent studies, however, have demonstrated that fatty acids and acylcarnitines that are normally destined for mitochondrial FAO can be rerouted to the peroxisome if the mitochondrial pathway is blocked [25,49] (Fig. 2). We found that fibroblasts of patients with a defect in the carnitine cycle could produce C10-carnitine, as well as shorter acylcarnitines, when loaded with lauric acid (C12), a fatty acid that normally undergoes mitochondrial FAO [49]. Subsequent knockdown of PEX13 in these cells, which essentially depletes functional peroxisomes, prevented the C10-carnitine accumulation proving that its origin was peroxisomal [49]. In a follow-up study, we performed a molecular dissection of this pathway using CRISPR-Cas9 genome editing in HEK-293 cells [25]. We found that HEK-293 cells can oxidize medium- and long-chain fatty acids in peroxisomes when the carnitine cycle is blocked. By creating double KOs with different defects in peroxisomal FAO and the carnitine cycle, we furthermore showed that ABCD3, a peroxisomal ABC transporter, and HSD17B4, a peroxisomal FAO enzyme, were essential in this process [25].

Plasma acylcarnitine profiles of patients with defects in the carnitine cycle may provide evidence that a similar pathway also occurs in vivo. Patients with CPT2 and CACT deficiency are identified by the accumulation of plasma long-chain acylcarnitines (C16 and C18) in particular an elevated (C16 + C18:1)/C2 ratio. Interestingly, shorter acylcarnitines such as C12-carnitine are sometimes also reported as elevated in a diagnostic plasma sample (i.e. before starting any treatment [50–58]). The defect in the carnitine cycle and the absence of C12 fatty acids from regular diets suggests that these acylcarnitines may have a peroxisomal origin. In an effort to prove this, we treated mice with L-aminocarnitine [25], a potent, versatile and specific inhibitor of CPT2 [59]. Treated animals not only showed a pronounced increase in C16 and C18 acylcarnitine species, but also several other acylcarnitines, including C10:1-, C10-, C12:1-, C12-, C14:1-, and C14-carnitine. We found that the accumulation of most of these chain-shortened species was decreased in the *HSD17B4* KO mice [25]. This result should be confirmed in another model system with potentially larger effects such as the *ABCD3* KO mouse. Our work has demonstrated that peroxisomal FAO can oxidize mitochondrial substrates when the mitochondrial pathway is blocked (Fig. 2). A more general interpretation of these results would be that peroxisomes always oxidize a small portion of the "mitochondrial" substrates and that blocking mitochondrial FAO at the level of the carnitine cycle unveils this contribution because the subsequent and final mitochondrial metabolism of peroxisomal intermediates is blocked. This interpretation is consistent with early biochemical studies that demonstrated a contribution of peroxisomes to the oxidation of canonical mitochondrial substrates such as palmitate [23,31,32,60–65].

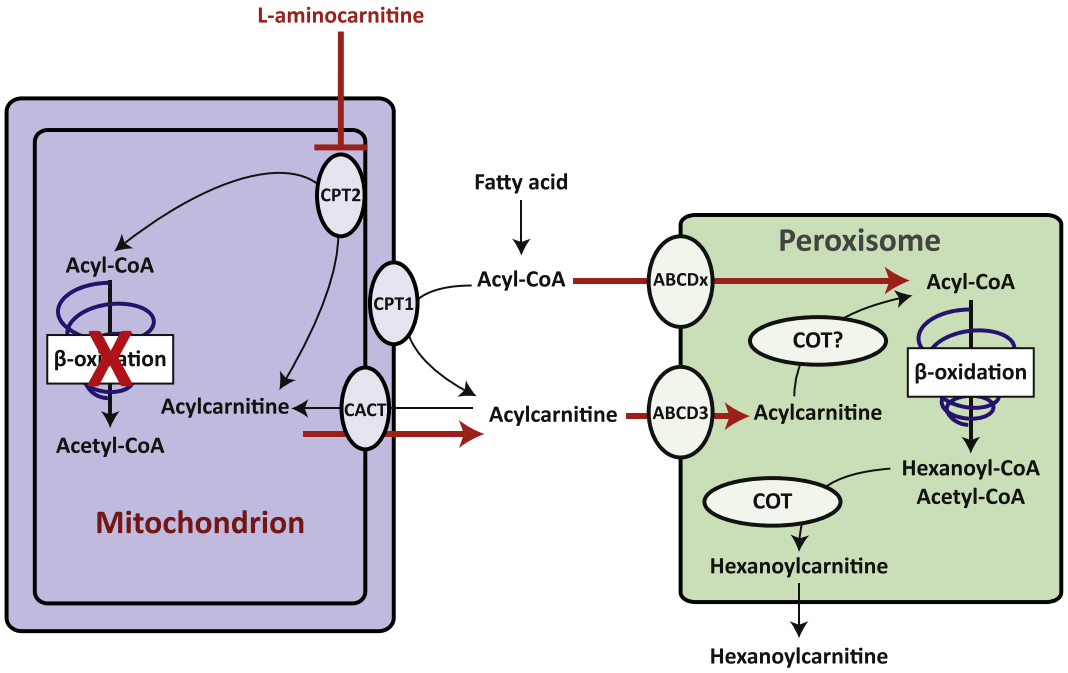

Fig. 2. Schematic representation of the interactions between mitochondria and peroxisomes for the β-oxidation of medium- and long-chain fatty acids. The figure highlights the relevance of this interaction in the case of mitochondrial fatty acid β-oxidation dysfunction due to an enzyme deficiency or inhibition of CPT2 by L-aminocarnitine (red arrows). Details of the pathways and the individual enzymes are omitted. Abbreviations: ABCD3, ATP Binding Cassette Subfamily D Member 3. The remaining abbreviations are specified in the legend of Fig. 1. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

6. Potential physiological role for the oxidation of mitochondrial substrates in peroxisome

The physiological importance of peroxisomes is demonstrated by the severe disease presentations in disorders caused by defects in peroxisomal metabolism and biogenesis [20,21]. The pathophysiology of these disorders, however, can be largely explained by defects in the metabolism of canonical peroxisomal metabolites such as bile acids precursors, VLCFAs and plasmalogens, and it is unclear if a defect in the peroxisomal metabolism of mitochondrial substrates plays a role as well. As highlighted before, it is known that acetyl-CoA formed by peroxisomal FAO can enter the cytosolic pool of acetyl-CoA and is used for cholesterol biosynthesis in rat hepatocytes [31]. Consistent with this role, induction of the cholesterol biosynthesis pathway and SREBP induction has also been reported in mouse models with defects in peroxisomal metabolism and biogenesis [66–69]. Stable isotope labeling studies by Brunengraber and Des Rosiers have provided additional insights in the physiological role of this process. These studies demonstrated that peroxisomes contribute to the oxidation of long- and medium-chain fatty acids in rat heart [32,70]. And although the rate of peroxisomal acetyl-CoA production is 100 times smaller than the mitochondrial rate, it can contribute 50% of the acetyl-CoA for the synthesis of malonyl-CoA [32]. A similar phenomenon was reported for rat liver [71], although in this case it cannot be excluded that the employed medium-chain fatty acids first underwent microsomal omega-oxidation. Malonyl-CoA is an interesting metabolite with at least two functions. It is a substrate for fatty acid synthesis and an inhibitor of CPT1 and therefore a regulator of mitochondrial long-chain FAO [72–74]. Combined, these studies suggest that peroxisomes may play a role in the regulation of lipid synthesis and oxidation. Further experiments using stable isotopes in model organisms with defects in peroxisomal metabolism are necessary to further expand our understanding of these unexpected physiological roles of peroxisomal FAO.

7. Conclusion

Initially, when peroxisomal β-oxidation was discovered, it was thought to play a role in the oxidation of long-chain fatty acids, similar to mitochondria [23,62,65]. With the identification of peroxisomal diseases such as Zellweger syndrome and the characterization of the specific substrates for the peroxisomal β-oxidation system, a potential general role for peroxisomes has been forgotten and remains largely unexplored. In this review, we have tried to highlight some studies that demonstrate that such a role exists and what its function may be. It is clear that we have only just started to understand the significance of the interactions between the different cell organelles, and future research on this topic using a combination of genetic and biochemical techniques is expected to yield important new insights.

Declaration of competing interest

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

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