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Mitochondrial fatty acid synthesis, fatty acids and mitochondrial physiology

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ABSTRACT

Mitochondria and fatty acids are tightly connected to a multiplicity of cellular processes that go far beyond mitochondrial fatty acid metabolism. In line with this view, there is hardly any common metabolic disorder that is not associated with disturbed mitochondrial lipid handling. Among other aspects of mitochondrial lipid metabolism, apparently all eukaryotes are capable of carrying out *de novo* fatty acid synthesis (FAS) in this cellular compartment in an acyl carrier protein (ACP)-dependent manner. The dual localization of FAS in eukaryotic cells raises the questions why eukaryotes have maintained the FAS in mitochondria in addition to the "classic" cytoplasmic FAS and what the products are that cannot be substituted by delivery of fatty acids of extramitochondrial origin. The current evidence indicates that mitochondrial FAS is essential for cellular respiration and mitochondrial biogenesis. Although both β-oxidation and FAS utilize thioester chemistry, CoA acts as acyl-group carrier in the breakdown pathway whereas ACP assumes this role in the synthetic direction. This arrangement metabolically separates these two pathways running towards opposite directions and prevents futile cycling. A role of this pathway in mitochondrial metabolic sensing has recently been proposed. This article is part of a Special Issue entitled: Lipids of Mitochondria edited by Guenther Daum.

1. Introduction

The metabolism of living organisms is exposed to a large variety of fatty acids originating either from exogenous sources or arising from endogenous synthesis. Depending on the cellular compartment, these lipid carboxylic acids play multiple roles in cellular processes. Concerning mitochondria, fatty acids serve as energy sources, membrane constituents, molecules for post-translational modifications of proteins and as signaling factors. The largest fraction of fatty acid metabolism proceeds through fatty acyl thioesters, which are more reactive than their oxyester counterparts such as in sterolesters, phospholipids or triacylglycerols [1]. In many organisms, similar fatty acid processing reactions are frequently found to occur in several different cellular compartments. Pieces of evidence provided from many sources indicate that these reactions are not mere metabolic redundancies, but are either functionally complementary to each other or serve completely different metabolic roles. Among the many examples illustrating this observation are mitochondrial and peroxisomal β-oxidation pathways, synthesis of 3-hydroxymethylglutaryl-CoA for the generation of cholesterol in the cytosol or for ketogenesis in liver mitochondria, duplicity of fatty acid synthesis (FAS) in cytosol and mitochondria, presence of multiple acyl-CoA synthetases, acyl-CoA thioesterases and fatty acid binding proteins in various subcellular compartments.

As a recent addition to the plethora of mitochondrial processes, it has been recognized that these organelles are able to synthesize fatty acids in an acyl carrier protein (ACP)-dependent manner (mitochondrial fatty acid synthesis, mtFAS) [2–5]. Yeast strains deficient in mtFAS function display failure in mitochondrial RNA processing, highly diminished cytochromes of the mitochondrial respiratory chain and loss of lipoic acid. Consequently, these cells are unable to respire and can grow only on fermentable carbon source. Concerning mammals, the total knock-out of mtFAS pathway components in mice leads to embryonic lethality (our unpublished observations), and an induced conditional knockout of the fatty acid synthetic *Mcat*, the gene encoding the mitochondrial malonyl-CoA:ACP transacylase in adult mice, results in severe defects resembling phenotypes of other mitochondrial dysfunction models [6].The dual localization of FAS in eukaryotic cells raises the question why eukaryotes have maintained the FAS in mitochondria in addition to the "classic" cytoplasmic FAS (FASI). It is noteworthy that functional cytoplasmic fatty acid synthesis or fatty acids added externally to the culture medium cannot rescue the respiratory deficient

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phenotype in yeast. This review summarizes our current understanding on mitochondrial FAS and its relations to other mitochondrial processes and physiology.

2. Components of mitochondrial fatty acid synthesis

Although the first component of mtFAS - a fungal mitochondrial acyl carrier protein (ACP) [7] - was identified more than a quarter century ago, mtFAS has remained to be perhaps one of the most puzzling aspects of mitochondrial lipid metabolism. While the pathway is highly conserved in eukaryotes in general, there are more or less subtle interspecies variations in the composition of the enzymes involved. Questions about some of the components involved in mtFAS in mammals as well as the overall physiologically relevant spectrum of products of this pathway persist. Nevertheless, the data produced and collected over the past three decades has allowed the identification of surprising links of mtFAS to the regulation of mitochondrial enzyme activities, RNA processing and control of mitochondrial gene expression. The mtFAS pathway (Fig. 1A) closely resembles a bacterial type II FAS system (FASII). In contrast to the eukaryotic cytosolic FASI machinery, where the required enzymatic activities are harbored by one or two polypeptides constituting multifunctional proteins carrying out all the steps of FAS, the FASII route proceeds by the action of individual polypeptides catalyzing the separate reactions [8]. Plant chloroplasts, the photosynthetic endosymbiont cousins of mitochondria, also follow a FASII mode, and it is not unreasonable to regard this phenomenon as corroborative evidence for the prokaryotic heritage of these organelles.

Despite the clearly prokaryotic origin of mtFAS, the systems found in yeasts and mammals appear to be mosaics, for which the components were recruited from different sources. Several of the proteins involved in mtFAS (Table 1) have been drafted straight from the bacterial pathway. The *S. cerevisiae*/human (mammalian) malonyl-CoA:ACP transferase (Mct1/MCAT) and the 3-ketoacyl-ACP synthase (KAS) (Cem1/OXSM) are highly similar to the enzymes acting in the *Escherichia coli* FASII system and can therefore be unequivocally identified as orthologs [9–11]. KAS enzymes and domains of multifunctional FASI polypeptides share a common architecture [12] that is also likely to make them susceptible to the same inhibitors. It has been shown previously that OXSM binds the drug cerulenin [11] and, like mammalian FAS, the yeast FASI complex containing a KAS domain [13] and the yeast mitochondrial Cem1 KAS [14], are inhibited by this compound. The speculation that OXSM is also affected by other KAS inhibitors *in vivo* was confirmed recently by Chen et al. [15] who showed that treatment of HEK293Tcells with the FAS inhibitor 4-methylene-2-octyl-5-oxotetrahydrofuran-3-carboxylic acid (C75) resulted in cellular defects consistent with mtFAS dysfunction. As suggested previously [11], it is likely that other KAS-inhibitors like platensimycin [16] and the FASII specific inhibitor thiolactomycin [17] will have similar effects.

Other components of mammalian mtFAS show subtle or strong divergence from the bacterial pathways. The mitochondrial ACP (Acp1 in *Saccharomyces cerevisiae*/NDUFAB1 in humans) is highly similar to prokaryotic ACPs. In addition to existing in a soluble pool, it has acquired a new role as a structural component of respiratory complex I in many non-plant eukaryotes [18–21]. Interestingly, the observation that mitochondrial ACP in *Arabidopsis thaliana* does not appear to be associated

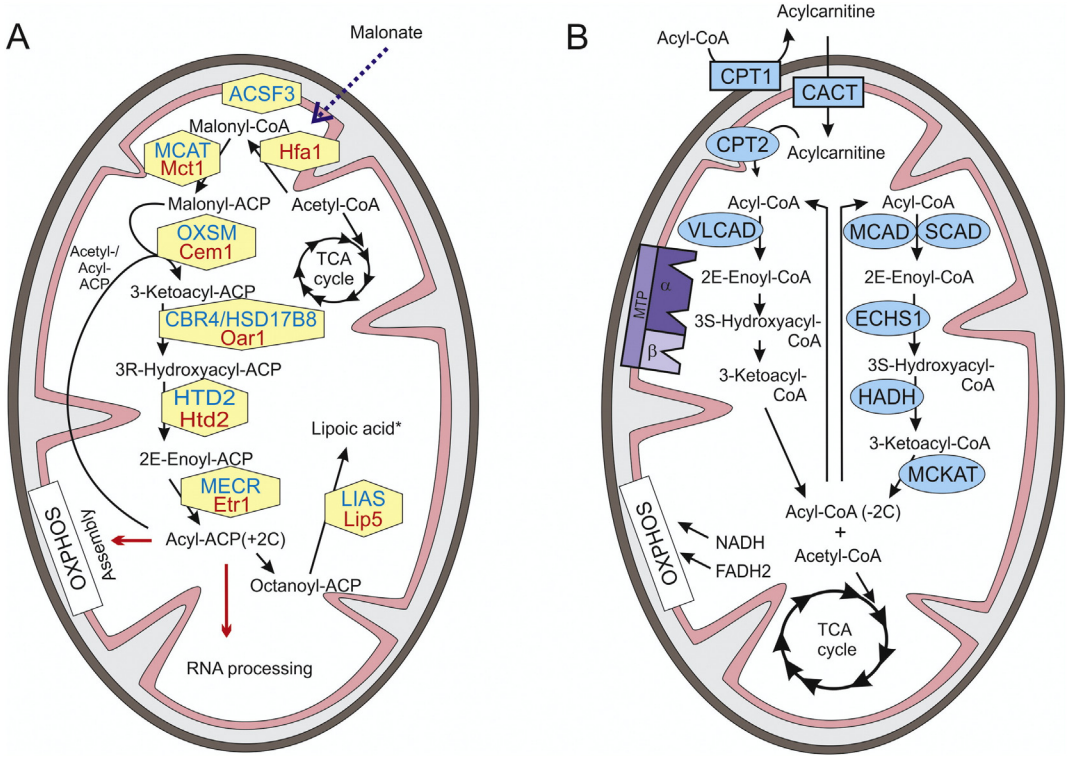

Fig. 1. Organization of fatty acid synthesis and β-oxidation in mitochondria. (A) Human enzymes/proteins of mtFAS in symbols are labeled in blue font, the corresponding or alternative *S. cerevisiae* enzymes are in red font. The red arrows indicate the influence of the functional mtFAS on assembly of mitochondrial respiratory chain and mitochondrial RNA processing as demonstrated using yeast as a model organism. (*)It is likely that insertion of sulfurs in the C6 and C8 positions of the octanoyl group by LIAS/Lip5 occurs on the target proteins (DLAT/Lat1 of PDH, DLST/Kgd2 of KGD, GCSH/Gcv3 of GCS and DBT of branched chain dehydrogenase in mammals) after transfer of the octanoyl moiety rather than on octanoyl–ACP. For discussion, see the text, Section 3. The abbreviations for the names of enzymes are as given in the Table 1. (B) Mitochondrial β-oxidation pathway is organized into a membrane associated and a matrix set of enzymes. Although not shown in the Figure, the matrix set of the enzymes is apparently organized into a multienzyme complex [123,124]. The abbreviations: CACT, carnitine acyl-carnitine translocase; CPT1, carnitine palmitoyltransferase 1 A or B; CPT2, carnitine palmitoyltransferase 2; ECHS1, enoyl-CoA hydratase 1, (crotonase); HADH, 3S-hydroxyacyl-CoA dehydrogenase; MCAD, medium-chain acyl-CoA dehydrogenase; MCKAT, medium-chain 3-ketoacyl-CoA thiolase; MTP, mitochondrial trifunctional protein containing long-chain-3-hydroxyacyl-CoA dehydrogenase and enoyl-CoA hydratase activities in the α-subunit and long-chain 3-ketoacyl-CoA thiolase activity in the β-subunit; SCAD, short-chain acyl-CoA dehydrogenase; VLCAD, very long-chain acyl-CoA dehydrogenase.

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