New players on the metabolic stage

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How do you like *Them* Acots?

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Members of the acyl-CoA thioesterase (*Acot*) gene family catalyze the hydrolysis of fatty acyl-CoA thioesters. Thioesterase superfamily member (Them) 1 (synonym: Acot11) is enriched in brown adipose tissue and is markedly upregulated when mice are exposed to cold ambient temperatures. In a recent study, we demonstrated that *Them1*$^{-/-}$ mice exhibit increased energy expenditure and are resistant to diet-induced obesity and its metabolic consequences. This mini-review places these findings in the context of an emerging understanding of *Them/Acot* genes.

Introduction

Acyl-CoA thioesterases (Acots) are enzymes that catalyze the hydrolysis of acyl-CoA molecules, including fatty acyl-CoAs.[1,2] Although their reactions are relatively well defined, the cellular and biological consequences of Acot activity are poorly understood. Hypotheses include control of the intracellular balance between fatty acyl-CoAs and free fatty acids, the intracellular and intra-organelle concentrations of coenzyme A (CoASH) and the availability of fatty acids for the biosynthesis of inflammatory mediators.[1,2]

Acots have been identified in a broad array of organisms from prokaryotes to mammals. In mammals, convergent evolution has resulted in two structurally distinct types of Acot enzymes. Type I enzymes (Acots 1–6) contain an α/β-hydrolase domain near the C-terminus, which comprises all amino acid (aa) residues required for catalysis, and typically an N-terminal regulatory acyl-CoA thioester hydrolase domain that is not required for enzymatic activity. Members of the α/β-hydrolase fold enzyme superfamily include enzymes such as carboxyl-esterases and lipases. Type 1 Acots exhibit considerable aa sequence identity, ranging from 54–98% for the human enzymes[3] and 65–94% for the mouse enzymes.[1]

Type II enzymes (Acots 7–13) share much lower degrees of sequence identity (typically $< 25\%$)[1,3] and are instead related by a common hotdog fold structural motif.[1] The "hotdog" domain proteins contain highly divergent sequences that fold to create very well conserved structural elements in which an antiparallel β-sheet is the "bun," which wraps around an α-helical "hotdog."[4] With the exception of Acot13, which consists of a single hotdog fold domain, the other established type II Acots (i.e., Acots 7–12) comprise tandem hotdog fold domains. The significance of tandem hotdog fold thioesterase domains is presumably related to the requirement that these structures oligomerize to create enzyme active sites. Uniquely, Acots 11 and 12 each contain a C-terminal lipid-binding steroidogenic acute regulatory transfer-related (START) domain.

Because type II enzymes are related principally by structure and not sequence, the possibility remains open that more family members exist than are currently designated as Acots. Important examples are four genes that were each categorized as a thioesterase superfamily member (*Them*). The corresponding proteins were not initially appreciated because of their enzymatic activities, but were subsequently understood to function as Acots. Recent studies of these *Them* genes have provided considerable new insights into the biological functions of Acots in nutrient metabolism and energy homeostasis.

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Them1 (Acot11)

Them1 was initially named brown fat inducible thioesterase (BFIT) because it is highly enriched in brown adipose tissue (BAT), with much lower expression levels in other tissues, including white adipose, brain, liver, skeletal muscle, kidney, heart and testis, and because it was markedly upregulated when mice were exposed to cold ambient temperatures.[5] When taken together with the observation that *Them1* gene expression was higher in BAT of mouse strains that were resistant to diet-induced obesity, it was predicted that Them1 might function to promote energy expenditure. Although not systematically characterized as an enzyme, the same investigators commented that recombinant Them1 functioned as a medium- to long-chain fatty acyl-CoA thioesterase. Them1 was subsequently incorporated into the Acot family as Acot11[6] and into the START domain family as StarD14.[7,8]

Our own attention was drawn to *Them1* because of its ties to both the Acot and START domain gene families. In an effort to understand the regulatory effects of another START domain protein, phosphatidylcholine transfer protein (PC-TP; synonym, StarD2) in hepatic glucose and lipid metabolism[9] and energy homeostasis,[9,10] we performed a yeast two-hybrid screen that identified Them2 as a PC-TP-binding protein.[11] The motivation for seeking a binding partner was that PC-TP is an example of a

START domain minimal protein that comprises a lipid binding pocket, but contains no other apparent functional domains.[8] It was curious to unearth an interaction between a START minimal domain protein and a hotdog fold thioesterase, when two related proteins (i.e., Them1 and Acot12) each contained tandem hotdog fold thioesterase domains plus a START domain within the same multidomain protein.

To test its own role in nutrient metabolism and energy homeostasis, we created *Them1*$^{-/-}$ mice.[12] Unexpectedly, *Them1*$^{-/-}$ mice exhibited increased energy expenditure and were resistant to diet-induced obesity, as well as associated metabolic disorders. Increased concentrations of fatty acyl-CoAs in BAT and decreased thioesterase activities of BAT homogenates suggested that Them1 functions as an Acot in vivo. Consistent with increased rates of energy expenditure, rates of fatty acid oxidation in BAT were increased in the absence of Them1 expression.

Them1$^{-/-}$ mice also displayed resistance to diet induced inflammation in white adipose tissue (WAT) and to hepatic steatosis and insulin resistance. Whereas these effects may have been ascribed to increased energy consumption by BAT, the data indicated that Them1 expression in WAT and liver per se played important roles in the development of obesity-associated metabolic disorders. In WAT, Them1 expression was upregulated several-fold in response to high fat feeding. Using white adipocytes from chow-fed animals, we demonstrated a reduced capacity of conditioned media to activate cultured wild type macrophages. This suggested the possibility that Them1 activity in wild type adipocytes led to the release of one or more pro-inflammatory molecules, possibly including free fatty acids. Along similar lines, endoplasmic reticulum (ER) stress led to upregulation of Them1 expression in mouse liver, and livers of *Them1*$^{-/-}$ mice exhibited reduced response to ER stress. This effect appeared to be cell autonomous, as evidence by reduced ER stress responses in cultured hepatocytes and MEFs prepared from *Them1*$^{-/-}$ mice. Collectively, these observations suggest a pathogenic role for Them1 in the metabolic abnormalities that accompany over-nutrition, potentially by liberating excess free fatty acids intracellularly.

Although the molecular mechanism by which Them1 reduces energy consumption is not yet known, a key regulatory role for this enzyme is in line with evidence that interconversion of free fatty acids and fatty acyl-CoAs is important for the control of thermogenesis in BAT. Studies in mice with adipose-specific deletion of long-chain acyl-CoA synthetase 1 (ASCL1), which catalyzes the formation of fatty acyl-CoA thioesterases from free fatty acids and CoASH, have revealed that activation of free fatty acids to form fatty acyl-CoAs facilitates their mitochondrial oxidation in BAT.[13] By reversing this reaction, Them1 could play an important role in reducing rates of fatty acid oxidation. We also provided evidence in *Them1*$^{-/-}$ mice for the differential regulation of genes that are under the control of fatty acid-activated nuclear hormone receptors that transcriptionally regulate BAT differentiation and thermogenesis (e.g., PPARγ and PPARα). This suggests that Them1 activity may regulate intracellular concentrations of selected ligands, which activate these nuclear hormone receptors.[2,13]

Whereas our paper suggests that Them1 functions in vivo as an acyl-CoA thioesterase, additional mechanistic insights into metabolic regulation and energy homeostasis will no doubt emerge from a deeper understanding of both the cellular biology and the structure-function relationships of the protein. Using subcellular fractionation techniques, we found that Them1 was mainly concentrated in the ER and to a lesser extent mitochondria and cytosol. In liver, the protein was mainly concentrated in cytosol. However, unlike the other Them proteins discussed below, Them1 was not identified as a component of the mitochondrial proteome.[14] A clearer understanding of the cellular localization and its determinants would contribute to our understanding of Them1's biological function.

At present, neither the enzymatic characteristics of Them1 nor the lipid ligand of the START domain have been elucidated. Whereas the crystal structure of the unliganded Them1 START domain revealed a hydrophobic binding pocket, it did not provide firm clues as to the identity of the endogenous ligand.[15] A number of lines of indirect evidence led the authors to propose that fatty acids ranging up to 18 carbons could constitute the natural ligands. Once a ligand is identified, it will be important to discern whether its binding to the START domain regulates the enzymatic activity of Them1. Knowledge of the enzymatic characteristics and endogenous ligand should also help to determine the feasibility of targeting Them1 for the management of obesity and its associated metabolic disorders.

Them2 (Acot13)

Them2 was first identified as a component of the mouse mitochondrial proteome.[16] It is broadly expressed,[17] with highest levels in liver and oxidative tissues including heart, kidney and BAT.[18] The crystal structure of human Them2 revealed a homotetrameric assembly of back-to-back hotdog folds.[19] Whereas an initial substrate survey suggested that Them2 primarily hydrolyzes a polar aromatic CoA thioester,[19] subsequent analyses by our group[18] and another[20] concluded that the endogenous substrates of Them2 were likely to be medium- and long-chain fatty acyl-CoAs. This led to the inclusion of Them2 within the Acot family as Acot13.[18]

To understand the biological functions of Them2, we created *Them2*$^{-/-}$ mice.[21] In livers of *Them2*$^{-/-}$ mice compared with *Them2*$^{+/+}$ controls, a decrease in mitochondrial thioesterase activity was accompanied by an increase in hepatic concentrations of long-chain fatty acyl-CoAs and a reciprocal decrease in free fatty acid concentrations. Fatty acid oxidation rates were unchanged in livers of *Them2*$^{-/-}$ mice despite reduced activation of PPARα. This suggested that Them2 functions, at least in part, to limit β-oxidation. In the setting of reduced HNF4α expression, rates of hepatic glucose production were also decreased in chow fed mice. Considering that fatty acids are putative ligands for both PPARα and HNF4α,[22,23] these findings further suggested that Them2 regulates activation of these nuclear receptors in the liver, a possibility that was supported by promoter-reporter experiments in a cell culture system. When fed a high fat diet, *Them2*$^{-/-}$ mice were also resistant to increases in hepatic glucose production and

steatosis. Taken together, these findings revealed a key role for Them2 in regulating lipid and glucose metabolism in the liver.

Having identified Them2 as PC-TP binding protein,[11] we sought evidence of a functional interaction between these two proteins. Accordingly, the in vitro fatty acyl-CoA thioesterase activity of purified recombinant Them2 was increased by the addition of purified recombinant PC-TP.[11,18] Circumstantial evidence of a biologically impactful interaction included the observations that both proteins are enriched in liver and oxidative tissues and are transcriptionally upregulated by PPARα.[18,24] Cell fractionation studies and confocal microscopy revealed that Them2 is primarily associated with mitochondria, but is also present in cytosol.[11,18] This is complementary to the subcellular distribution of PC-TP, which is enriched in cytosol, but has an appreciable fraction that associates with mitochondria.[11,18,25] Moreover, experiments in cell culture systems[25] have revealed that PC-TP may relocate from cytosol to mitochondria in response to certain PKA agonists, with indirect evidence to suggest that phosphorylation is the mechanism. As observed with Them2 in promoter-reporter experiments, PC-TP expression similarly regulated the transcriptional activity of both PPARα and HNF4α.[24] Finally, *Pctp*$^{-/-}$ mice exhibit increased hepatic insulin sensitivity[9] and are also resistant to high fat diet-induced increases in hepatic glucose production.[26] Although *Pctp*$^{-/-}$ mice do not entirely phenocopy *Them2*$^{-/-}$ mice, key similarities suggest that Them2-PC-TP interactions regulate fatty acid oxidation and glucose production by the liver.

Them4

Them4 was initially identified as the C-terminal modulator protein (CTMP). Mainly expressed in skeletal muscle, testis, uterus, brain and kidney, Them4 specifically binds to the carboxyl-terminal regulatory domain of Akt/PKBα at the plasma membrane.[27] In this study, binding of Them4 at the plasma membrane was shown to reduce Akt activity, as evidenced by decreases in phosphorylation at S473 and T308. This in turn decreased insulin and insulin-like growth factor 1 (IGF-1) signaling. Interestingly, Them4 is a nuclear-encoded mitochondria-associated protein,[14] which is targeted to the inner mitochondrial membrane and the inner mitochondrial space.[28] There it regulates mitochondrial dynamics, appearing to play a role in the fission process.[29] Them4 is released from mitochondria in response to stimuli that promote apoptosis and helps to facilitate apoptosis by inhibiting Akt activation.[28] In a separate study of relatively similar design, Them4 was shown to induce Akt phosphorylation and reduce apoptosis,[30] although the reason for this discrepancy is unclear.[31] In hippocampal neurons, Them4 was found within cytosol, where it suppressed Akt activity and promoted ischemia-induced neuronal cell death.[32] Based upon a bioinformatics analysis suggesting that Them4 belonged to the hotdog fold thioesterase family, the protein was modeled as a tetramer similar to Them2 and shown to hydrolyze a broad range of substrates including medium- to long-chain fatty acyl-CoAs.[33] Consequently, it has been proposed that Them4 be incorporated into the Acot family as Acot14.[3] At present, it is unclear whether a relationship exists between the enzymatic activity of Them4 and its regulatory activity in cell signaling.

Them5 (Acot15)

Them5 is a mitochondrial protein[14] that is localized to the matrix by a targeting sequence that is subsequently cleaved.[34] Like Them2 and Them4, it is a single domain hotdog fold thioesterase. In accordance with its crystal structure, a recent study showed that Them5 forms a homodimer in solution with enzymatic selectivity for medium- to long-chain fatty acyl-CoAs, particularly linoleoyl-CoA.[34] As a result, Them5 has been newly incorporated into the Acot family as Acot15. Although the tissue distribution of Them5 has not been reported, the same paper demonstrated that liver mitochondria from *Them5*$^{-/-}$ mice are characterized by a reduction in cardiolipin, an important constituent of the inner mitochondrial membrane. There was a reciprocal increase in the precursor monolyso-cardiolipin, suggesting that Them5 plays a key role in regulating the remodeling of mitochondria that is critical for optimal functioning of the electron transport chain. *Them5*$^{-/-}$ mice exhibited mitochondrial dysfunction as evidenced by measurements in cells and isolated mitochondria. There were also changes in morphology, with increased sizes as well as the development of interconnections among mitochondria. Loss of Them5 expression led to a decrease in mitochondrial free fatty acid concentrations, particularly C18 polyunsaturated fatty acids. These decreases were apparently due to the export of fatty acids into the cytosol, where they accumulated and may have contributed to the age-dependent development of fatty liver in *Them5*$^{-/-}$ mice. This was accompanied by decreased fatty acid oxidation, which likely also played a role in the development of fatty liver and was attributable, at least in part, to the failure of re-feeding to induce fatty acid synthase expression in livers of *Them5*$^{-/-}$ mice.

Conclusions

Although they have come to attention for different reasons, collectively the *Them* genes now appear to play key regulatory roles in fatty acid and glucose metabolism and in mitochondrial function. These initial studies, which have begun to shed light on the biological roles of Acots, further suggest that efforts to delineate the functions of other type I and type II *Acot* genes should broaden our understanding of metabolic regulation, as well as the consequences of overnutrition and obesity.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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