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REVIEWS

Spotlight

Sensing Mitochondrial Acetyl-CoA to Tune Respiration

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Fatty acid synthesis (FAS) in mitochondria produces a key metabolite called lipoic acid. However, a new study by Van Vranken *et al.* [1] (*Mol. Cell* 2018;71:567–580) shows that mitochondrial FAS regulates the assembly of oxidative phosphorylation complexes, thereby functioning as a nutrient sensor for mitochondrial respiration.

Eukaryotic cells have two types of endogenous FAS, termed type I and type II. Type I FAS occurs in the cytosol via the enzyme FASN and uses acetyl-CoA and malonyl-CoA to synthesize long-chain fatty acids for phospholipids, triglycerides, and the like. A lesser-studied type II FAS occurs in mitochondria (mtFAS), which generates the backbone for lipoic acid, a lipid-based prosthetic group required by several mitochondrial enzymes. Recent investigations into mtFAS have revealed roles beyond generating lipoic acid, including RNA processing, synthesis of long-chain mitochondrial lipids, and mitochondrial respiration (for a recent review, see [2]). However, the mechanisms by which mtFAS controls these auxiliary processes are unknown. A new study by Van Vranken *et al.* shows that mtFAS regulates the assembly of oxidative phosphorylation complexes and may function as a nutrient sensor for mitochondrial metabolism [1].

In contrast to type I FAS, in which a single, multiactivity enzyme catalyzes a series of reactions resulting in the formation of palmitate, type II FAS comprises a group of nuclear-encoded, mitochondrial-targeted enzymes (Figure 1). This complex performs a series of reactions resulting primarily in the formation of an eight-carbon lipid called octanoate [3]. One of the key enzymes in this complex is the acyl-carrier protein (ACP). Studies of ACP found that it contains a 'coenzyme A-like' 4′-phosphopantetheine (4′-PP) prosthetic group bound in its active site, which is a key step in shuttling the elongating acyl-chain between enzymes in the mtFAS complex [4]. mtFAS deficiency has been linked to decreased mitochondrial translation and RNA processing [5]. Furthermore, mtFAS has been linked to mitochondrial biogenesis, with increased mtFAS resulting in large mitochondria and decreased mtFAS resulting in small mitochondria [5]. Despite this progress, the mechanisms that link these non-canonical functions of mtFAS to important mitochondrial processes were unknown.

Van Vranken *et al.* began their studies on ACP with the curious observation that it is essential for cell viability in yeast, but lipoic acid production is not. These findings suggested essential roles for ACP in mitochondrial function beyond lipoic acid production [6]. The authors discovered that 4′-PP-bound ACP (holo-ACP) stabilizes proteins involved in iron-sulfur (FeS) cluster biogenesis. Without holo-ACP to act as scaffold protein for FeS-forming complexes, FeS-dependent proteins were unable to interact; these results indicated that ACP is essential for FeS biogenesis. They also found that, in ACP-knockdown yeast, complex II and complex III were destabilized, consistent with the idea that these proteins lacked FeS clusters. This first study suggested that acylated, 4′-PP-bound ACP (or acyl-ACP) was important for this regulation; however, the authors were unable to directly show that acylation was necessary for these interactions. These findings begged the question whether acyl-ACP is important outside of lipoic acid synthesis.

Several protein structure-based observations indicated that acyl-ACP binds to proteins containing Leu-Tyr-Arg (LYR) motifs. This information, combined with their previous work on ACP and FeS biogenesis, led Van Vranken *et al.* to investigate the function of the interaction between ACP and LYR proteins. They found that acyl-ACP displayed enhanced binding to LYR proteins compared with holo-ACP, and that this interaction was important for LYR target incorporation during electron transport chain (ETC) assembly (Figure 1). Subsequently, they showed that acyl-ACP is sensitive to mitochondrial acetyl-CoA levels. Integrating these findings, Van Vranken *et al.* described a new model in which cells sense mitochondrial acetyl-CoA levels via mtFAS-mediated synthesis of acyl-ACP. They proposed that, in a state of low acetyl-CoA, cells decrease acyl-ACP production and ETC assembly, thereby decreasing overall oxidative capacity. Conversely, when acetyl-CoA is high, cells increase acyl-ACP, and activate or stabilize ETC assembly, resulting in increased oxidative capacity (Figure 1). In this way, mitochondrial respiration can be tuned to the nutrient status of the system by the ability of mtFAS to continuously sample acetyl-CoA to generate acyl-lipids.

This provocative model raises several exciting possible mechanisms by which this sensing could occur: (i) acyl-ACP could fluctuate with global mitochondrial acetyl-CoA levels. Changes in nutrient status, such as physiological swings from feeding to fasting, are associated with myriad coordinated metabolic shifts to repress anabolic processes and activate catabolic processes. Whether mitochondrial acetyl-CoA levels change with the concordant metabolic condition is not known. Directly measuring subcellular organellar changes in metabolites under various metabolic conditions has only recently been made possible [7], and will facilitate these studies; (ii) acyl-ACP could sense discrete pools of acetyl-CoA. The physiological conditions under which an organism or cells are presented with

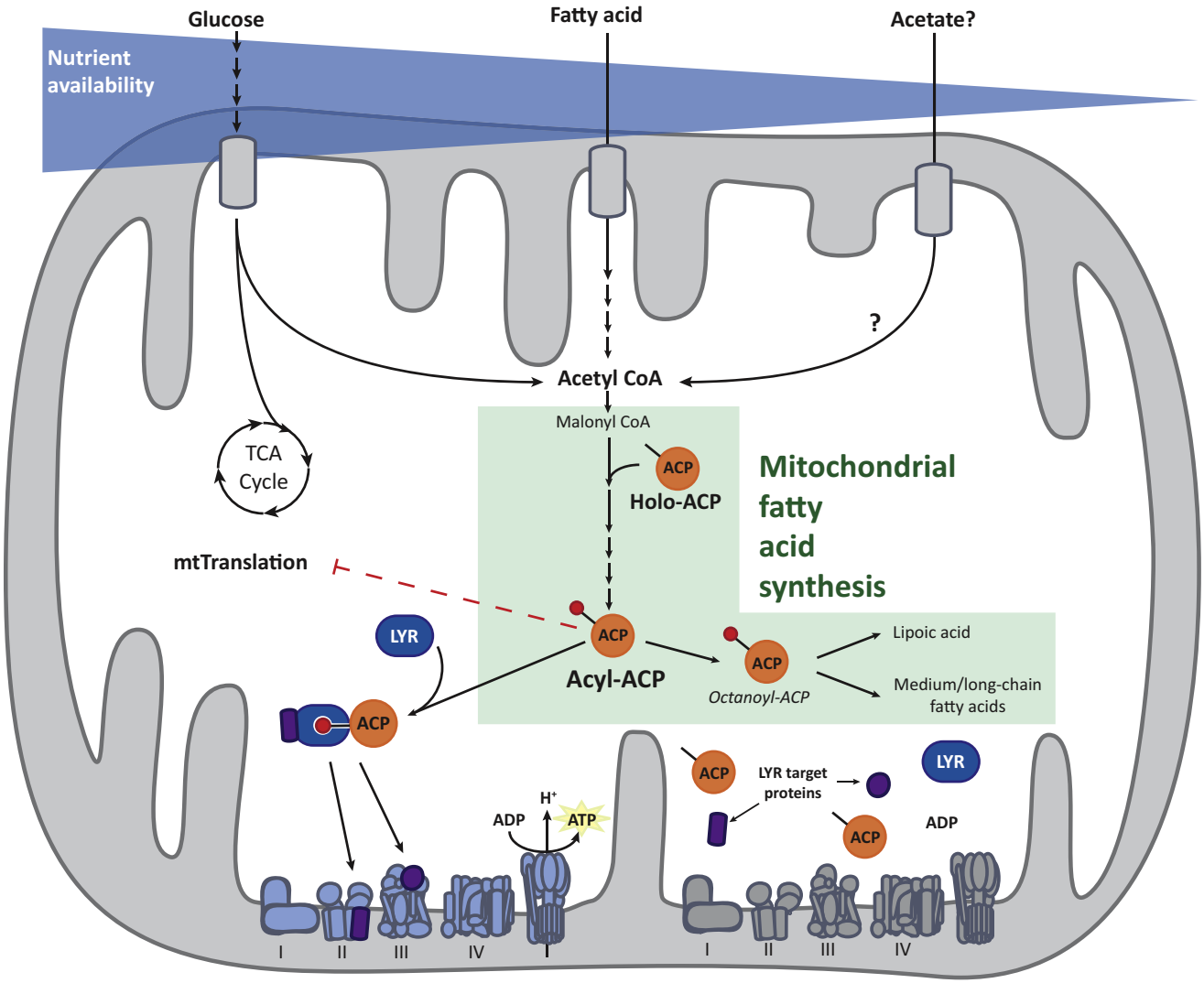

Figure 1. Acyl-Carrier Protein (ACP) Senses Acetyl-CoA and Tunes Mitochondrial Respiration Accordingly. The primary product of mitochondrial fatty acid synthesis (mtFAS; highlighted in green) is lipoic acid, an important cofactor for many mitochondrial proteins. However, new data from Van Vranken *et al.* show that mtFAS also functions as a nutrient sensor of mitochondrial acetyl-CoA levels via acylation of acyl carrier protein (ACP; orange). When acetyl-CoA levels are high, acyl-ACP is produced and interacts with Leu-Tyr-Arg (LYR)-motif-containing proteins (dark blue), which promotes assembly of LYR target proteins (purple) into electron transport chain (ETC) complexes, and ultimately supports mitochondrial respiration (bottom left). When acetyl-CoA levels are low, acyl-ACP is not produced and LYR targets are not efficiently incorporated into oxidative phosphorylation complexes, ultimately decreasing mitochondrial oxidative capacity (bottom right). It is possible that this nutrient-sensing pathway responds to specific mitochondrial acetyl-CoA sources and/or levels, such as glucose, fatty acids, or acetate, to tune mitochondrial respiration rates to nutrient availability. Abbreviation: holo-ACP, 4′-phosphopantetheine-bound ACP.

glucose versus fatty acids versus acetate vary greatly, from nutrient replete to nutrient deplete conditions. Thus, acyl-ACP could have specificity based on the carbon source of acetyl-CoA. Isotope tracing could be used to determine whether acyl-ACP functions as a specific or global sensor of mitochondrial acetyl-CoA; (iii) specific acyl-ACP moieties could have different signaling roles. The exact chemical nature of the carbon length for ACP acylation and subsequent LYR binding and complex stabilization is not known and could be important for downstream physiological regulation; (iv) acyl-ACP could be modified by other metabolites. Multiple acyl-CoA species exist in the mitochondria, including negatively

charged acyl-CoAs such as succinyl-CoA. Given that blocking acylation of ACP reduces FAS activity [8], determining whether other acyl-CoA species can acylate ACP, and the consequence of such acylation, will be important. Future studies interrogating the chemical composition, number of carbons, and possible acyl modifications will be important to better understand how acyl-ACP changes in response to nutrient conditions, subsequent effects on metabolism, and integration into this new nutrient-sensing model.

Despite the outstanding questions surrounding the mechanisms by which acyl-ACP integrates cellular nutrient status, the overall model that biosynthetic enzymes have auxiliary roles is an emergent theme in cellular nutrient sensing. For example, cytosolic FAS is canonically a producer of palmitate for energy storage; however, recent studies discovered that FAS has a role in cellular signaling. Different subcellular pools of FASN control discrete cellular processes, such as generating lipids for energy storage, synthesizing lipids to activate the nuclear receptor PPARα, to make palmitate for protein palmitoylation, and influencing growth signaling through lipid raft formation [9]. Similar to the model purposed by Van Vranken *et al.*, all these functions require particular energy states in the cell, predominantly reflected by acetyl-CoA, malonyl-CoA, and NADPH levels.

In conclusion, the findings of Van Vranken *et al.* provide a mechanistic explanation for the longstanding observation that mtFAS and ACP have key roles in mitochondrial dynamics and respiration. Furthermore, the authors proposed a new model of metabolite sensing in mitochondria in which acyl-ACP acts as a fuel sensor for respiration. Further work on this exciting new model will lead to deeper understanding of the integration and coordination of nutrient sensing and cellular homeostasis.

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