Coenzyme A levels influence protein acetylation, CoAlation and 4'-phosphopantetheinylation

Yu, Yi; Moretti, Isabele Fattori; Grzeschik, Nicola A; Sibon, Ody C M; Schepers, Hein

Published in:
Biochimica et Biophysica Acta - Molecular Cell Research

DOI:
10.1016/j.bbamcr.2021.118965

Publication date:
2021

BBA - Molecular Cell Research 1868 (2021) 118965

Contents lists available at ScienceDirect

BBA - Molecular Cell Research

journal homepage: www.elsevier.com/locate/bbamcr

Minireview

Coenzyme A levels influence protein acetylation, CoAlation and 4′-phosphopantetheinylation: Expanding the impact of a metabolic nexus molecule

Yi Yu [a], Isabele Fattori Moretti [a,b], Nicola A. Grzeschik [a], Ody C.M. Sibon [a], Hein Schepers [a,*]

[a] Department of Biomedical Sciences of Cells and Systems, University Medical Center Groningen, University of Groningen, 9713 AV, the Netherlands
[b] Laboratory of Molecular and Cellular Biology (LIM15), Department of Neurology, Faculdade de Medicina FMUSP, Universidade de Sao Paulo, Sao Paulo, Brazil

A B S T R A C T

Coenzyme A (CoA) is a key molecule in cellular metabolism including the tricarboxylic acid cycle, fatty acid synthesis, amino acid synthesis and lipid metabolism. Moreover, CoA is required for biological processes like protein post-translational modifications (PTMs) including acylation. CoA levels affect the amount of histone acetylation and thereby modulate gene expression. A direct influence of CoA levels on other PTMs, like CoAlation and 4′-phosphopantetheinylation has been relatively less addressed and will be discussed here. Increased CoA levels are associated with increased CoAlation, whereas decreased 4′-phosphopantetheinylation is observed under circumstances of decreased CoA levels. We discuss how these two PTMs can positively or negatively influence target proteins depending on CoA levels. This review highlights the impact of CoA levels on post-translational modifications, their counteractive interplay and the far-reaching consequences thereof.

1. Introduction

Coenzyme A (CoA) is essential for numerous metabolic reactions in eukaryotic and prokaryotic cells. CoA is involved in approximately 9% of all metabolic pathways including the tricarboxylic acid cycle, fatty acid regulation, amino acid synthesis and lipid metabolism [1,2]. In eukaryotes, the *de novo* biosynthesis of CoA occurs *via* five consecutive enzymatic steps starting with the substrate vitamin B5 (pantothenic acid/pantothenate). The five enzymatic steps are carried out by pantothenate kinase (PANK), phosphopantothenoylcysteine synthetase (PPCS), phosphopantothenoylcysteine decarboxylase (PPCDC), phosphopantetheine adenylyltransferase (PPAT) and dephospho-CoA kinase (DPCK) respectively (Fig. 1) [1]. In various organisms, including *Drosophila melanogaster*, mice and humans, PPAT and DPCK enzymatic activities are performed by a single bifunctional protein, CoA synthase (COASY) [3]. It was demonstrated that PANK is a rate limiting enzyme in the CoA biosynthesis pathway [4,5]. In eukaryotic cells, the canonical CoA biosynthesis pathway starts with the uptake of extracellular vitamin B5 *via* the sodium dependent multivitamin transporter [6]. In addition to this route, in *Drosophila melanogaster* S2 cells, the CoA precursor 4′-phosphopantetheine can be taken up by the cells as well and converted into CoA [7]. It remains to be investigated whether this also occurs in mammalian cells. Indications that this may occur came from a recent publication, demonstrating that metabolic defects induced by the absence of PANK2 in the mouse brain are restored by orally administered 4′-phosphopantetheine, but not by pantetheine or vitamin B5 [8]. Although the mechanism of cellular uptake of 4′-phosphopantetheine remains to be investigated, these publications reveal that eukaryotic cells may be able to synthesize CoA directly, following the uptake of 4′-phosphopantetheine.

The existence of alternative ways for cells to generate sufficient levels of CoA underscores the importance of CoA for cellular survival and its role in health and disease. The CoA biosynthesis pathway, compartmentalization of CoA and the essential influence of CoA and acetyl-CoA on metabolism and protein acetylation have been the focus of extensive excellent reviews [1,9–18]. What has received relatively little attention is the newly emerging understanding of the influence of CoA levels on other post-translational modifications of proteins (PTMs). This review discusses how the PTMs CoAlation and 4′-phosphopantetheinylation can be affected by enhanced or disturbed CoA *de novo* biosynthesis (Fig. 2).

2. CoA levels influence protein acetylation

PTMs refer to all covalent modifications that modify protein function. Acetylation is, in addition to phosphorylation and glycosylation, one of the most well-known forms of PTM [24]. Histones were the first acetylated proteins identified over 60 years ago [25,26] and now,

* Corresponding author.
E-mail address: h.schepers@umcg.nl (H. Schepers).

https://doi.org/10.1016/j.bbamcr.2021.118965
Received 4 October 2020; Received in revised form 31 December 2020; Accepted 11 January 2021
Available online 13 January 2021

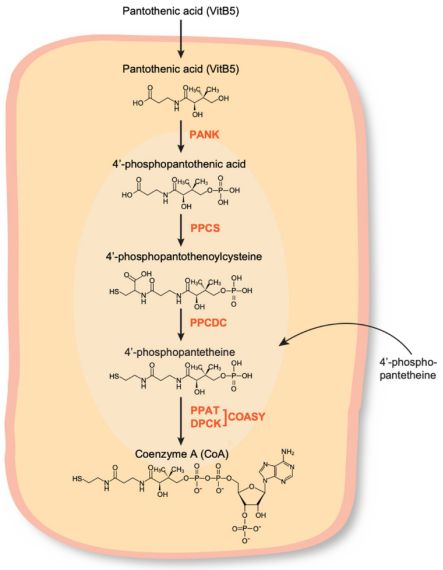

Fig. 1. CoA biosynthesis pathway. In most eukaryotic cells, *de novo* CoA biosynthesis starts by taking up extracellular pantothenic acid, which is then converted by the action of five consecutive enzymes, PANK, PPCS, PPCDC, PPAT and DPCK, forming 4′-phosphopantothenic acid, 4′-phosphopantothenoylcysteine, 4′-phosphopantetheine and CoA respectively. PPAT and DPCK enzyme activities are combined in COASY in *Drosophila melanogaster*, mice and humans. In *Drosophila melanogaster* S2 cells, 4′-phosphopantetheine can be taken up as well and converted to CoA, only requiring the last enzyme COASY.

profiling of the acetylome in numerous cell types and organisms has revealed a broad spectrum of additional proteins that undergo acetylation [27], indicating that protein acetylation-modifying factors broadly influence cellular processes. Levels of protein acetylation on a lysine residue are mediated by lysine acetylating and deacetylating enzymes. The donor source for the acetyl group is acetyl-CoA, and events that affect acetylation of CoA also affect acetylation of proteins [28]. It is therefore to be expected that levels of CoA also influence levels of protein acetylation. Consistent with this, is the demonstration in *C. elegans*, *Drosophila* S2 cells and mammalian cells that a decrease in the cellular CoA content is associated with decreased histone and tubulin acetylation [19]. Such changes are restored upon replenishing CoA in these cells. Furthermore, an association between impaired CoA homeostasis and decreased tubulin acetylation was also demonstrated in mouse liver [29] and in *Xenopus laevis* embryos, changed levels of acetyl-CoA correlate with changed levels of acetylation of many proteins including histones H3 and H2B [30].

Other lines of research show that the ratio of acetyl-CoA to CoA critically influences overall histone acetylation levels. Most lysine acetyltransferases (KATs) including GCN5, PCAF and p300/CBP, bind acetyl-CoA and CoA with similar affinity, thus the activity of KATs might be more regulated by the ratio of acetyl CoA/CoA than by the concentration of the individual compounds [31]. Consistently, upon reducing the ratio of acetyl-CoA/CoA when culturing LN229 cell nuclei *in vitro* together with defined acetyl-CoA and CoA concentrations, histone acetylation decreased, suggesting that the ratio of acetyl-CoA/CoA in the nucleus affects the levels of histone acetylation [32]. In addition, in a CoA synthase (COASY)-knockdown cell line, the acetylation levels of the majority of acetylated peptides were unchanged compare to control, in line with an unchanged ratio of acetyl-CoA/CoA, even though the individual levels of acetyl-CoA and CoA were decreased. This further underscores that the acetyl-CoA/CoA ratio may be a more relevant determinant of protein acetylation [33]. However, in the COASY knockdown cell line, a small set of hyperacetylated proteins, like CBP and TPX2, was found, leading to an increased activity and subsequently causing a prolongation of mitosis [33]. Those data indicate that decreased levels of acetyl-CoA and CoA may affect acetylation of a small set of proteins, whereas the ratio of acetyl-CoA/CoA influences overall levels of protein acetylation. Cellular compartmentalization of acetyl-CoA/CoA may help to explain the opposing observations of hyper *versus* hypo acetylation of specific proteins under CoA reducing circumstances and the consequences of decreased CoA levels *versus* those resulting from a changed ratio of acetyl-CoA to CoA. To further increase the complexity, an increase in KAT activity may lead to a local increase of free CoA and thereby the acetyl-CoA/CoA ratio and levels of protein acetylation are influenced. Taken together, these observations indicate the presence of a multifaceted impact of CoA levels on acetylation.

In addition to acetylation, forms of non-acetyl protein acylation also occur, including succinylation, butyrylation, malonylation, palmitoylation, propionylation, crotonylation and others [34–39]. Among these acylations, recent studies profiling the malonylome, succinylome and butyrylome have revealed the protein landscape influenced by these PTMs [40–42]. The corresponding acyl-CoAs are the likely source of these modifications, further underscoring the influence of CoA levels on cellular processes. Consistently, palmitoylation of the Transferrin receptor is reduced in fibroblasts from patients carrying mutations in *PANK2*, one of the rate-limiting enzymes in the *de novo* biosynthesis pathway of CoA. Adding a surplus of CoA to the culture medium restores the level of Transferrin receptor palmitoylation in these cells [43], suggesting a direct link between CoA availability and palmitoylation. Though various types of CoA acylation (succinyl-CoA, butyryl-CoA, *etc.*) can form PTMs, different CoA-acylation forms have various abilities to impact the efficiency of making such PTMs. KATs can catalyze propionylation and butyrylation of histones, but experiments indicate that KATs catalyze the transfer of acetyl groups more efficiently than propionyl and butyryl groups, suggesting that histone acetylation might occur more rapidly than propionylation and butyrylation [31]. However, malonyl-CoA and succinyl-CoA were observed to cause acylation of BSA more easily than acetyl-CoA [44,45]. UV spectroscopy analysis further confirmed that a malonyl thioester was cleaved much faster than its acetyl analogue [44]. Apart from such enzyme-mediated protein acylation, nonenzymatic protein acylation can also happen due to the interaction of acyl-CoA thioesters with nucleophilic cysteine and lysine residues. This process depends on the local acyl-CoA and nucleophile concentrations, and also the chemical potential energy of acyl-CoA/CoA couples that drive slower nonenzymatic side reactions [46]. These PTMs, which may be related to CoA/acylated-CoA levels, show various cellular functions (Supplementary Table 1). Additional evidence for a link between decreased levels of CoA and altered levels of these PTMs and cellular functional changes remain to be investigated. Altogether, it is likely that levels of CoA influence the protein acylation landscape and thereby a multitude of cellular processes.

3. CoA levels influence protein CoAlation

A recently identified PTM form that is directly influenced by CoA levels is CoAlation [21,23,47–50]. CoA contains a thiol group that can interact with other thiol groups to form a disulphide or mixed disulphide, such as CoA-cysteine and CoA-glutathione. Protein CoAlation was demonstrated by using a CoA-specific antibody to immunoprecipitate, purify and identify CoAlated proteins with mass spectrometry [51].

With this approach over 500 CoAlated proteins have been identified under various cellular conditions, including proteins involved in metabolism, protein synthesis, muscle development and stress responses [21,48,49]. CoAlation is a reversible PTM that is induced by fasting and oxidative stress [49]. Under *PANK1*β (CoA *de novo* biosynthesis enzyme) overexpressing conditions, the level of CoAlation increased compared to the parental HEK293 cells, suggesting that levels of CoAlation correlate with levels of CoA [49]. Moreover, *in vitro* pre-incubation of CoA with recombinant protein Aurora A showed Aurora A CoAlation, and subsequent microinjection of CoA in mouse oocytes caused abnormal spindle formation and chromosome misalignment [23]. Since Aurora A is a key enzyme involved in mitosis, these data suggest that high levels of CoA might cause Aurora A CoAlation, which could subsequently impair mitosis. In addition, CoAlation was found to preferentially target metabolic enzymes under oxidative stress conditions, including CK (creatine kinase), GAPDH (glyceraldehyde 3-phosphate dehydrogenase), IDH2 (isocitrate dehydrogenase) and PDK2 (pyruvate dehydrogenase kinase), decreasing their activities [49]. It remains to be determined whether the level of CoAlation is decreased under conditions of decreased CoA.

Interestingly, CoAlation seems to be related to stress. In exponentially growing cells, protein CoAlation is present at a low level, but CoAlation levels can be dramatically induced under oxidative or metabolic stress. When the conditions of oxidative stress were decreased, CoAlation disappeared, which suggests that protein CoAlation is an antioxidant defense [23,49,52]. When HEK293/*PANK1*β cells were under glucose and pyruvate deprivation conditions, the basal level of protein CoAlation was increased, which is consistent with the observation of induction of protein CoAlation in rat liver cells after fasting. The induction of protein CoAlation under metabolic stress can be relieved by recovering physiological metabolic conditions [49]. In summary, protein CoAlation is a newly identified and potentially influential post-translational modification. It affects various cellular processes including protection from overoxidation, regulatory interactions between CoA and target proteins, modulation of activity of metabolic enzymes including CK, GAPDH, IDH2 and PDK2, subcellular localization of

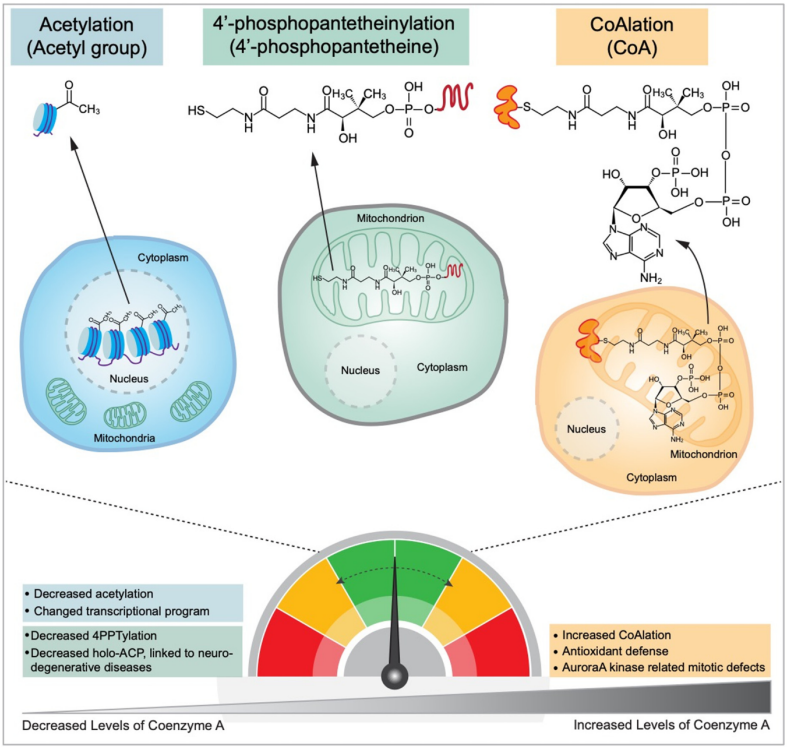

Fig. 2. CoA level-related protein post-translational modifications. Decreased levels of CoA reduce protein acetylation, especially histone acetylation, resulting in changes of transcriptional programs [14,19]. The covalent attachment of 4′-phosphopantetheine to specific serine residues in specific proteins, such as acyl carrier proteins (ACPs), is called 4′-phosphopantetheinylation. In *Drosophila*, impaired *de novo* CoA biosynthesis result in the reduction of the availability of 4′-phosphopantetheine moieties, which leads to a decrease of 4′-phosphopantetheinylation of ACPs (holo-ACPs). Decreased holo-mitochondrial ACP explains similarities of four genetically distinct CoA-linked neurodegenerative diseases [20]. In contrast, increased levels of CoA boost the covalent binding of the CoA thiol group with cysteine in proteins, forming protein CoAlation, which improves cellular antioxidant defense and leads to decreased activity of CoAlated enzymes [21–23].

CoAlated proteins and changes in conformation of proteins [21]. Since CoAlation has mainly been detected under oxidative or metabolic stress conditions, it will be important to investigate CoAlation under normal physiological conditions as well. Another intriguing question is what the (long-term) consequences are for cells and organisms when CoAlation is disturbed.

4. CoA levels influence 4′-phosphopantetheinylation of mtACP

Protein 4′-phosphopantetheinylation (hereafter referred to as 4PPTylation) is also a type of post-translational modification, directly linked to CoA levels, that affects cellular functions. 4′-Phosphopantetheine is a precursor and moiety of CoA (Fig. 1). Despite the discovery of 4PPTylation over 50 years ago, currently, only a few proteins [53], including 10-formyltetrahydrofolate dehydrogenase, nonribosomal peptide synthase, polyketide synthase [54,55], cytosolic fatty acid synthase and mitochondrial acyl carrier protein (mtACP) [56] have been shown to be 4PPTylated. The 4PPTylome has not been studied and most likely more proteins remain to be identified. The influence of 4PPTylation therefore remains largely unknown. Among the known 4PPTylated proteins, acyl carrier protein (ACP) has been widely investigated. Acyl carrier protein (ACP) was first found as a protein involved in mitochondrial fatty acid synthesis [57]. ACP was later identified as an essential subunit in many enzymes or protein complexes and it plays a key role in mitochondrial functions including lipoic acid metabolism, RNA processing, mito-ribosome function, assembly of respiratory chain complexes and iron-sulphur cluster biosynthesis [58]. A 4′-phosphopantetheine group is covalently attached to a conserved serine site in ACP and thus forms active 4PPTylated mtACP (also referred to as holo-mtACP) [59,60]. Holo-ACP synthetase catalyzes the transfer of 4′-phosphopantetheine from CoA (note: free 4′-phosphopantetheine cannot serve as a direct source for 4PPTylation) to apo-ACP in *E. coli* according to the following reaction [61,62]:

$$\text{CoA} + \text{apo-ACP} \xrightarrow{Mg^{++}} \text{holo-ACP} + 3',5'\text{-adenosine diphosphate}$$

Since 4PPTylation of apo-ACP requires CoA, CoA levels may influence protein 4′-phosphopantetheinylation. Indeed, the turnover of the 4′-phosphopantetheine prosthetic group is dependent on the concentration of CoA in *E. coli*, and the highest rate of turnover was found at the lowest CoA concentration [63]. More recent research also indicated that 4PPTylation levels of mtACP (holo-ACP) are related to CoA levels in *Drosophila melanogaster*. When *Drosophila* S2 cells were treated with HoPan (an inhibitor of CoA biosynthesis), CoA levels decreased [7] and this resulted in reduced levels of holo-mtACP. Holo-mtACP levels recovered when S2 cells were supplemented with CoA [20].

New insights in four neurodegenerative diseases arose recently from the finding that 4PPTylation of mACP is influenced by CoA levels in *Drosophila* cells. Key to these insights is the knowledge that holo-mtACP is required for lipoylation of and thereby activation of PDH. Indeed, disrupted CoA metabolism led to decreased levels of holo-mtACP, decreased levels of lipoylated PDH-E2 and decreased PDH-E2 enzyme activity in *Drosophila* S2 cells [20]. This CoA-mtACP-PDH pathway now links the four neurodegenerative diseases: PKAN, CoPAN, MePAN and PDH-E2 deficiency [20]. PKAN and CoPAN are neurodegenerative diseases caused by mutations in two genes of the CoA biosynthesis pathway. Pantothenate kinase-associated neurodegeneration (PKAN) is caused by mutations in the *PANK2* gene, and CoA synthase protein-associated neurodegeneration (COPAN) is caused by mutations in the *COASY* gene. MePAN, also a neurodegenerative disorder, is caused by mutations in the gene encoding mitochondrial enoyl-[acyl-carrier-protein] reductase (*MECR*) [64]. The substrate of MECR is trans-2-enoyl-*holo*-mtACP. MECR is required for the formation acyl-*holo*-mtACP and finally for the formation of lipoic acid. Lipoylation of PDH-E2 is indeed altered in MePAN patients [64]. Finally, PDH-E2-deficiency is a disease associated with mutations causing impairment of the pyruvate dehydrogenase complex, PDH-E2. PKAN, CoPAN, MePAN and PDH-E2-deficiency patients show overlapping clinical and neuroradiographic features, including abnormalities in the globus pallidus [20,64–67]. The CoA-mtACP-PDH axis in which 4PPTylation plays a central role, as demonstrated by Lambrechts et al. in S2 cells, together with the similar phenotypes of the diseases, suggest that the common element in these four diseases is an impairment of PDH activity. In a CoA metabolism-deficient (*Pank2* knock-out) mouse model, abnormalities in the globus pallidus region (GP) were observed together with a decreased activity of PDH and complex I [8]. However, levels of 4PPTylated mtACP (holo-mtACP) were not investigated.

Interestingly, the disruption of CoA metabolism by PANK2 depletion in mammalian HEK293 and SH-SY5Y cells also caused a reduction of holo-mtACP [20]. However, total CoA levels in HEK293 and SH-SY5Y cells transfected with *PANK2 RNAi* constructs were not changed, which is in contrast with the findings in S2 cells. These contradictory findings may be due to the variability in distribution of CoA in different subcellular compartments. It is possible that in mitochondria, where human *PANK2* is located in the intermembrane space [68], local CoA and holo-mtACP are decreased. Such local compartmental changes could influence 4PPTylation more than absolute levels of total cellular CoA [20]. CoA and acetyl-CoA are found within the mitochondria, cytosol, nucleus, peroxisomes and ER [69–71]. Total intracellular CoA levels fluctuate in response to metabolic changes [9,10], but the accuracy of measuring metabolites in individual subcellular fractions hampers conclusive interpretations. Because of technical issues regarding purity, efficiency, reproducibility, variability and recovery of different subcellular extractions, one should be careful to directly compare measurements of CoA/Acetyl-CoA between compartments [72]. It is also possible that acetyl-CoA and CoA levels differ between cellular locations that are not limited by a membrane. No techniques currently exist able to measure *in situ*, local concentrations of acetyl-CoA and CoA. Only after these technical limitations have been solved, an accurate determination of sub-compartmentalization of CoA/acetyl-CoA levels can occur. Subsequently, this information will help to better understand the flow of CoA and acetyl-CoA and how they affect several downstream processes in various tissues.

Taken together, disruption of CoA metabolism causes the reduction of 4PPTylated mitochondrial acyl carrier protein (holo-mtACP), and result in abnormal phenotypes in both *Drosophila* and mouse models of PKAN. These observations highlight the influence of CoA levels on 4PPTylation of mtACP and its importance in cellular metabolism in health and disease. However, whether the findings in *Drosophila*, possessing one pantothenate kinase gene, can also be translated to higher eukaryotes including humans, possessing four pantothenate kinase genes, remain to be investigated. In addition, a causative link between CoA levels and 4PPTylation in eukaryotes other than *Drosophila* also remains to be experimentally proven.

5. Future perspectives

In this review, we discuss how changes in CoA levels influence three different types of post-translational modifications including protein acetylation, CoAlation and 4′-phosphopantetheinylation, all with broad consequences for cellular physiology and underscoring the importance of CoA homeostasis. CoA is recognized as a nexus molecule in intermediary metabolism, serving as a central regulator linking these reactions to more global regulation of cell function. Yet many unanswered questions remain as we gain understanding of a new level of interdependencies and complexities of CoA-influenced processes. Of special interest is the example of the effect of CoA levels on PDH-E2 activity. As explained here, decreased CoA levels are, *via* decreased 4PPTylation, associated with decreased lipoylation of PDH-E2 and thereby decreased activity of PDH-E2. In contrast, an increase in CoA is associated with increased CoAlation of PDK causing decreased activity. PDK is an inhibitor of PDH-E2; thus an increase in CoA levels lead to an increase in

PDH-E2 activity. Ultimately, the activity of PDH-E2 can be positively influenced by increased CoA levels *via* increased CoAlation and negatively by decreased CoA levels *via* decreased 4PPTylation. It will be of interest to identify other enzymes with activities that can be positively and negatively influenced by CoA levels and to determine if CoA-dependent post translational modifications are involved. For a deeper understanding of the complexity it will be essential to be able to determine subcellular levels of CoA and specific post-translational modifications. How we accomplish this will be a challenge for the future.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbamcr.2021.118965.

CRediT authorship contribution statement

Yi Yu: Writing, Reviewing and Editing**; Isabele Fattori Moretti**: Writing, Reviewing; **Nicola A. Grzeschik**: Writing, Reviewing, Visualization; **Ody C.M. Sibon**: Writing, Reviewing and Editing, Supervision; **Hein Schepers**: Writing, Reviewing and Editing, Supervision.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Dr. Sibon is a co-inventor on 3 patent applications: (EP 2 868 662 A1, P-201400452, 1933-P48EP/15). Dr. Sibon serves as non-compensated executive for two not-for-profit organizations: the Stichting Lepelaar and the Spoonbill foundation.

Acknowledgements

We thank Susan Hayflick for critical reading of the manuscript. This work was supported by two NWO grants (ALWOP.252 and ALWOP.550) and a China Scholarship Council PhD fellowship (CSC No. 201606040182).

References

[1] R. Leonardi, Y.M. Zhang, C.O. Rock, S. Jackowski, Coenzyme A: back in action, Prog. Lipid Res. 44 (2–3) (2005) 125–153.
[2] E. Strauss, 7.11 - Coenzyme A biosynthesis and enzymology, in: H.-W. Liu, L. Mander (Eds.), Comprehensive Natural Products II, Elsevier, Oxford, 2010, pp. 351–410.
[3] I. Di Meo, M. Carecchio, V. Tiranti, Inborn errors of coenzyme A metabolism and neurodegeneration, J. Inherit. Metab. Dis. 42 (1) (2019) 49–56.
[4] S. Jackowski, C.O. Rock, Regulation of coenzyme A biosynthesis, J. Bacteriol. 148 (3) (1981) 926–932.
[5] J.D. Robishaw, D. Berkich, J.R. Neely, Rate-limiting step and control of coenzyme A synthesis in cardiac muscle, J. Biol. Chem. 257 (18) (1982) 10967–10972.
[6] M. Quick, L. Shi, The sodium/multivitamin transporter: a multipotent system with therapeutic implications, Vitam. Horm. 98 (2015) 63–100.
[7] B. Srinivasan, M. Baratashvili, M. van der Zwaag, B. Kanon, C. Colombelli, R. A. Lambrechts, O. Schaap, E.A. Nollen, A. Podgorsek, G. Kosec, H. Petkovic, S. Hayflick, V. Tiranti, D.J. Reijngoud, N.A. Grzeschik, O.C. Sibon, Extracellular 4′-phosphopantetheine is a source for intracellular coenzyme A synthesis, Nat. Chem. Biol. 11 (10) (2015) 784–792.
[8] S.Y. Jeong, P. Hogarth, A. Placzek, A.M. Gregory, R. Fox, D. Zhen, J. Hamada, M. van der Zwaag, R. Lambrechts, H. Jin, A. Nilsen, J. Cobb, T. Pham, N. Gray, M. Ralle, M. Duffy, L. Schwanemann, P. Rai, A. Freed, K. Wakeman, R.L. Woltjer, O.C. Sibon, S.J. Hayflick, 4′-Phosphopantetheine corrects CoA, iron, and dopamine metabolic defects in mammalian models of PKAN, EMBO Mol Med 11 (12) (2019), e10489.
[9] P. Naquet, E.W. Kerr, S.D. Vickers, R. Leonardi, Regulation of coenzyme A levels by degradation: the 'Ins and Outs', Prog. Lipid Res. 78 (2020) 101028.
[10] S. Jackowski, R. Leonardi, Deregulated coenzyme A, loss of metabolic f lexibility and diabetes, Biochem. Soc. Trans. 42 (4) (2014) 1118–1122.
[11] B. Srinivasan, O.C. Sibon, Coenzyme A, more than 'just' a metabolic cofactor, Biochem. Soc. Trans. 42 (4) (2014) 1075–1079.
[12] O.C. Sibon, E. Strauss, Coenzyme A: to make it or uptake it? Nat Rev Mol Cell Biol 17 (10) (2016) 605–606.
[13] L. Shi, B.P. Tu, Acetyl-CoA and the regulation of metabolism: mechanisms and consequences, Curr. Opin. Cell Biol. 33 (2015) 125–131.
[14] F. Pietrocola, L. Galluzzi, J.M. Bravo-San Pedro, F. Madeo, G. Kroemer, Acetyl coenzyme A: a central metabolite and second messenger, Cell Metab. 21 (6) (2015) 805–821.
[15] X. Su, K.E. Wellen, J.D. Rabinowitz, Metabolic control of methylation and acetylation, Curr. Opin. Chem. Biol. 30 (2016) 52–60.
[16] A. Ronowska, A. Szutowicz, H. Bielarczyk, S. Gul-Hinc, J. Klimaszewska-Łata, A. Dyś, M. Zyśk, A. Jankowska-Kulawy, The regulatory effects of acetyl-CoA distribution in the healthy and diseased brain, Front. Cell. Neurosci. 12 (2018) 169.
[17] M.A. Farrugia, L. Puglielli, Nε-lysine acetylation in the endoplasmic reticulum - a novel cellular mechanism that regulates proteostasis and autophagy, J. Cell Sci. 131 (22) (2018).
[18] S. Trefely, C.D. Lovell, N.W. Snyder, K.E. Wellen, Compartmentalised acyl-CoA metabolism and roles in chromatin regulation, Molecular metabolism 38 (2020) 100941.
[19] K. Siudeja, B. Srinivasan, L. Xu, A. Rana, J. de Jong, E.A. Nollen, S. Jackowski, L. Sanford, S. Hayflick, O.C. Sibon, Impaired Coenzyme A metabolism affects histone and tubulin acetylation in Drosophila and human cell models of pantothenate kinase associated neurodegeneration, EMBO Mol Med 3 (12) (2011) 755–766.
[20] R.A. Lambrechts, H. Schepers, Y. Yu, M. van der Zwaag, K.J. Autio, M.A. Vieira-Lara, B.M. Bakker, M.A. Tijssen, S.J. Hayflick, N.A. Grzeschik, O.C. Sibon, CoA-dependent activation of mitochondrial acyl carrier protein links four neurodegenerative diseases, EMBO Mol Med (2019) e10488.
[21] I. Gout, Coenzyme A, protein CoAlation and redox regulation in mammalian cells, Biochem. Soc. Trans. 46 (3) (2018) 721–728.
[22] I. Gout, Coenzyme A: a protective thiol in bacterial antioxidant defence, Biochem. Soc. Trans. 47 (1) (2019) 469–476.
[23] Y. Tsuchiya, D.P. Byrne, S.G. Burgess, J. Bormann, J. Bakovic, Y. Huang, A. Zhyvoloup, B.Y.K. Yu, S. Peak-Chew, T. Tran, F. Bellany, A.B. Tabor, A.E. Chan, L. Guruprasad, O. Garifulin, V. Filonenko, M. Vonderach, S. Ferries, C.E. Eyers, J. Carroll, M. Skehel, R. Bayliss, P.A. Eyers, I. Gout, Covalent Aurora A regulation by the metabolic integrator coenzyme A, Redox Biol. 28 (2020) 101318.
[24] G.A. Khoury, R.C. Baliban, C.A. Floudas, Proteome-wide post-translational modification statistics: frequency analysis and curation of the swiss-prot database, Sci Rep 1, 2011.
[25] D.M. Phillips, The presence of acetyl groups of histones, Biochem. J. 87 (1963) 258–263.
[26] R. Allfrey Vg Fau - Faulkner, A.E. Faulkner R Fau - Mirsky, A.E. Mirsky, Acetylation and methylation of histones and their possible role in the regulation of RNA synthesis, (0027–8424 (Print)) (1964).
[27] M.J. Rardin, J.C. Newman, J.M. Held, M.P. Cusack, D.J. Sorensen, B. Li, B. Schilling, S.D. Mooney, C.R. Kahn, E. Verdin, B.W. Gibson, Label-free quantitative proteomics of the lysine acetylome in mitochondria identifies substrates of SIRT3 in metabolic pathways, Proc. Natl. Acad. Sci. U. S. A. 110 (16) (2013) 6601–6606.
[28] C. Choudhary, B.T. Weinert, Y. Nishida, E. Verdin, M. Mann, The growing landscape of lysine acetylation links metabolism and cell signalling, Nat Rev Mol Cell Biol 15 (8) (2014) 536–550.
[29] I. Di Meo, C. Colombelli, B. Srinivasan, M. de Villiers, J. Hamada, S.Y. Jeong, R. Fox, R.L. Woltjer, P.G. Tepper, L.L. Lahaye, E. Rizzetto, C.H. Harris, T. de Boer, M. van der Zwaag, B. Jenko, A. Cusak, J. Pahor, G. Kosec, N.A. Grzeschik, S. J. Hayflick, V. Tiranti, O.C.M. Sibon, Acetyl-4′-phosphopantetheine is stable in serum and prevents phenotypes induced by pantothenate kinase deficiency, Sci. Rep. 7 (1) (2017) 11260.
[30] Y. Tsuchiya, U. Pham, W. Hu, S. Ohnuma, I. Gout, Changes in acetyl CoA levels during the early embryonic development of Xenopus laevis, PLoS One 9 (5) (2014), e97693.
[31] B.N. Albaugh, K.M. Arnold, J.M. Denu, KAT(ching) metabolism by the tail: insight into the links between lysine acetyltransferases and metabolism, Chembiochem 12 (2) (2011) 290–298.
[32] J.V. Lee, A. Carrer, S. Shah, N.W. Snyder, S. Wei, S. Venneti, A.J. Worth, Z.F. Yuan, H.W. Lim, S. Liu, E. Jackson, N.M. Aiello, N.B. Haas, T.R. Rebbeck, A. Judkins, K. J. Won, L.A. Chodosh, B.A. Garcia, B.Z. Stanger, M.D. Feldman, I.A. Blair, K. E. Wellen, Akt-dependent metabolic reprogramming regulates tumor cell histone acetylation, Cell Metab. 20 (2) (2014) 306–319.
[33] C.C. Lin, M. Kitagawa, X. Tang, M.H. Hou, J. Wu, D.C. Qu, V. Srinivas, X. Liu, J. W. Thompson, B. Mathey-Prevot, T.P. Yao, S.H. Lee, J.T. Chi, CoA synthase regulates mitotic fidelity via CBP-mediated acetylation, Nat. Commun. 9 (1) (2018) 1039.
[34] G.R. Wagner, R.M. Payne, Widespread and enzyme-independent Nepsilon-acetylation and Nepsilon-succinylation of proteins in the chemical conditions of the mitochondrial matrix, J. Biol. Chem. 288 (40) (2013) 29036–29045.
[35] C. Peng, Z. Lu, Z. Xie, Z. Cheng, Y. Chen, M. Tan, H. Luo, Y. Zhang, W. He, K. Yang, B.M. Zwaans, D. Tishkoff, L. Ho, D. Lombard, T.C. He, J. Dai, E. Verdin, Y. Ye, Y. Zhao, The first identification of lysine malonylation substrates and its regulatory enzyme, Mol. Cell. Proteomics 10 (12) (2011) M111–012658.
[36] Y. Chen, R. Sprung, Y. Tang, H. Ball, B. Sangras, S.C. Kim, J.R. Falck, J. Peng, W. Gu, Y. Zhao, Lysine propionylation and butyrylation are novel post-translational modifications in histones, Mol. Cell. Proteomics 6 (5) (2007) 812–819.
[37] M.D. Hirschey, Y. Zhao, Metabolic regulation by lysine malonylation, succinylation, and glutarylation, Mol Cell Proteomics 14 (9) (2015) 2308–2315.
[38] B.R. Sabari, D. Zhang, C.D. Allis, Y. Zhao, Metabolic regulation of gene expression through histone acylations, Nat Rev Mol Cell Biol 18 (2) (2017) 90–101.

[39] C.E. Barnes, D.M. English, S.M. Cowley, Acetylation & Co: an expanding repertoire of histone acylations regulates chromatin and transcription, Essays Biochem. 63 (1) (2019) 97–107.
[40] M.J. Rardin, W. He, Y. Nishida, J.C. Newman, C. Carrico, S.R. Danielson, A. Guo, P. Gut, A.K. Sahu, B. Li, R. Uppala, M. Fitch, T. Riiff, L. Zhu, J. Zhou, D. Mulhern, R. D. Stevens, O.R. Ilkayeva, C.B. Newgard, M.P. Jacobson, M. Hellerstein, E. S. Goetzman, B.W. Gibson, E. Verdin, SIRT5 regulates the mitochondrial lysine succinylome and metabolic networks, Cell Metab. 18 (6) (2013) 920–933.
[41] N. Basisty, J.G. Meyer, L. Wei, B.W. Gibson, B. Schilling, Simultaneous quantification of the acetylome and succinylome by 'one-pot' affinity enrichment, Proteomics 18 (17) (2018), e1800123.
[42] J.Y. Xu, Z. Xu, X. Liu, M. Tan, B.C. Ye, Protein acetylation and Butyrylation regulate the phenotype and metabolic shifts of the endospore-forming Clostridium acetobutylicum, Mol. Cell. Proteomics 17 (6) (2018) 1156–1169.
[43] A. Drecourt, J. Babdor, M. Dussiot, F. Petit, N. Goudin, M. Garfa-Traore, F. Habarou, C. Bole-Feysot, P. Nitschke, C. Ottolenghi, M.D. Metodiev, V. Serre, I. Desguerre, N. Boddaert, O. Hermine, A. Munnich, A. Rotig, Impaired transferrin receptor palmitoylation and recycling in neurodegeneration with brain iron accumulation, Am. J. Hum. Genet. 102 (2) (2018) 266–277.
[44] R.A. Kulkarni, A.J. Worth, T.T. Zengeya, J.H. Shrimp, J.M. Garlick, A.M. Roberts, D.C. Montgomery, C. Sourbier, B.K. Gibbs, C. Mesaros, Y.C. Tsai, S. Das, K.C. Chan, M. Zhou, T. Andresson, A.M. Weissman, W.M. Linehan, I.A. Blair, N.W. Snyder, J. L. Meier, Discovering targets of non-enzymatic acylation by thioester reactivity profiling, Cell Chem Biol 24 (2) (2017) 231–242.
[45] G.R. Wagner, D.P. Bhatt, T.M. O'Connell, J.W. Thompson, L.G. Dubois, D.S. Backos, H. Yang, G.A. Mitchell, O.R. Ilkayeva, R.D. Stevens, P.A. Grimsrud, M.D. Hirschey, A class of reactive acyl-CoA species reveals the non-enzymatic origins of protein acylation, Cell Metab 25(4) (2017) 823–837 e8.
[46] A.M. James, C.L. Smith, A.C. Smith, A.J. Robinson, K. Hoogewijs, M.P. Murphy, The causes and consequences of nonenzymatic protein acylation, Trends Biochem. Sci. 43 (11) (2018) 921–932.
[47] L. Aloum, C.A. Brimson, A. Zhyvoloup, R. Baines, J. Bakovic, V. Filonenko, C.R. L. Thompson, I. Gout, Coenzyme A and protein CoAlation levels are regulated in response to oxidative stress and during morphogenesis in Dictyostelium discoideum, Biochem. Biophys. Res. Commun. 511 (2) (2019) 294–299.
[48] Y. Tsuchiya, A. Zhyvoloup, J. Bakovic, N. Thomas, B.Y.K. Yu, S. Das, C. Orengo, C. Newell, J. Ward, G. Saladino, F. Comitani, F.L. Gervasio, O.M. Malanchuk, A. I. Khoruzhenko, V. Filonenko, S.Y. Peak-Chew, M. Skehel, I. Gout, Protein CoAlation and antioxidant function of coenzyme A in prokaryotic cells, Biochem. J. 475 (11) (2018) 1909–1937.
[49] Y. Tsuchiya, S.Y. Peak-Chew, C. Newell, S. Miller-Aidoo, S. Mangal, A. Zhyvoloup, J. Bakovic, O. Malanchuk, G.C. Pereira, V. Kotiadis, G. Szabadkai, M.R. Duchen, M. Campbell, S.R. Cuenca, A. Vidal-Puig, A.M. James, M.P. Murphy, V. Filonenko, M. Skehel, I. Gout, Protein CoAlation: a redox-regulated protein modification by coenzyme A in mammalian cells, Biochem. J. 474 (14) (2017) 2489–2508.
[50] K. Tsuji, K.S. Yoon, S. Ogo, Glyceraldehyde-3-phosphate dehydrogenase from Citrobacter sp. S-77 is post-translationally modified by CoA (protein CoAlation) under oxidative stress, FEBS Open Bio 9(1) (2019) 53–73.
[51] O.M. Malanchuk, G.G. Panasyuk, N.M. Serbin, I.T. Gout, V.V. Filonenko, Generation and characterization of monoclonal antibodies specific to Coenzyme A, Biopolymers and Cell 31 (3) (2015) 187–192.
[52] J. Bakovic, B.Y.K. Yu, D. Silva, S.P. Chew, S. Kim, S.H. Ahn, L. Palmer, L. Aloum, G. Stanzani, O. Malanchuk, M.R. Duchen, M. Singer, V. Filonenko, T.H. Lee, M. Skehel, I. Gout, A key metabolic integrator, coenzyme A, modulates the activity of peroxiredoxin 5 via covalent modification, Mol. Cell. Biochem. 461 (1–2) (2019) 91–102.
[53] J. Beld, E.C. Sonnenschein, C.R. Vickery, J.P. Noel, M.D. Burkart, The phosphopantetheinyl transferases: catalysis of a post-translational modification crucial for life, Nat. Prod. Rep. 31 (1) (2014) 61–108.
[54] K.C. Strickland, L.A. Hoeferlin, N.V. Oleinik, N.I. Krupenko, S.A. Krupenko, Acyl carrier protein-specific 4′-phosphopantetheinyl transferase activates 10-formylte-trahydrofolate dehydrogenase, J. Biol. Chem. 285 (3) (2010) 1627–1633.
[55] H. Donato, N.I. Krupenko, Y. Tsybovsky, S.A. Krupenko, 10-formyltetrahydrofolate dehydrogenase requires a 4′-phosphopantetheine prosthetic group for catalysis, J. Biol. Chem. 282 (47) (2007) 34159–34166.
[56] A.K. Joshi, L. Zhang, V.S. Rangan, S. Smith, Cloning, expression, and characterization of a human 4′-phosphopantetheinyl transferase with broad substrate specificity, J. Biol. Chem. 278 (35) (2003) 33142–33149.
[57] S. Brody, S. Mikolajczyk, Neurospora mitochondria contain an acyl-carrier protein, Eur. J. Biochem. 173 (2) (1988) 353–359.
[58] A.J. Masud, A.J. Kastaniotis, M.T. Rahman, K.J. Autio, J.K. Hiltunen, Mitochondrial acyl carrier protein (ACP) at the interface of metabolic state sensing and mitochondrial function, Biochim Biophys Acta Mol Cell Res 1866 (12) (2019) 118540.
[59] R.S. Flugel, Y. Hwangbo, R.H. Lambalot, J.E. Cronan Jr., C.T. Walsh, Holo-(acyl carrier protein) synthase and phosphopantetheinyl transfer in Escherichia coli, J. Biol. Chem. 275 (2) (2000) 959–968.
[60] M.L. Polacco, J.E. Cronan Jr., A mutant of Escherichia coli conditionally defective in the synthesis of holo-[acyl carrier protein], J. Biol. Chem. 256 (11) (1981) 5750–5754.
[61] J. Elovson, P.R. Vagelos, Acyl carrier protein, X. Acyl carrier protein synthetase, J Biol Chem 243 (13) (1968) 3603–3611.
[62] G.L. Powell, J. Elovson, P.R. Vagelos, Acyl carrier protein, XII. Synthesis and turnover of the prosthetic group of acyl carrier protein in vivo, J Biol Chem 244 (20) (1969) 5616–5624.
[63] S. Jackowski, C.O. Rock, Turnover of the 4′-phosphopantetheine prosthetic group of acyl carrier protein, J. Biol. Chem. 259 (3) (1984) 1891–1895.
[64] G. Heimer, J.M. Keratar, L.G. Riley, S. Balasubramaniam, E. Eyal, L.P. Pietikainen, J.K. Hiltunen, D. Marek-Yagel, J. Hamada, A. Gregory, C. Rogers, P. Hogarth, M.A. Nance, N. Shalva, A. Veber, M. Tzadok, A. Nissenkorn, D. Tonduti, F. Renaldo, G. University of Washington Center for Mendelian, I. Kraoua, C. Panteghini, L. Valletta, B. Garavaglia, M.J. Cowley, V. Gayevskiy, T. Roscioli, J.M. Silberstein, C. Hoffmann, A. Raas-Rothschild, V. Tiranti, Y. Anikster, J. Christodoulou, A.J. Kastaniotis, B. Ben-Zeev, S.J. Hayflick, MECR mutations cause childhood-onset dystonia and optic atrophy, a mitochondrial fatty acid synthesis disorder, Am J Hum Genet 99(6) (2016) 1229–1244.
[65] R.A. Head, R.M. Brown, Z. Zolkipli, R. Shahdadpuri, M.D. King, P.T. Clayton, G. K. Brown, Clinical and genetic spectrum of pyruvate dehydrogenase deficiency: dihydrolipoamide acetyltransferase (E2) deficiency, Ann. Neurol. 58 (2) (2005) 234–241.
[66] C.A. McWilliam, C.K. Ridout, R.M. Brown, R.C. McWilliam, J. Tolmie, G.K. Brown, Pyruvate dehydrogenase E2 deficiency: a potentially treatable cause of episodic dystonia, Eur. J. Paediatr. Neurol. 14 (4) (2010) 349–353.
[67] V. Leoni, L. Strittmatter, G. Zorzi, F. Zibordi, S. Dusi, B. Garavaglia, P. Venco, C. Caccia, A.L. Souza, A. Deik, C.B. Clish, M. Rimoldi, E. Ciusani, E. Bertini, N. Nardocci, V.K. Mootha, V. Tiranti, Metabolic consequences of mitochondrial coenzyme A deficiency in patients with PANK2 mutations, Mol. Genet. Metab. 105 (3) (2012) 463–471.
[68] A. Alfonso-Pecchio, M. Garcia, R. Leonardi, S. Jackowski, Compartmentalization of mammalian pantothenate kinases, PLoS One 7 (11) (2012), e49509.
[69] S. Sivanand, I. Viney, K.E. Wellen, Spatiotemporal control of acetyl-CoA metabolism in chromatin regulation, Trends Biochem. Sci. 43 (1) (2018) 61–74.
[70] A. Van Broekhoven, M.-C. Peeters, L.J. Debeer, G.P. Mannaerts, Subcellular distribution of coenzyme A: evidence for a separate coenzyme a pool in peroxisomes, Biochem. Biophys. Res. Commun. 100 (1) (1981) 305–312.
[71] S. Horie, M. Isobe, T. Suga, Changes in CoA pools in hepatic peroxisomes of the rat under various conditions, J. Biochem. 99 (5) (1986) 1345–1352.
[72] K.E. Wellen, N.W. Snyder, Should we consider subcellular compartmentalization of metabolites, and if so, how do we measure them? Curr Opin Clin Nutr 22 (5) (2019) 347–354.