Coenzyme A and Its Derivatives in Cellular Metabolism and Disease

A Biochemical Society Focused Meeting held at Charles Darwin House, London, U.K., 20–21 March 2014. Organized and Edited by Ivan Gout (University College London, U.K.), Suzanne Jackowski (St. Jude Children's Research Hospital, U.S.A.) and Ody Sibon (University of Groningen, The Netherlands).

Coenzyme A and its derivatives: renaissance of a textbook classic

Frederica L. Theodoulou*[1], Ody C.M. Sibon†, Suzanne Jackowski‡ and Ivan Gout§

*Biological Chemistry and Crop Protection Department, Rothamsted Research, Harpenden AL5 2JQ, U.K.

†Department of Cell Biology, University Medical Center Groningen, University of Groningen, Antonius Deusinglaan 1, 9713 AV Groningen, The Netherlands

‡Department of Infectious Diseases, St. Jude Children's Research Hospital, 262 Danny Thomas Place, Memphis, TN 38105-3678, U.S.A.

§Institute of Structural and Molecular Biology, University College London, Gower Street, London WC1E 6BT, U.K.

Abstract

In 1945, Fritz Lipmann discovered a heat-stable cofactor required for many enzyme-catalysed acetylation reactions. He later determined the structure for this acetylation coenzyme, or coenzyme A (CoA), an achievement for which he was awarded the Nobel Prize in 1953. CoA is now firmly embedded in the literature, and in students' minds, as an acyl carrier in metabolic reactions. However, recent research has revealed diverse and important roles for CoA above and beyond intermediary metabolism. As well as participating in direct post-translational regulation of metabolic pathways by protein acetylation, CoA modulates the epigenome via acetylation of histones. The organization of CoA biosynthetic enzymes into multiprotein complexes with different partners also points to close linkages between the CoA pool and multiple signalling pathways. Dysregulation of CoA biosynthesis or CoA thioester homoeostasis is associated with various human pathologies and, although the biochemistry of CoA biosynthesis is highly conserved, there are significant sequence and structural differences between microbial and human biosynthetic enzymes. Therefore the CoA biosynthetic pathway is an attractive target for drug discovery. The purpose of the Coenzyme A and Its Derivatives in Cellular Metabolism and Disease Biochemical Society Focused Meeting was to bring together researchers from around the world to discuss the most recent advances on the influence of CoA, its biosynthetic enzymes and its thioesters in cellular metabolism and diseases and to discuss challenges and opportunities for the future.

CoA, as remembered from your biochemistry textbook

Anyone who took a first year undergraduate biochemistry course will (hopefully!) recall that coenzyme A (CoA) is a ubiquitous coenzyme which functions as an acyl group carrier and a carbonyl-activating group in diverse biochemical reactions [1] (Figure 1). The majority of students probably first encounter CoA in the context of energy metabolism, which is appropriate since Hans Krebs shared the 1953 Nobel Prize with Fritz Lipmann for his elucidation of the eponymous TCA (tricarboxylic acid) cycle. However, nearly 70 years on, CoA and its thioester derivatives are conservatively estimated to participate in approximately 4% of cellular reactions in *Escherichia coli*, and are similarly ubiquitous in eukaryotes, involving virtually every compartment of the cell [2,3]. These include the biosynthesis and degradation of lipids, many secondary metabolic pathways, and biosynthesis of amino acids, cholesterol and the neurotransmitter acetylcholine, to name

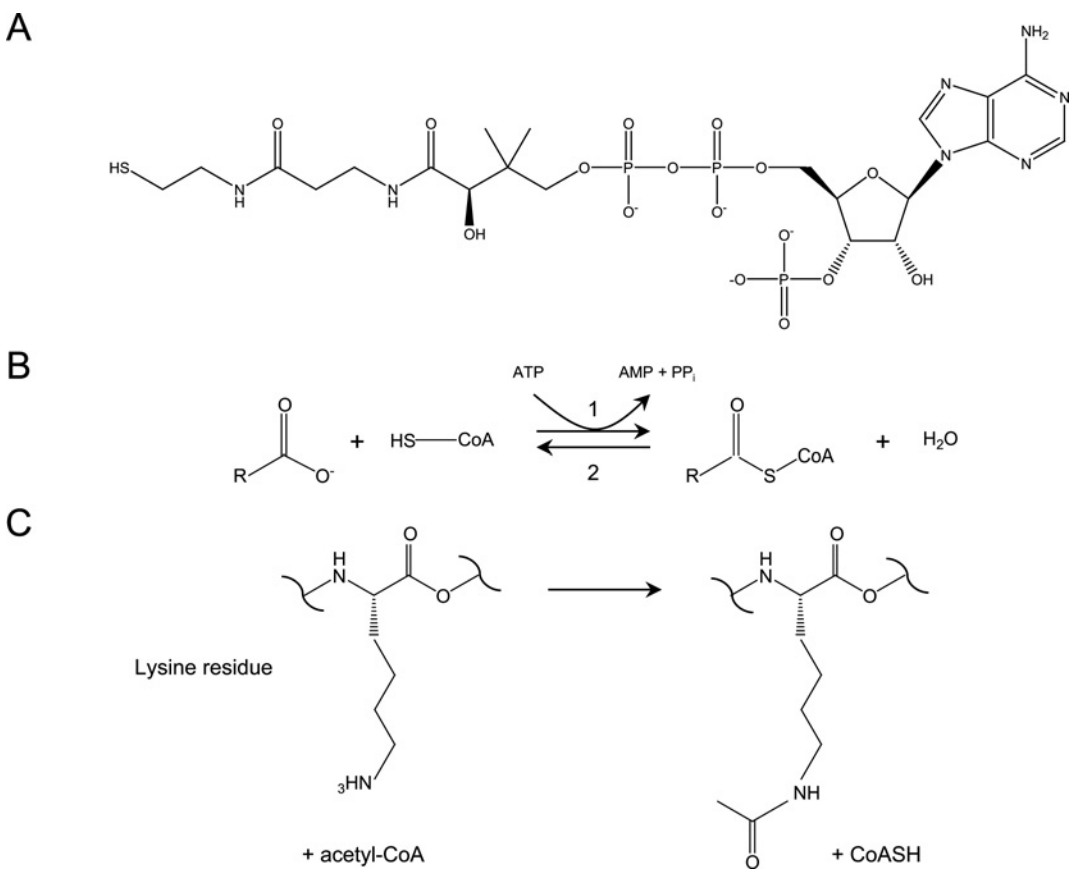
Key words: anti-metabolite, coenzyme A (CoA) , neurodegeneration, pantothenate, protein acetylation, vanin.

Abbreviations: CoASY, CoA synthase; DPCK, dephospho-CoA kinase; *fbl*, *fumble*; mTOR, mammalian target of rapamycin; NBIA, neurodegeneration with brain iron accumulation; PanK, pantothenate kinase; PKAN, pantothenate kinase-associated neurodegeneration; PPAT, phosphopantetheine adenylyltransferase; PPCD, phosphopanthenoylcysteine decarboxylase; PPCS, phosphopantothenoylcysteine synthase; SAGA, Spt/Ada/Gcn5/acetyltransferase; SIRT, sirtuin; S6K, S6 kinase; TCA, tricarboxylic acid.

[1]**To whom correspondence should be addressed (email freddie.theodoulou@rothamsted.ac.uk).**

Figure 1 | **Fundamental reactions involving CoA**

(**A**) Structure of Coenzyme A. (**B**) Formation of thioesters (acyl-CoAs). Acyl groups (R-) are linked to CoA by the action of acyl-activating enzymes (**1**, also known as acyl-CoA synthetases) and the reverse reaction (**2**) is catalysed by thioesterases. (**C**) Protein acetylation. The acetyl moiety is transferred from acetyl-CoA to the ε-amino groups of lysine residues in a polypeptide chain. The reaction is catalysed by acetyltransferases, but can also occur non-enzymatically. Deacetylation is catalysed by deacetylases such as SIRTs. Proteins can also be acetylated at the N-terminus (not shown). This reaction, which occurs co-translationally, is catalysed by N^{α}-terminal acetyltransferases (NATs) and influences protein stability and function.



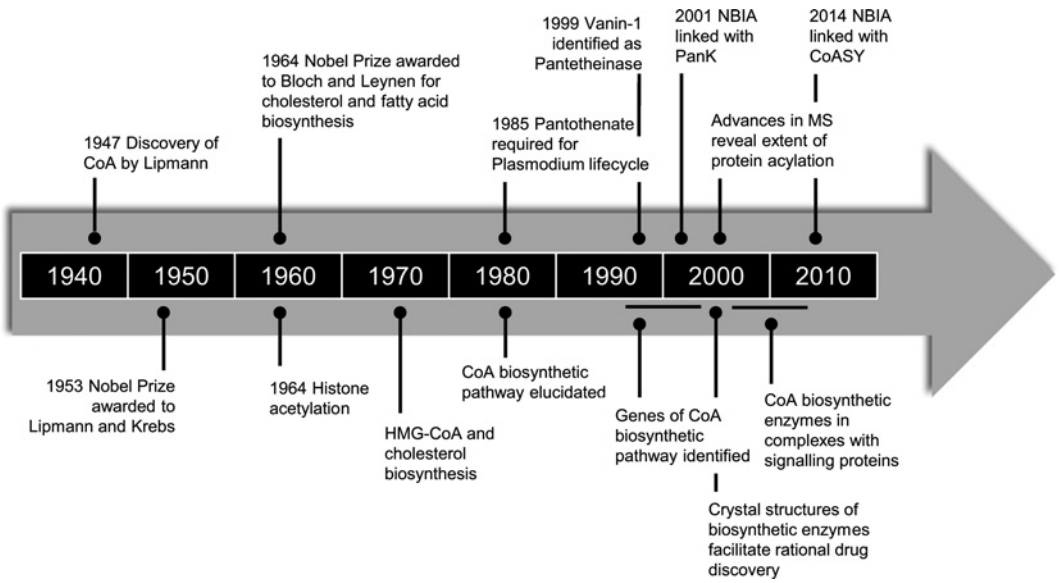
but a few. There is an extensive literature documenting roles of CoA and its derivatives in cellular metabolism. However, over the last 20 years, the significance of CoA as a key regulator has gradually emerged beyond its acknowledged 'textbook' role in metabolic pathways.

A number of disparate, but intriguing, discoveries have contributed to the resurgence of interest in CoA, some of which are highlighted in Figure 2. An important factor underpinning the renaissance of CoA research has been the elucidation of the biosynthetic pathway and identification of corresponding genes. This has opened the way to understanding novel biochemical and physiological roles, not only through genetic manipulation in cellular and whole-organism models including knockout mice, *Drosophila* mutants, *Arabidopsis* T-DNA (transferred DNA) insertion lines and *Schizosaccharomyces pombe* mutants [4–8], but also via selective chemical intervention [9,10]. The purpose of the Coenzyme A and its Derivatives in Cellular Metabolism and Disease Biochemical Society Focused Meeting was to bring together researchers with distinct backgrounds and expertise, working on organisms from different kingdoms, but with a common interest in CoA. Key goals were to advance collective understanding of the regulatory roles of CoA and to stimulate ideas for future biomedical applications, combining the experience and insights of well-established researchers with fresh perspectives from those new to the field.

Theme and variations in CoA biosynthesis

CoA is synthesized from pantothenate (vitamin B_5) in a five-step pathway [3,11]. Plants, fungi and bacteria synthesize pantothenate by a largely conserved route, but animals obtain vitamin B_5 from the diet and their gut flora [12,13]. The biochemical route from pantothenate to CoA is highly conserved across kingdoms, but the enzymatic activities are encoded in different permutations and combinations of proteins (Figure 3) and with multiple isoforms in some organisms. Regulation of the pathway potentially

Figure 2 | **Timeline showing key discoveries and events in CoA research**
HMG-CoA, 3-hydroxy-3-methylglutaryl-CoA.



occurs at several levels: expression of the genes encoding biosynthetic enzymes, regulation of enzyme activity (including post-translational modification), compartmentation, degradation, and interconversion between CoA and its thioester derivatives. Some of these mechanisms have been studied intensively, whereas others, such as transport, remain relatively underexplored. Suzanne Jackowski opened the meeting with a discussion of the physiological roles of pantothenate kinases (PanKs) which catalyse the first and rate-limiting step of CoA biosynthesis [14]. There are three classes of PanK: types I and III are restricted to bacteria, whereas type II is predominantly found in eukaryotes. With the exception of the bacterial type II and III enzymes, PanK activity is regulated by feedback inhibition by CoA or CoA thioesterases. In mammals, three genes encode four distinct PanK isoforms, which respond differentially to these allosteric regulators, potentially permitting them to act as metabolic sensors [14]. In this context, it is pertinent that the mammalian PanK isoforms have distinct subcellular localizations, enabling CoA homoeostasis in different subcellular compartments. Despite the distinct localization and regulatory properties of mammalian PanK enzymes, the different isoforms appear to afford some degree of functional compensation, since knockout mice which lack expression of individual *Pank* genes exhibit relatively mild phenotypes. However, double knockouts are embryo lethal (*Pank1*/*Pank3* and *Pank2*/*Pank3*) or die shortly after birth (*Pank1*/*Pank2*) [14], illustrating the fundamental importance of CoA.

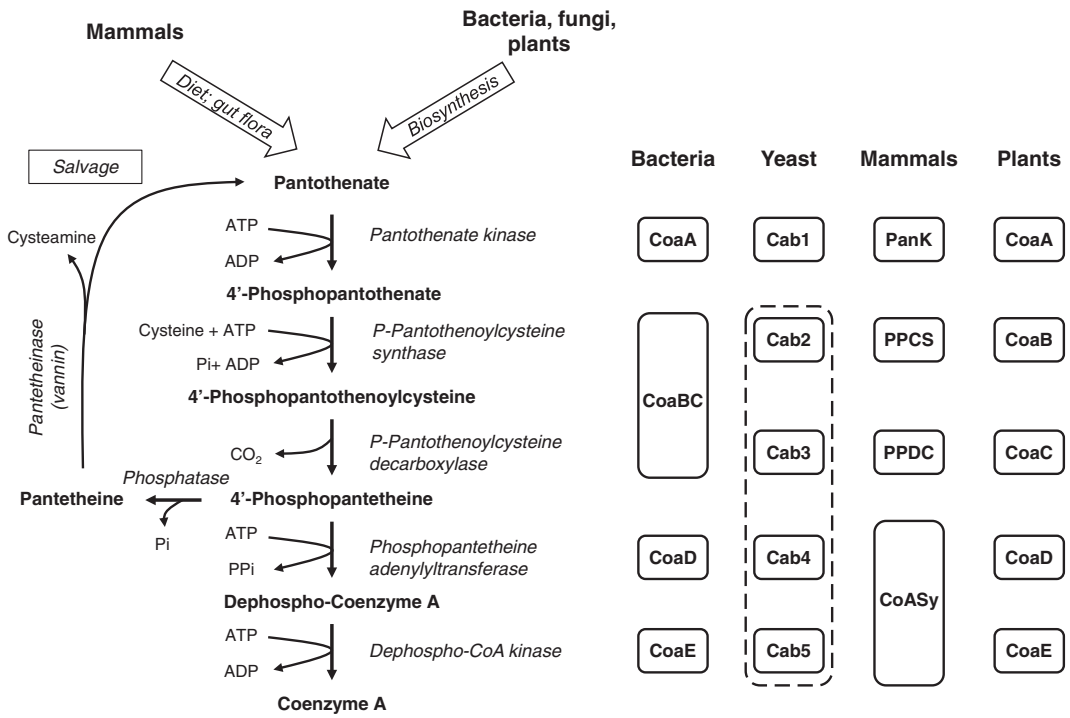
The themes of subcellular localization and regulation of CoA biosynthesis were explored further by Ivan Gout, who discussed the controversial subcellular localization of CoASY (CoA synthase) and presented evidence for the existence of a mammalian CoA biosynthetic complex [11]. This is currently the subject of intensive research owing to the possibility of interactions with key signalling proteins, such as S6K (S6 kinase) and mTOR (mammalian target of rapamycin) [15]. A multifunctional CoA biosynthetic complex exists in yeast, with the Cab3 subunit of PPCD (phosphopanthenoylcysteine decarboxylase) acting as a scaffold for a CoA-synthesizing protein complex (CoA-SPC), which intersects with signalling pathways involved in salinity tolerance and cell cycle progression [16,17].

CoAs as versatile signals in metabolism and beyond

Using cardiac energy metabolism as an exemplar, Gary Lopaschuk demonstrated how CoA and its metabolites have the capacity to regulate metabolic pathways at several different levels: as substrates and products of these pathways, as allosteric regulators and via post-translational regulation by protein acetylation [18]. CoA and acetyl-CoA are important allosteric modulators of fatty acid and glucose oxidation in the heart and the CoA derivative malonyl-CoA is also a key regulator of fatty acid uptake and oxidation by mitochondria. In recent years, however, much attention has focused on the control of energy metabolic pathways by protein acetylation. Lysine acetylation was originally identified some 50 years ago as a histone modification [19], focusing attention on the regulation of gene expression, and it is only relatively recently with improvements in protein mass spectrometry that the pervasive extent and importance of acetylation of metabolic proteins has become apparent [20,21]. In human liver, virtually every enzyme involved in glycolysis, fatty acid metabolism and the TCA and urea cycles is acetylated [20] and acetylation of

Figure 3 | Biosynthesis and degradation of CoA

The left-hand panel shows the biosynthetic pathway from pantothenate to CoA, which is common to all organisms. In animals, pantetheinases belonging to the vanin family hydrolyse pantetheine to yield cysteamine and pantothenate which can be salvaged for further CoA synthesis. The right-hand panel depicts how the enzymes of CoA biosynthesis are encoded in different kingdoms, and shows the different nomenclature for the genes. Note that, in several cases, there is more than one isoform, for example PanK in mammals and plants. The broken-line box indicates the existence of a multiprotein CoA biosynthetic complex in yeast.



β-oxidation enzymes appears to be particularly important in the heart [18]. This provides a mechanism by which changes in acetylation status can alter enzymatic activity in response to fluctuations in metabolic demand. This has implications for anti-cancer therapies, since metabolic reprogramming has long been recognized as a hallmark of cancer cells, the so-called 'Warburg effect' describing the preferential use of glycolysis to produce lactate and metabolic intermediates under normal oxygen tensions. In this context, recent knowledge of acetylation of metabolic enzymes in tumorigenesis has opened the door to novel potential therapies [22].

Continuing the theme of regulatory protein acetylation, Benjamin Tu demonstrated how protein function is modulated in concert with acetyl-CoA availability and the metabolic state of the cell in baker's yeast (*Saccharomyces cerevisiae*) [23]. Yeast cells become highly synchronized during continuous growth under nutrient-limited conditions, and the cell population cycles between growth and quiescent phases. Acetyl-CoA levels oscillate as a function of the growth and metabolic state of these cells, falling as cells enter the quiescent phase and rising sharply upon entry into the growth phase. Stable isotope labelling demonstrated that components of the transcriptional coactivator complex SAGA (Spt/Ada/Gcn5/acetyltransferase) are acetylated precisely upon the rise in acetyl-CoA, co-ordinating with entry into the growth phase. The increase in acetyl-CoA causes SAGA-mediated acetylation of histones which activate a distinctive set of genes important for cell growth. Although this study implicated the Gcn5p acetyltransferase of the SAGA complex, it is not clear whether all protein acetylation events are enzyme-catalysed and, indeed, it has been suggested that non-enzymatic protein acetylation might be driven by acetyl-CoA accumulation under certain conditions. The extent to which different pools of acetyl-CoA control protein acetylation in different subcellular compartments is an interesting question which remains to be investigated in detail. Another important regulatory consideration is deacetylation. Protein acetylation is reversed by the action of histone deacetylases, including the SIRTs (sirtuins). An increasing body of evidence supports a role for SIRTs in metabolic disorders including diabetes and heart pathologies, and suggests that manipulation of CoA regulation of metabolism could be a promising therapeutic approach [18].

In addition to global regulation by protein acetylation, there is a sketchy, but tantalizing, literature suggesting other signalling functions for CoA and CoA thioesters

(reviewed in [24]). CoA has been implicated in CaMKII (Ca^{2+}/calmodulin-dependent protein kinase II) activation [25], CoASY has been proposed to interact with the PI3K (phosphoinositide 3-kinase)/mTOR/S6K signalling cascade [15,26] and there is evidence that acetyl-CoA levels are influential in autophagy [27]. These examples merit further investigation, as do the regulatory possibilities afforded by multiprotein complexes containing CoA biosynthetic enzymes [11,24].

The elusive link between neurodegenerative disease and CoA biosynthesis

One of the factors contributing to a renewed interest in CoA was the unexpected discovery that a subgroup of disorders known as NBIA (neurodegeneration with brain iron accumulation) is caused by mutations in *PANK2* [28]. Three presentations, from Ody Sibon, Susan Hayflick and Valeria Tiranti, explored different aspects of the link between CoA metabolism and NBIA. Susan Hayflick discussed the pathology of PKAN (pantothenate kinase-associated neurodegeneration) in detail [29]. Following the identification of *PANK2* as the causative gene, the known phenotypic spectrum has broadened as up to 50% of NBIA patients have been confirmed as PKAN cases. Although the mechanistic link between CoA biosynthesis and neurodegeneration is obscure in PKAN, specific areas of the brain are known to be affected, i.e. the globus pallidus and substantia nigra, functionally related regions with high metabolic demand which are vulnerable to oxidative stress resulting from mitochondrial dysfunction or extrinsic factors. However, neither the mechanism of iron accumulation in specific cell types of the brain nor its relationship to impaired CoA biosynthesis is understood.

Animal models have been studied in an attempt to unravel the mechanistic links between CoA biosynthesis and the pathology of PKAN. Ody Sibon discussed insights from a *Drosophila* model, *fumble* (*fbl*), first described in the year that the genetic basis for PKAN was uncovered [8,30]. *fbl* fruitflies, which carry mutations in the *Drosophila* orthologue of *PANK* (*dPANK*/*fbl*), exhibit male sterility, neurodegeneration and impaired locomotor abilities, but brain iron accumulation has never been demonstrated. Similarly, Valeria Tiranti outlined ways in which the mouse PKAN model does not mirror precisely the human pathology and discussed the importance of analysing subcellular CoA pools [31]. These findings have led some authors to question the causal link between CoA and neurodegeneration; however, provision of pantethine (the disulfide dimer of pantetheine) partially rescues the *Drosophila dPANK*/*fbl* mutant phenotypes, restoring the decreased CoA levels [8,32] and also relieves clinical symptoms in *Pank2*$^{-/-}$ mice fed on a ketogenic diet [33]. Moreover, the discovery in 2014 of a distinct form of NBIA, known as CoPAN (CoASY protein-associated neurodegeneration), in which the final steps of CoA biosynthesis are impaired, added strong support for an important role of CoA in neurodegenerative disease [34]. In agreement with this, *Drosophila* carrying mutations in the CoA biosynthetic enzymes PPCS (phosphopantothenoylcysteine synthase) and PPAT (phosphopantetheine adenylyltransferase)–DPCK (dephospho-CoA kinase) are phenotypically similar to *fbl* fruitflies [8]. Both PanK2 and CoASY are associated with mitochondria in humans and an important question is whether NBIA is specifically associated with a disruption in the mitochondrial CoA pool. Despite the outstanding mechanistic questions in NBIA, there are hopeful prospects for PKAN therapy in the form of synthetic compounds which bypass the enzymatic blocks in CoA biosynthesis.

CoA degradation

CoA degradation is much less well characterized than CoA biosynthesis, but is clearly an important factor in CoA homoeostasis [3]. Several Nudix hydrolase enzymes which cleave CoA and oxidatively damaged CoA have been ascribed to different subcellular compartments, including peroxisomes and mitochondria [35], but attention has also focused on pantetheinases as regulators of CoA levels. Pantetheine is produced from the CoA biosynthetic intermediate 4′-phosphopantetheine by phosphatase action or from cleavage of orally administered pantethine. Philippe Naquet [36] described the role of extracellular pantetheinases belonging to the vanin protein family. These enzymes hydrolyse D-pantetheine to yield pantothenate which may be reused for CoA biosynthesis (salvage pathway; see Figure 3) and cysteamine which is a precursor for taurine and hypotaurine and also interacts with glutathione metabolism. Vanin-knockout mice have revealed important physiological functions for pantetheinases, including roles in inflammation and stress responses. *Vnn1* mice are resistant to intestinal inflammation and oxidative stress, and vanins have consequently become an important target for chemical intervention (see below). Vanin-1 is also a target for PPARα (peroxisome-proliferator-activated receptor α), suggesting a link to energy metabolism [10].

CoA biosynthesis as a target for chemical intervention: prospects for novel therapeutics

For many years, the CoA biosynthetic pathway has been recognized as a potential drug target. Three presentations addressed this topic: Kevin Saliba explored the potential for developing anti-malarial compounds targeting CoA biosynthesis in *Plasmodium* species [37], Joost Schalkwijk discussed chemical biology tools for vanin inhibition [10], and Erik Strauss outlined the structural and mechanistic differences between bacterial and human CoA biosynthetic enzymes which identify specific proteins as targets for anti-microbial drug discovery [9].

In addition to catalysing the rate-limiting step of CoA biosynthesis, PanK isoforms display significant diversity between kingdoms and have consequently received the most attention in the search for enzyme inhibitors [9]. High-throughput structure-guided screens have identified selective and potent *in vitro* inhibitors of the *Mycobacterium tuberculosis* type I PanK (*Mt*PanK$_1$). Unfortunately, these compounds proved ineffective *in vivo*, since steady-state CoA levels greatly exceed those required for cell survival and, although other bacterial PanK enzymes remain valid targets for drug development, compounds which inhibit cell growth have yet to be developed. Inhibitors of PPCS and PPCD, the second and third enzymes of the pathway have also been reported, but have not yet found clinical application for a variety of reasons, including the inability to penetrate cells. The final enzyme in the CoA biosynthetic pathway, DPCK, is highly conserved between bacteria and mammals, suggesting that it is not a suitable target for chemical intervention, but the penultimate step, catalysed by a single PPAT enzyme in bacteria has been the subject of high-throughput and *in silico* screens.

An alternative approach to selective enzyme inhibition which has been pursued since the 1940s is the development of pantothenic acid derivatives (anti-Pans) that could act as CoA anti-metabolites (anti-CoAs) [9,10]. These compounds prevent incorporation of the catalytically essential thiol into the CoA structure or, alternatively, incorporate detrimental reactive moieties, in both cases leading to the formation of molecules which interfere with CoA-dependent processes. The N-substituted pantothenamides, N5-Pan (*N*-pentylpantothenamide) and N7-Pan (*N*-heptylpantothenamide) are the most potent inhibitors of bacterial growth discovered to date [9,10]. These compounds have also been investigated as anti-plasmodial agents, but are only effective when vanin pantetheinases are inactive or inhibited. High-throughput screens targeting pantetheinase activity have identified reversible, competitive, *in vitro* vanin inhibitors, and optimization of lead compounds yielded inhibitors with IC_{50} values in the nanomolar range [10]. Although the original intended application of these compounds was in skin disease, the structure–activity relationships of pantetheinases suggested that antibiotic pantothenamides could also be substrates for these enzymes and that vanin inhibitors might protect these compounds against hydrolysis. Thus vanin inhibitors have found an alternative potential use in combination therapies with CoA anti-metabolites.

Measuring and manipulating CoA

Knowledge of tissue CoA levels and the size and status of intracellular CoA pools is central to understanding and manipulating CoA and its metabolites. CoA levels are not only responsive to endogenous and exogenous stimuli, but also vary between different tissues and cell types. For example, the CoA content of mammalian tissues varies 10-fold under normal conditions, the CoA/acetyl-CoA ratio of *E. coli* can be altered 4-fold by growth in different media and acetyl-CoA levels are tightly regulated with the growth cycle in synchronized yeast cells [3,14,23]. In their article in this issue of *Biochemical Society Transactions*, Tsuchiya et al. [38] discuss methods that are commonly used to measure CoA and its derivatives in biological samples. The lability and broad range of chemical properties (ranging from polar to hydrophobic/amphipathic), together with the wide static and dynamic ranges of these compounds (millimolar levels for CoA; picomolar–nanomolar levels for very-long-chain acyl-CoA) present significant analytical challenges. A theme which recurred throughout the meeting was the need for reliable and straightforward methods to quantify CoA and its thioesters. Several methods for CoA measurement have been published, but many are laborious and time-consuming and there is no 'gold standard' method accepted by the research community. Commercially available kits have apparently not been widely adopted, in many cases because they are not sufficiently sensitive to detect CoA and acetyl-CoA at the levels found in biological material. However, robust methods have been published for the quantification of acyl-CoAs, which, although requiring specialist instrumentation, are versatile enough to permit identification of novel species, as well as quantification of species in complex mixtures [39–41].

It is important to remember that CoA is not evenly distributed between different subcellular compartments. Indeed, the compartmentalization of CoA in all eukaryotes is tightly regulated, with cytosol and organelles maintaining separate pools via dedicated transporters [3]. Although some attempts have been made to measure organellar CoA pools following subcellular fractionation, these approaches are susceptible to experimental artefacts and cannot give meaningful information about transient responses to different stimuli. In this respect, tools such as genetically encoded sensors would be of great utility, permitting real-time spatially resolved quantification of CoA and metabolites [42]. Together with manipulation of subcellular CoA pools, for example by targeted ectopic expression of enzymes and transporters, such approaches would be valuable in investigating the contribution of specific CoA pools to different functions of this coenzyme.

Conclusions and outstanding questions

Although recent years have seen exciting progress in both fundamental and applied aspects of CoA research, many questions remain. These include the detailed elucidation of the subcellular localization and regulation of CoA biosynthesis in different organisms, identification of mechanisms by which subcellular pools are maintained and dissection of their roles in diverse CoA-requiring processes. Elucidation of factors controlling protein acetylation and deacetylation are also of great interest. Technological issues to address include the development of new and appropriate cell and whole-organism models and methods to quantify different CoA species and their spatial and temporal dynamics.

Unravelling the roles of CoA and its metabolites in different types of disease is an important goal for the future, and it is possible that next-generation sequencing projects may reveal yet more examples of rare diseases linked to CoA metabolism. In conclusion, the CoA field is vibrant and well-placed to face the challenges ahead. Remarkably, this meeting was the first time that this research community has come together, but it will undoubtedly not be the last.

Acknowledgements

We thank all speakers, poster presenters, other participants and sponsors of the Coenzyme A and Its Derivatives in Cellular Metabolism and Disease Biochemical Society Focused Meeting.

Funding

Rothamsted Research receives grant-aided support from the Biotechnology and Biological Sciences Research Council of the U.K.

References

1 Baddiley, J., Thain, E.M., Novelli, G.D. and Lipmann, F. (1953) Structure of coenzyme A. Nature **171**, 76 CrossRef PubMed
2 Begley, T.P., Kinsland, C. and Strauss, E. (2001) The biosynthesis of coenzyme A in bacteria. Vitam. Horm. **61**, 157–171 CrossRef PubMed
3 Leonardi, R., Zhang, Y.M., Rock, C.O. and Jackowski, S. (2005) Coenzyme A: back in action. Prog. Lipid Res. **44**, 125–153 CrossRef PubMed
4 Rubio, S., Larson, T.R., Gonzalez-Guzman, M., Alejandro, S., Graham, I.A., Serrano, R. and Rodriguez, P.L. (2006) An *Arabidopsis* mutant impaired in coenzyme A biosynthesis is sugar dependent for seedling establishment. Plant Physiol. **140**, 830–843 CrossRef PubMed
5 Tilton, G.B., Wedemeyer, W.J., Browse, J. and Ohlrogge, J. (2006) Plant coenzyme A biosynthesis: characterization of two pantothenate kinases from *Arabidopsis*. Plant Mol. Biol. **61**, 629–42 CrossRef PubMed
6 Garcia, M., Leonardi, R., Zhang, Y.M., Rehg, J.E. and Jackowski, S. (2012) Germline deletion of pantothenate kinases 1 and 2 reveals the key roles for CoA in postnatal metabolism. PLoS ONE **7**, e40871 CrossRef PubMed
7 Nakamura, T., Pluskal, T., Nakaseko, Y. and Yanagida, M. (2012) Impaired coenzyme A synthesis in fission yeast causes defective mitosis, quiescence-exit failure, histone hypoacetylation and fragile DNA. Open Biol. **2**, 120117 CrossRef PubMed
8 Srinivasan, B. and Sibon, O.C.M. (2014) Coenzyme A, more than 'just' a metabolic cofactor. Biochem. Soc. Trans. **42**, 1075–1079
9 Moolman, W.J.A., de Villiers, M. and Strauss, E. (2015) Recent advances in targeting coenzyme A biosynthesis and utilization for antimicrobial drug development. Biochem. Soc. Trans. **42**, 1080–1086
10 Schalkwijk, J. and Jansen, P. (2014) Chemical biology tools to study pantetheinases of the vanin family. Biochem. Soc. Trans. **42**, 1052–1055
11 Lopez Martinez, D., Tsuchiya, Y. and Gout, I. (2014) Coenzyme A biosynthetic machinery in mammalian cells. Biochem. Soc. Trans. **42**, 1112–1117
12 Coxon, K.M., Chakauya, E., Ottenhof, H.H., Whitney, H.M., Blundell, T.L., Abell, C. and Smith, A.G. (2005) Pantothenate biosynthesis in higher plants. Biochem. Soc. Trans. **33**, 743–746 CrossRef PubMed
13 Webb, M.E. and Smith, A.G. (2011) Pantothenate biosynthesis in higher plants. Adv. Bot. Res. **58**, 204–255
14 Dansie, L.E., Reeves, S., Miller, K., Zano, S.P., Frank, M., Pate, C., Wang, J. and Jackowski, S. (2014) Physiological roles of pantothenate kinases. Biochem. Soc. Trans. **42**, 1033–1036
15 Nemazanyy, I., Panasyuk, G., Zhyvoloup, A., Panayotou, G., Gout, I.T. and Filonenko, V. (2004) Specific interaction between S6K1 and CoA synthase: a potential link between the mTOR/S6K pathway, CoA biosynthesis and energy metabolism. FEBS. Lett. **578**, 357–362 CrossRef PubMed
16 Ruiz, A., González, A., Muñoz, I., Serrano, R., Abrie, J.A., Strauss, E. and Ariño, J. (2009) Moonlighting proteins Hal3 and Vhs3 form a heteromeric PPCDC with Ykl088w in yeast CoA biosynthesis. Nat. Chem. Biol. **5**, 920–928 CrossRef PubMed
17 Olzhausen, J., Moritz, T., Neetz, T. and Schüller, H.-J. (2013) Molecular characterization of the heteromeric coenzyme A-synthesizing protein complex (CoASPC) in the yeast *Saccharomyces cerevisiae*. FEMS Yeast Res. **13**, 565–573 CrossRef PubMed
18 Abo Alrob, O. and Lopaschuk, G.D. (2014) Role of CoA and acetyl-CoA in regulating cardiac fatty acid and glucose oxidation. Biochem. Soc. Trans. **42**, 1043–1051
19 Allfrey, V.G., Faulkner, R. and Mirsky, A.E. (1964) Acetylation and methylation of histones and their possible role in the regulation of RNA synthesis. Proc. Natl. Acad. Sci. U.S.A. **51**, 786–794 CrossRef PubMed
20 Wang, Q., Zhang, Y., Yang, C., Xiong, H., Lin, Y., Yao, J., Li, H., Xie, L., Zhao, W., Yao, Y. et al. (2010) Acetylation of metabolic enzymes coordinates carbon source utilization and metabolic flux. Science **327**, 1004–1007 CrossRef PubMed
21 Zhao, S., Xu, W., Jiang, W., Yu, W., Lin, Y., Zhang, T., Yao, J., Zhou, L., Zeng, Y., Li, H. et al. (2010) Regulation of cellular metabolism by protein lysine acetylation. Science **327**, 1000–1004 CrossRef PubMed
22 Lin, R., Zhou, X., Huang, W., Zhao, D., Lv, L., Xiong, Y., Guan, K.L. and Lei, Q.Y. (2014) Acetylation control of cancer cell metabolism. Curr. Pharm. Des. **20**, 2627–2633 CrossRef PubMed
23 Shi, L. and Tu, B.P. (2014) Protein acetylation as a means to regulate protein function in tune with metabolic state. Biochem. Soc. Trans. **42**, 1037–1042
24 Davaapil, H., Tsuchiya, Y. and Gout, I. (2014) Signalling functions of coenzyme A and its derivatives in mammalian cells. Biochem. Soc. Trans. **42**, 1056–1062
25 McCoy, F., Darbandi, R., Lee, H.C., Bharatham, K., Moldoveanu, T., Royappa, G., Dodd, K., Lin, W., Chen, S.I., Tangallapally, R. et al. (2013) Metabolic activation of CaMKII by coenzyme A. Mol. Cell **52**, 325–339 CrossRef PubMed
26 Breus, O., Panasyuk, G., Gout, I.T., Filonenko, V. and Nemazanyy, I. (2009) CoA synthase is in complex with p85αPI3K and affects PI3K signaling pathway. Biochem. Biophys. Res. Commun. **385**, 581–585 CrossRef PubMed
27 Mariño, G., Pietrocola, F., Eisenberg, T., Kong, Y., Malik, S.A., Andryushkova, A., Schroeder, S., Pendl, T., Harger, A., Niso-Santano, M. et al. (2014) Regulation of autophagy by cytosolic acetyl-coenzyme A. Mol. Cell **53**, 710–725 CrossRef PubMed
28 Zhou, B., Westaway, S.K., Levinson, B., Johnson, M.A., Gitschier, J. and Hayflick, S.J. (2001) A novel pantothenate kinase gene (*PANK2*) is defective in Hallervorden–Spatz syndrome. Nat. Genet. **28**, 345–349 CrossRef PubMed
29 Hayflick, S.J. (2014) Defective pantothenate metabolism and neurodegeneration. Biochem. Soc. Trans. **42**, 1063–1068
30 Afshar, K., Gonczy, P., DiNardo, S. and Wasserman, S.A. (2001) *fumble* encodes a pantothenate kinase homolog required for proper mitosis and meiosis in *Drosophila melanogaster*. Genetics **157**, 1267–1276 PubMed
31 Venco, P., Dusi, S., Valletta, L. and Tiranti, V. (2014) Alteration of the coenzyme A biosynthetic pathway in neurodegeneration with brain iron accumulation syndromes. Biochem. Soc. Trans. **42**, 1069–1074
32 Rana, A., Seinen, E., Siudeja, K., Muntendam, R., Srinivasan, B., van der Want, J.J., Hayflick, S., Reijngoud, D.J., Kayser, O. and Sibon, O.C. (2010) Pantethine rescues a *Drosophila* model for pantothenate kinase-associated neurodegeneration. Proc. Natl. Acad. Sci. U.S.A. **107**, 6988–6993 CrossRef PubMed
33 Brunetti, D., Dusi, S., Giordano, C., Lamperti, C., Morbin, M., Fugnanesi, V., Marchet, S., Fagiolari, G., Sibon, O., Moggio, M. et al. (2013) Pantethine treatment is effective in recovering the disease phenotype induced by ketogenic diet in a pantothenate kinase associated neurodegeneration mouse model. Brain **137**, 57–68 CrossRef PubMed
34 Dusi, S., Valletta, L., Haack, T.B., Tsuchiya, Y., Venco, P., Pasqualato, S., Goffrini, P., Tigano, M., Demchenko, N., Wieland, T. et al. (2014) Exome sequence reveals mutations in CoA synthase as a cause of neurodegeneration with brain iron accumulation. Am. J. Hum. Genet. **94**, 11–22 CrossRef PubMed
35 Hunt, M.C., Tillander, V. and Alexson, S.E. (2014) Regulation of peroxisomal lipid metabolism: the role of acyl-CoA and coenzyme A metabolizing enzymes. Biochimie **98**, 45–55 CrossRef PubMed
36 Naquet, P., Pitari, G., Duprè, S. and Galland, F. (2014) Role of the Vnn1 pantetheinase in tissue tolerance to stress. Biochem. Soc. Trans. **42**, 1094–1100

37 Saliba, K.J. and Spry, C. (2014) Exploiting the coenzyme A biosynthesis pathway for the identification of new antimalarial agents: the case for pantothenamides. Biochem. Soc. Trans. **42**, 1087–1093
38 Tsuchiya, Y., Phan, U. and Gout, I. (2014) Methods for measuring CoA and CoA derivatives in biological samples. Biochem. Soc. Trans. **42**, 1107–1111
39 Larson, T.R. and Graham, I.A. (2001) Technical advance: a novel technique for the sensitive quantification of acyl CoA esters from plant tissues. Plant J. **25**, 115–125 CrossRef PubMed
40 Haynes, C.A. (2011) Analysis of mammalian fatty acyl-coenzyme A species by mass spectrometry and tandem mass spectrometry. Biochim. Biophys. Acta **1811**, 663–668 CrossRef PubMed
41 Zadravec, D., Tvrdik, P., Guillou, H., Haslam, R., Kobayashi, T., Napier, J.A., Capecchi, M.R. and Jacobsson, A. (2011) ELOV2 controls the level of $n-6$ 28:5 and 30:5 fatty acids in testis, a prerequisite for male fertility and sperm maturation in mice. J. Lipid Res. **52**, 245–255 CrossRef PubMed
42 Okumoto, S., Jones, A. and Frommer, W.B. (2012) Quantitative imaging with fluorescent biosensors. Annu. Rev. Plant Biol. **63**, 663–706 CrossRef PubMed

Received 23 June 2014
doi:10.1042/BST20140176