

Coenzyme A: to make it or uptake it?

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Abstract | The consensus has been that intracellular coenzyme A (CoA) is obtained exclusively by *de novo* biosynthesis via a universal, conserved five-step pathway in the cell cytosol. However, old and new evidence suggest that cells (and some microorganisms) have several strategies to obtain CoA, with 4'-phosphopantetheine (P-PantSH; the fourth intermediate in the canonical CoA biosynthetic pathway) serving as a 'nexus' metabolite.

The central role of coenzyme A (CoA) (see [Supplementary information S1](#) (figure)) in energy and fatty acid metabolism has been firmly established since its discovery more than 70 years ago as the cofactor bearing 'activated acetate' (that is, an acetyl group primed for transfer, indicated by the 'A' in CoA)¹. Since then, the prominence of CoA in cell biology has expanded owing to evidence that the ratio of acetyl-CoA to CoA controls protein acetylation to influence key cellular processes, such as cell growth, regulated cell death and autophagy². The importance of CoA has stimulated new interest in the mechanisms that determine intracellular acetyl-CoA levels, specifically in the enzymes that produce and consume it and the transport systems that shuttle it across membranes within cells. However, the CoA moiety typically is not transported between intracellular compartments, an important and often overlooked point; instead, the acyl group of acyl-CoAs undergoes a hand-off that causes no change in compartmental CoA levels. Consequently, the routes by which the various intracellular CoA pools are established and maintained — and the impact that this has on the acetyl-CoA to CoA ratio — have largely been ignored.

The consensus has been that intracellular CoA is obtained exclusively by *de novo* biosynthesis via a universal, conserved five-step pathway in the cytosol of each cell, beginning with the uptake of its vitamin precursor, pantothenate (Pan; also known as vitamin B5), by transporters³ (see [Supplementary information S1](#) (figure)). The highly compartmentalized nature of CoA, which has distinct cytosolic, nuclear, mitochondrial, peroxisomal and intrareticular pools⁴, coupled with the paradigm that charged metabolites are membrane-impermeable, would therefore dictate that free CoA must be distributed to subcellular locations via dedicated transporters localized within organelle membranes. Mitochondrial and peroxisomal transporters with affinity for CoA and dephospho-CoA (dPCoA; see [Supplementary information S1](#) (figure)) have been reported^{5,6}, and acetyl-CoA transporter 1 (AT-1) has

been linked to protein acetylation in the endoplasmic reticulum⁷. However, it has not been conclusively demonstrated that these transporters translocate intact CoA or dPCoA across organelle membranes. Thus, our understanding of the mechanisms of intracellular CoA production and its distribution are incomplete.

Now, a series of recent articles demonstrate that cells (and some microorganisms) in fact have several strategies to obtain CoA. In retrospect, such evidence is present in older literature but the implications were largely overlooked in the absence of our current knowledge of the myriad roles of CoA. Here, we highlight these data to underscore that pools of this crucial co-factor can be built by important mechanisms in addition to *de novo* biosynthesis.

Evidence of an alternate route for cells to obtain CoA was presented in 2011 ([REF. 8](#)); intracellular CoA levels were shown to be reduced, and protein acetylation decreased, when the *de novo* CoA biosynthesis pathway was impaired in *Drosophila melanogaster* Schneider 2 (S2) cells. However, acetylation levels could be restored by adding CoA to the culture medium. Subsequently, it was shown that CoA from external sources (food or medium) could supply intracellular CoA pools⁹: extracellular ectonucleotide pyrophosphatases (ENPPs) cleave CoA into 3',5'-ADP and 4'-phosphopantetheine (P-PantSH), the latter of which is stable in culture medium or in the circulation of multicellular organisms (for example, *D. melanogaster* and mice) for several hours (see [Supplementary information S1](#) (figure)). Importantly, this study also provided strong evidence that P-PantSH crosses membranes in a transporter-independent manner in S2 cells⁹. Consequently, when the internal CoA biosynthetic route is blocked in its initial steps in *Caenorhabditis elegans*, *D. melanogaster* or cultured mammalian cells (including in human cells), intracellular CoA levels are replenished via the uptake of P-PantSH, followed by its conversion to CoA by the last two enzymes of the canonical CoA biosynthetic pathway (see [Supplementary information S1](#) (figure))⁹.

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Whether P-PantSH is membrane permeable in some cell types and whether dedicated P-PantSH transporters exist in some systems are open questions, although it is tempting to speculate that P-PantSH is involved in the translocation of CoA across organelle membranes. Regardless, the apparent role of P-PantSH as a 'nexus' metabolite in CoA biosynthesis, degradation and supply becomes clear when viewed in the context of other knowledge. Apart from being formed upon degradation of CoA and the acyl carrier proteins (ACPs) involved in lipid biosynthesis¹⁰, P-PantSH is also the product of the third step in *de novo* CoA biosynthesis (see [Supplementary information S1](#) (figure))³. With the exception of some bacteria, many organisms can produce P-PantSH directly by converting pantetheine (PantSH, a structurally related derivative of Pan) using the promiscuous activity of some types of pantothenate kinase (PanK), the first enzyme in the CoA biosynthetic pathway that normally produces 4'-phosphopantothenate (P-Pan)^{3,11} (see [Supplementary information S1](#) (figure)). In fact, when the CoA pathway was first elucidated, it was proposed that PantSH is formed first, followed by its phosphorylation by a 'pantetheine kinase' (REF. 3). This proposal was strongly supported by the identification of PantSH (or its oxidized — that is, its disulfide — form) as the enigmatic *Lactobacillus bulgaricus* factor (LBF) that promotes the growth of many lactic acid bacteria. In combination, these pathways can increase P-PantSH to such levels that it is excreted (but not taken up again), as was found to be the case in *Escherichia coli*¹².

The potential supply of P-PantSH by *E. coli* and other members of the gut microbiota provides an elegant explanation for the results of earlier feeding studies in higher organisms. For example, fruit fly larvae in which endogenous PanK is inactivated, and therefore unable to synthesize CoA from Pan or PantSH, still contain low levels of CoA, allowing them to survive early embryonal and larval development⁹. Furthermore, when mice are maintained on a Pan-depleted diet, severe signs of deprivation are observed only after adding antibiotics¹³. In these cases, it is possible that CoA could be obtained from the conversion of P-PantSH supplied by bacteria in the digestive system; only when this alternative route to CoA is eliminated by antibiotics do severe effects occur.

The CoA-related interplay between host and microbiota could be bidirectional; evidence for this is found in comparative genomics studies that show that some human-associated bacteria are dependent on an external source for their CoA needs. For example, the genome of *Treponema pallidum* (which causes syphilis) does not encode for a complete *de novo* CoA biosynthetic pathway, and its PanK enzyme cannot convert PantSH to P-PantSH³. In fact, a 1954 study showed that the growth of this organism is supported by the addition of P-PantSH (but not Pan, PantSH or P-Pan) to the media¹⁴. Currently, it is unclear if P-PantSH would be provided by the human host or by other closely associated microbial communities. Nonetheless, comparative genomics analyses suggest that specific members of the human microbiota (for example, *Bifidobacterium* spp.) and selected human pathogens (for example, *Gardnerella vaginalis* and some species of *Mycoplasma*) follow the same approach, whereas

Chlamydia spp. apparently obtain their CoA by scavenging dPCoA (the penultimate biosynthetic intermediate) from the host³. Most recently, the development of a synthetic *Mycoplasma* species with a minimal genome demonstrated that the *de novo* CoA biosynthetic pathway could be dispensed with altogether; it is therefore possible — at least in this model of the core functions of life — that intact CoA can be sourced directly from the environment¹⁵.

Taken together, both recent and older literature show complementary routes whereby cells and organisms can obtain and exchange CoA, with the CoA precursor P-PantSH at the nexus. The implication that these routes could make *de novo* CoA biosynthesis redundant in some cases has important implications in cell biology. In addition, it offers hope for patients who are affected by inborn errors in CoA metabolism in the form of P-PantSH-based therapies. Clearly, the details of intracellular CoA supply and exchange deserve much closer attention, and with the availability of sensitive analytic methods, this is now possible.

1. Lipmann, F., Kaplan, N. O., Novelli, G. D., Tuttle, L. C. & Guirard, B. M. Coenzyme for acetylation, a pantothenic acid derivative. *J. Biol. Chem.* **167**, 869–870 (1947).
2. Pietrocola, F., Galluzzi, L., Bravo-San Pedro, J. M., Madeo, F. & Kroemer, G. Acetyl coenzyme A: a central metabolite and second messenger. *Cell Metab.* **21**, 805–821 (2015).
3. Strauss, E. in *Comprehensive Natural Products II Chemistry and Biology* Vol. 7 (eds Mander, L. & Hung-Wen, L.) 351–410 (Elsevier, 2010).
4. Leonardi, R., Zhang, Y.-M., Rock, C. O. & Jackowski, S. Coenzyme A: back in action. *Prog. Lipid Res.* **44**, 125–153 (2005).
5. Fiermonte, G., Paradies, E., Todisco, S., Marobbio, C. M. T. & Palmieri, F. A. Novel member of solute carrier family 25 (SLC25A42) is a transporter of coenzyme A and adenosine 3',5'-diphosphate in human mitochondria. *J. Biol. Chem.* **284**, 18152–18159 (2009).
6. Agrimi, G., Russo, A., Scarcia, P. & Palmieri, F. The human gene *SLC25A17* encodes a peroxisomal transporter of coenzyme A, FAD and NAD⁺. *Biochem. J.* **443**, 241–247 (2012).
7. Jonas, M. C., Pehar, M. & Puglielli, L. AT-1 is the ER membrane acetyl-CoA transporter and is essential for cell viability. *J. Cell Sci.* **123**, 3378–3388 (2010).
8. Siudeja, K. *et al.* Impaired coenzyme A metabolism affects histone and tubulin acetylation in *Drosophila* and human cell models of pantothenate kinase associated neurodegeneration. *EMBO Mol. Med.* **3**, 755–766 (2011).
9. Srinivasan, B. *et al.* Extracellular 4'-phosphopantetheine is a source for intracellular coenzyme A synthesis. *Nat. Chem. Biol.* **11**, 784–792 (2015).
10. Jackowski, S. & Rock, C. O. Turnover of the 4'-phosphopantetheine prosthetic group of acyl-carrier protein. *J. Biol. Chem.* **259**, 1891–1895 (1984).
11. Balibar, C. J., Hollis-Symynkiewicz, M. F. & Tao, J. Pantetheine rescues phosphopantothenoylcysteine synthetase and phosphopantothenoylcysteine decarboxylase deficiency in *Escherichia coli* but not in *Pseudomonas aeruginosa*. *J. Bacteriol.* **193**, 3304–3312 (2011).
12. Jackowski, S. & Rock, C. O. Metabolism of 4'-phosphopantetheine in *Escherichia coli*. *J. Bacteriol.* **158**, 115–120 (1984).
13. Stein, E. D. & Diamond, J. M. Do dietary levels of pantothenic acid regulate its intestinal uptake in mice? *J. Nutr.* **119**, 1973–1983 (1989).
14. Steinman, H. G., Oyama, V. I. & Schulze, H. O. Carbon dioxide, cocarboxylase, citrovorum factor, and coenzyme A as essential growth factors for a saprophytic treponeme. *J. Biol. Chem.* **211**, 327–335 (1954).
15. Hutchison, C. A. *et al.* Design and synthesis of a minimal bacterial genome. *Science* **351**, aad6253 (2016).

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Competing interests statement

The authors declare no competing interests.

SUPPLEMENTARY INFORMATION

See online article: [S1](#) (table)

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