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Review Article

How are Vitamin B_{12} and *S*-Adenosylmethionine Related?

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An important biological form of Vitamin B_{12}, known as coenzyme B_{12} or 5'-deoxyadenosylcob(III)alamin (AdoCbl), features a weak covalent bond between cobalt(III) and C5' of 5'-deoxyadenosine. AdoCbl functions as a coenzyme for enzymes that catalyze isomerization reactions following a chemical pattern in which a carbon-bound hydrogen changes places with a group bonded to an adjacent carbon. Approximately a dozen such reactions are known in mammals and bacteria, but not in plants. These include methylmalonyl-coenzyme A mutase, glycol dehydratases, glutamate mutase, lysine 5,6-aminomutase and others. All of these reactions proceed by homolytic scission of the Co(III)—C5' bond in AdoCbl to form cob(II)alamin and the 5'-deoxyadenosyl-5'-yl radical, which abstracts a hydrogen atom from the substrate to form, transiently, 5'-deoxyadenosine and a substrate-based radical. The substrate radical undergoes the requisite rearrangement to the product-related radical, which is quenched by hydrogen transfer from C5' of 5'-deoxyadenosine to form the final product and regenerate AdoCbl.

For many years the AdoCbl-dependent reactions were regarded as a unique family [1]. However, in 1970 H. A. Barker and associates discovered a pyridoxal phosphate (PLP)) and *S*-adenosyl-L-methionine (AdoMet)-dependent lysine-2,3-aminomutase (LAM) in bacteria and found it to follow the chemical pattern of AdoCbl-dependent lysine 5,6-aminomutase but not to require AdoCbl [2]. In 1987 Moss and Frey found that C5' in the 5'-deoxyadenisyl group of AdoMet mediates H-transfer in exactly the same manner as the 5'-deoxyadenosyl moiety of AdoCbl in the B_{12}-dependent reactions [3].

In AdoMet, the bond linking C5'-of the 5'-deoxyaenosyl group to sulfur in methionine is strong (> 60 kcal/mol), unlike the weak Co-C5' bond in AdoCbl, (31 kcal/mol) complicating cleavage of AdoMet to the 5'-deoxyadenosyl radical. The finding of an iron-sulfide cluster in LAM in 1991-92 [4,5] offered a possible solution. LAM purified anaerobically was found to contain a [3Fe–4S] cluster and to be activated by Fe^{2+} and a reducing agent, to form $[4Fe–4S]^{1+}$. Electron transfer from the reduced cluster to AdoMet could lead to cleavage of the C5'—S bond, with transient formation of the 5'-deoxyadenosyl radical.

Electron transfer-dependent cleavage of AdoMet suggested a chemical reaction mechanism involving four radicals. Lysine bound through its 6-aminogroup as an aldimine with PLP could react with the 5'-deoxyadenosyl radical to form the PLP-lysyl-C3 radical, which would rearrange to a PLP-lysyl-C2 radical through an aza-cyclopropyl radical intermediate. Three of these four radicals have been identified as kinetically competent intermediates by rapid-mix freeze-quench electron paramagnetic spectroscopy [6].

AdoMet, formerly regarded solely as the principal biochemical methylating agent, was found to be required for four apparently unrelated enzymes in 1984-2000: pyrivate-formate lyase [7,8], biotin synthase [9], lipoyl synthase [10], and anaerobic ribonucleoside triphosphate reductase [11]. All of the reactions involved the cleavage of unreactive C–H bonds in substrates, and all of them were found in the 1990s to incorporate the [4Fe–4S] cluster.

By the turn of the century, the genes encoding the above-referenced enzymes had been published. Heidi J. Sofia and her associates compared the translated amino acid sequences of these enzymes and found the iron-sulfide binding motif CxxxCxxC in common. They then searched the available genomic database for this motif and an AdoMet binding motif. They found nearly 600 proteins with the CxxxCxxC and an AdoMet binding motif in the database available at that time [12]. The members of this group were associated with more than forty distinct biochemical processes in all three kingdoms of life. Dr. Sofia and associates named this the Radical SAM superfamily.

At the time of its discovery, the Radical SAM enzymes engaged in catalysis of key steps in metabolism, the biosyntheses of vitamins and antibiotics, chemical modifications of enzymes and nucleic acids, activation of glycyl radical enzymes,, and maturation of complex metalloenzymes, as well as methylation of chemically unreactive, non-nucleophilic carbon and phosphorus atoms in metabolites. With the increase in genomic information, the size of the Radical SAM superfamily has grown to more than 500,000 proteins engaged in more than 90 distinct biological processes. Increasingly penetrating mechanistic investigations have verified the intermediacy of the 5'-deoxyadenosyl radical [13,14]. The number of Radical SAM enzymes utilizing AdoMet as the source of the 5'-deoxyadenosyl radical now outnumbers those utilizing AdpCbl by a factor of at leas six. The former primacy of AdoCbl in this capacity is overthrown by the simpler molecule AdoMet. Presumably, the Radical SAM enzymes preceded the AdoCbl enzymes in evolution.

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