Regulation of S-Adenosylmethionine Decarboxylase

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1. Introduction

The biosyntheses of the essential polyamines spermidine and spermine are dependent on the activity of S-adenosylmethionine decarboxylase (AdoMetDC; EC 4.1.1.50). AdoMetDC catalyzes the conversion of S-adenosylmethionine (AdoMet) to S-adenosyl-5′-(3-methylthiopropylamine), otherwise known as decarboxylated AdoMet (dcAdoMet), which in turn donates its aminopropyl group to either putrescine for the synthesis of spermidine, or spermidine for the synthesis of spermine. The latter two reactions are catalyzed by the transferase enzymes, spermidine synthase and spermine synthase, respectively. In Saccharomyces cerevisiae, a null mutation in the SPE2 gene, encoding AdoMetDC, conveys an absolute requirement for spermidine or spermine for growth (1), and mouse blastocysts lacking a functional copy of the AdoMetDC gene die at the early stage of gastrulation unless supplied with spermidine (2). As well as being the substrate for AdoMetDC, AdoMet is involved in many other essential biochemical processes in cells and is regarded as the major methyl donor in reactions catalyzed by methyltransferases. However, dcAdoMet is unable to fulfill these other functions, so AdoMetDC activity commits AdoMet to a role in polyamine biosynthesis.

AdoMetDC is synthesized as an inactive proenzyme (~38 kDa in humans) that undergoes an autocatalytic cleavage reaction to form the α and β subunits (~31 and ~7 kDa, respectively in humans) and the covalently bound pyruvoyl cofactor of the mature enzyme. In the decarboxylation reaction, the pyruvoyl group forms a Schiff base with AdoMet, providing an electron sink that facilitates removal of the α-carboxylate group. The negatively charged α-carbon of the substrate is then reprotonated, and Schiff base hydrolysis results in release of the product, dcAdoMet (Fig. 1). The most likely candidate for the role of proton donor in this reaction is the Cys-82 residue, because a C82A mutant protein has much reduced enzyme activity and exhibits a high incidence of incorrect protonation of the pyruvoyl group (3).

Recent elucidations of the crystal structures of the human wild-type and mutated AdoMetDCs have provided profound insight into the evolution, activity, and regulation
of the enzyme, and will undoubtedly lead to improved rational design of enzyme inhibitors for therapeutic intervention. The human AdoMetDC is an (αβ)_{2} dimer, with each (αβ) monomer forming a novel four-layer αββα sandwich fold (4). Two pieces of evidence suggest that the eukaryotic AdoMetDC probably evolved as a result of gene duplication. First, the human AdoMetDC exhibits an internal structural repeat, with the N- and C-terminal halves of the protein being related by an approximately twofold axis of symmetry (4). Second, despite very little sequence homology, the prokaryotic Thermotoga maritima AdoMetDC has a structure very similar to that of the human AdoMetDC protomer and exhibits structural conservation of key active site residues previously identified in eukaryotic AdoMetDC (5). The active site of the human AdoMetDC, located by the pyruvoyl residue, is within a cleft far from the dimer interface, and contains the catalytically important residues Glu-8, Glu-11, Ser-69, Ser-229, His-243, and the aforementioned Cys-82 (4). Crystal structures of the human AdoMetDC complexed with substrate analogs indicate that Cys-82, Ser-229, and His-243 are positioned close to the methionyl group of the substrate, and the side chains of Phe-7, Phe-223, and Glu-247 serve to bind and position the substrate within the active site (6). Interestingly, the AdoMet substrate is bound in the syn orientation, despite the fact that the anti conformation probably predominates in solution (7).

Reflecting its key role in both polyamine biosynthesis and AdoMet metabolism, AdoMetDC is a highly regulated enzyme, with changes in enzyme activity being achieved via control at the levels of transcription, messenger RNA (mRNA) stability, translation, proenzyme processing, enzyme activation, enzyme inactivation, and enzyme degradation. Furthermore, the mode and degree of regulation of AdoMetDC activity is dependent on cell type and growth rate, as well as cellular polyamine levels. 

Fig. 1. Mechanism for AdoMetDC decarboxylation reaction. (Reprinted with permission from ref. 6. © (2001) American Chemical Society.)