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Polyamines and S-Adenosylmethionine Decarboxylase

[Poliaminler ve S-Adenozilmetionin Dekarboksilaz]

Azmi Yerlikaya

Biyoloji Bölümü, Fen-Edebiyat Fakültesi, Dumlupınar Üniversitesi, Kütahya, 43100, Türkiye

Yazışma Adresi
[Correspondence Address]

Azmi Yerlikaya, Ph.D.; Tel: +90-274-265-3159;
E-mail: ayerlikaya@excite.com

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ABSTRACT

Polyamines are natural organic molecules with polybasic character. Although it is not well understood how polyamines function in cells, many studies have shown that polyamines are essential for cell survival and proliferation. S-adenosylmethionine decarboxylase (forming decarboxylated S-adenosylmethionine which provides aminopropyl groups for subsequent synthesis of spermidine and spermine) and ornithine decarboxylase (converting ornithine into putrescine) catalyze the major regulated steps in polyamine biosynthesis. This review paper outlines briefly the functions of polyamines and polyamine biosynthetic pathway with particular emphasis on the properties of S-adenosylmethionine decarboxylase.

Key Words: polyamines; S-adenosylmethionine decarboxylase; proenzymes processing; degradation.

ÖZET

Poliaminler, polibazik karaktere sahip doğal organik moleküllerdir. Hücre içinde nasıl fonksiyon gördükleri çok iyi anlaşılmamasına rağmen, bir çok çalışma poliaminlerin hücrenin canlılığını sürdürmesinde ve çoğalmasında zorunlu olduklarını göstermiştir. S-adenozilmetionin dekarboksilaz (spermidin ve spermin sentezi için aminopropil grubu sağlayan dekarboksile olmuş S-adenozilmetionin oluşturmaktadır) ve ornitin dekarboksilaz (ornitini pütresine çevirmektedir) poliamin biyosentezinde en önemli aşamaları katalize etmektedirler. Bu derleme poliaminlerin görevlerini, poliamin biyosentez yolunu ve özellikle S-adenozilmetionin dekarboksilaz enziminin özelliklerini kısaca özetlemektedir.

Anahtar Kelimeler: poliaminler; S-adenozilmetionin dekarboksilaz; proenzim işleme; protein yıkılımı.

1. FUNCTIONS OF POLYAMINES

Polyamines (putrescine, spermidine and spermine) are ubiquitous organic cations of low molecular weight. The most obvious characteristic feature of polyamines is their polybasic character which gives them a much higher affinity for acidic constituents than that exhibited by Na^+, K^+, Mg^{2+} or Ca^{2+}. Spermidine and spermine are a triamine and a tetramine, respectively. Both of them are derived from the diamine putrescine. The polybasic character of polyamines is mostly pronounced with spermine because of its four positive groups (1, 2). Due to their polybasic character, polyamines bind strongly to nucleic acids and stabilize DNA by neutralizing the negative charges of the phosphate groups and by decreasing the repulsion between strands. Polyamines also interact with RNA and influence various stages of protein synthesis by influencing the secondary structure of mRNA, tRNA and rRNA (3). In addition, it is well know that polyamines bind to ribosomes and facilitate the association of ribosomal subunits (4), and in eukaryotic *in vitro* translation systems, polyamines increase the fidelity of translation (5). Interactions of polyamines with receptor proteins have also been reported. For instance, spermidine is responsible for intrinsic gating and rectification of strong inward rectifier K^+ channels by directly plugging the ion channel pore (6). Furthermore, the eukaryotic initiation factor eIF-5A contains the amino acid hypusine [N-epsilon-(4-amino-2-hydroxybutyl)-lysine] which is formed by a unique post-translational modification reactions that involves the conjugation of the 4-aminobutyl moiety of a spermidine molecule to the epsilon-amino group of a specific lysine residue of the eIF-5A to form the deoxyhypusine and its subsequent hydroxylation. Although the physiological role of hypusine is still unknown, it is definitely required for the vital *in vivo* function of eIF5A, since yeast strain engineered to replace the wildtype eIF5A with a mutant eIF5A form (Lys residue at the site of hypusination was altered to an Arg residue, thereby producing a protein that is not modified to the hypusine) was unable to grow (7, 8).

The normal cell growth and differentiation requires polyamines. Many studies have shown that rapidly growing cells have higher levels of polyamines than slowly growing or quiescent cells (9). Conversely, inhibition of the polyamine biosynthetic enzymes leads to cessation of cell growth and/or cell death (10). A growing body of literature also suggests that aberrant polyamine metabolism plays a role in the development of tumors (11). Furthermore, polyamine pathway has been exploited successfully for the treatment of many parasitic diseases. D,L-α-Difluoromethylornithine (DFMO) (an irreversible inhibitor of ornithine decarboxylase, ODC) and MDL 73811 (a potent inhibitor of S-adenosylmethionine decarboxylase, SAMDC) are very effective in eradicating *Plasmodium falciparium* (the malarial parasite), *Trypanosoma brucie rhodesiense* (the causative agent of East African sleeping sickness), and *Leishmania donovani* (causative agent of visceral leishmaniasis) infections (12-14).

2. POLYAMINE BIOSYNTHESIS

The biosynthetic pathway for polyamines is now well established (see Fig. 1). In mammalian cells, polyamines are derived from amino acid arginine and methionine. Putrescine is formed from L-ornithine by the action of ODC. Application of a specific inhibitor of ODC (DFMO) in many cell lines causes a dramatic reduction of putrescine and spermidine, indicating that mammalian ODC is the major source of putrescine (11, 15). Mammalian ODC is a homodimer with two active sites formed at the interface between the dimers (16). Like most decarboxylases, ODC requires pyridoxal-5'-phosphate (PLP) as a cofactor (17). The ornithine used as a substrate may be derived from the plasma or from intracellular arginine by means of the action of arginase. Putrescine is further converted to spermidine and spermine through the consecutive action of two distinct aminopropyl transferases, spermidine synthase and spermine synthase respectively. Both of these enzymes use decarboxylated S-adenosylmethionine (dcSAM) as an aminopropyl donor but are specific with respect to their acceptors [putrescine and spermidine, respectively (11)]. SAMDC is responsible for decarboxylation of S-adenosylmethionine (SAM). The content of dcSAM is normally very low in mammalian cells and the activities of aminopropyltransferases are regulated by the availability of this nucleoside substrate. Therefore, the production of dcSAM by the action of SAMDC is an essential step in polyamine production. As seen in Fig. 1, 5'-methylthioadenosine (MTA) is the second product formed during the transfer of an aminopropyl group from dcSAM to putrescine or spermidine. This nucleoside is rapidly degraded by MTA phosphorylase to adenine and 5'-methylthioribose-1-phosphate. The adenine is then converted to 5'-AMP by action of adenine phosphoribosyltransferase and 5'-methylthioribose-1-phosphate is converted back to methionine. Thus, the aminopropyl groups for spermidine or spermine synthesis are ultimately derived from methionine amino acid (11, 18).

Polyamines are also interconverted and degraded back to putrescine by the action of two enzymes (polyamine oxidase and spermidine/spermine N^1-acetyltransferase). Spermidine/spermine N^1-acetyltransferase uses acetyl CoA to convert spermidine and spermine into N^1-acetylspermidine and N^1-acetylspermine respectively. The acetyl derivatives are then cleaved by polyamine oxidase into putrescine or spermidine depending on the substrate (Fig. 1). The extent to which the interconversion occurs in cells is not known. However, the process is induced by exposure to toxic agents, by fasting and by exposure to spermidine itself. The interconversion may be a regulatory response that acts to reduce intracellular

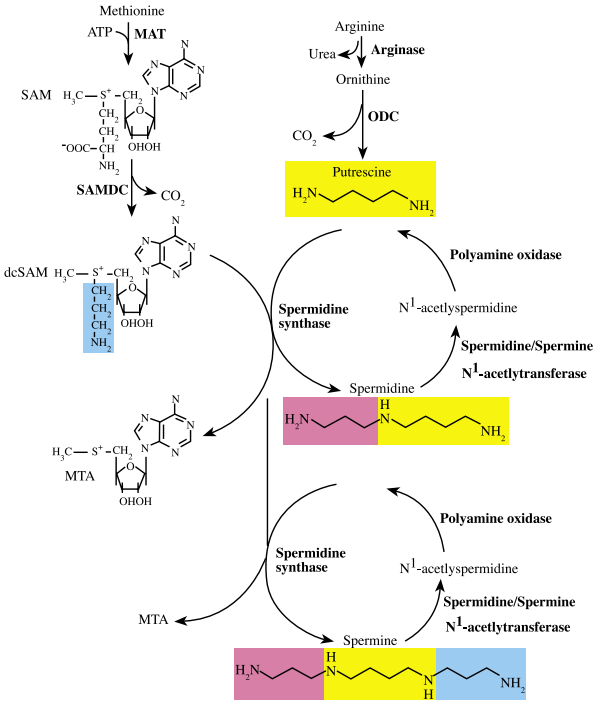

Figure 1 Pathway of polyamine biosynthesis and interconversion in mammalian cells.

In mammalian cells, polyamines are derived from amino acids methionine and arginine. The diamine putrescine is formed from ornithine by the action of ODC. Putrescine is subsequently converted to spermidine and spermine through the consecutive action of two distinct aminopropyl transferases, spermidine synthase and spermine synthase. Both of the enzymes use dcSAM as an aminopropyl donor (Ref. 11). The chemical structures shown are drawn with ISIS/DRAW software, and highlighted with Adobe Photoshop 7.0 software.

polyamine content when the level of spermidine and spermine exceeds certain limits (11, 18). Polyamines can also arise from exogenous sources such as diet. A specific membrane transport exists for putrescine, spermidine, and spermine. It is highly regulated and controls uptake of exogenous sources of these amines (15).

3. S-ADENOSYLMETHIONINE DECARBOXYLASE

As mentioned above, SAMDC is an essential enzyme for the synthesis of spermidine and spermine (18). It belongs to a small class of decarboxylases which uses a covalently bound pyruvate as a prosthetic group (19). These pyruvoyl-dependent decarboxylases form amines such as histamine, phosphatidylethanolamine (a component of membrane lipids), b-alanine (a precursor of coenzyme A), and decarboxylated SAM all of which are critical importance in cellular physiology and provide important targets for drug design (20).

All mammalian SAMDC primary sequences are very similar. There are only seven amino acid differences between human and the hamster proenzyme sequences and there are only four differences between the rat and the hamster sequences. On the other hand, there is only 12% identity between the *E.coli* and any of the eukaryotic enzymes even though they carry out the same reaction (21).

3.1. Processing and Activity of SAMDC

All known SAMDCs are synthesized as proenzymes. Upon synthesis, the proenzyme undergoes an autocatalytic cleavage reaction at an internal serine residue to generate two nonidentical subunits termed a and b (18). Human SAMDC is synthesized as a 38 kDa proenzyme which is subsequently cleaved to from 30.7 (a) and 7.7 kDa (b) subunits (17). The mature human SAMDC consists of a dimer of these two non-identical subunits [i.e., a_2b_2 (Ref. 23)]. The processing site of human SAMDC is between glutamic acid 67 and serine 68 in the sequence VLSESS which is highly conserved in all SAMDC sequences except *E.coli*, which has the sequence HLDKSH [the serine that generates pyruvate is underlined (Ref. 23, 24)]. Mutation of the critical serine to alanine completely prevents processing and the formation of active enzyme from SAMDC proenzyme (23).

The first step of SAMDC catalysis is the binding of substrate SAM through the pyruvate prosthetic group that reacts to form a Schiff base adduct with the substrate. The pyruvoyl cofactor in this Schiff base adduct linkage then acts as an electron sink to aid in the breaking of the C-COO- bond and the elimination of CO_2 from the enzyme-substrate complex. To release the final product (i.e., dcSAM), a protonation must occur at the a carbon of the product. Through this protonation, the pyruvate is regenerated and is available for another cycle of catalysis (25).

Processing and activity of the mammalian SAMDC and yeast enzymes is enhanced by the presence of putrescine (26, 27). Site-directed mutagenesis studies of the human SAMDC have indicated that the interaction of putrescine with four acidic residues (Glu11, Glu178, Glu256, and Asp174) is essential for the change in conformation that favors the processing reaction (28, 29). Likewise, site-directed mutagenesis has identified Glu8, Glu11, Cys82, His127, Glu133, Thr245, and Glu256 to play important roles in SAMDC activity (22, 28). Recently, it was also determined that changing Lys45 or Lys56 to Arg (a conserved mutation) had no effect on processing, but minimal effect on the activity; however, mutating Lys12 to Arg eliminated the catalytic activity completely without any effect on the proenzymes processing (Yerlikaya, A., and Stanley, B.A., unpublished results). Altogether, these results suggested that the small subunit is part of the active enzyme complex, and in fact contains residues which play critical roles in both processing and catalytic activity. In human SAMDC, mutation of Cys82 to serine or alanine greatly reduce activity, and it has been shown that a proton is donated from Cys82 to regenerate the pyruvate during catalysis (20).

3.2. Modulation of SAMDC Activity by its Substrate SAM

A significant part of the isolated *E.coli*, yeast and human SAMDC was reported to be inactive. It was later found that the inactivation was due to substrate-mediated inhibition in which SAMDC undergoes incorrect protonation on the pyruvate group instead of the a-carbon of the product. Such inactivation also occurs with dcSAM. This incorrect protonation converts the pyruvate cofactor to alanine and irreversibly inactivates the enzyme (20, 30, 31). Recently, additional modifications of *E.coli*, yeast and *Salmonella typhimurium* SAMDC enzymes by the substrate and the reaction product have been identified by mass spectrometry. These modifications were defined as the alkylation of the sulfhydryl of Cys-140 in *E.coli* SAMDC (32).

Substrate SAM is synthesized from methionine and ATP by the enzyme SAM synthase (33). In addition to being a precursor in polyamine biosynthesis, SAM is utilized in two other key metabolic pathways: transmethylation and transsulfuration. In transmethylation reactions, the methyl group of SAM is donated to a large variety of acceptor substrates including DNA, phospholipids and proteins. In transsulfuration reactions, the sulfur atom of SAM is converted via a series of enzymatic steps to cysteine, a precursor of taurine and glutathione, a major cellular anti-oxidant (34). Once SAM is decarboxylated, it is committed to polyamine production because dcSAM is inactive as a methyl donor and no other reactions utilizing dcSAM at any physiologically significant rate are known. SAMDC thus acts at a control point in SAM metabolism.

3.3. Regulation of SAMDC Gene Transcription and mRNA Translation

SAMDC is tightly regulated by putrescine, spermidine and spermine to link the supply of dcSAM to the need for spermidine and spermine (1). Putrescine activates SAMDC directly and also increases the rate of conversion of the proenzyme into the enzyme subunits, whereas spermidine and spermine negatively regulate SAMDC. There is a substantial increase in the amount of SAMDC protein when the polyamine content is reduced by application of inhibitors. Spermidine seems to have the predominant effect on the level of SAMDC mRNA, whereas much of the effect of spermine occurs at the translational level (11). For example, when the polyamine levels are decreased with ODC inhibitor DFMO, SAMDC mRNA levels increased about 7-fold (35). Furthermore, an 8-fold increase in SAMDC activity is observed when serum-starved SV-3T3 cells are reefed; however, addition of spermidine in the refeeding media, greatly reduced the serum-induced SAMDC activity increases. All of the decrease in enzyme activity can be accounted by a parallel decrease in SAMDC mRNA accumulation, implicating transcriptional control as the mechanism for spermidine's effects on SAMDC. In contrast, inclusion of spermine had a much greater overall inhibitory effect on serum-induced SAMDC increases, but without any change on mRNA levels, implying a translational and/or post-translational control by spermine (36). Decreasing polyamine levels with various inhibitors of polyamine biosynthetic enzymes results in more efficient translation of SAMDC mRNA as well. For example, depletion of spermine in SV-3T3 cells by the spermine synthase inhibitor S-methly-5'-thiomethyladenosine caused up to 30-fold increase in SAMDC activity. There was 6-fold stabilization of the enzyme and a 2.8-fold increase in SAMDC mRNA, which accounts for only 55% of the increase in SAMDC activity (37, 38). In another cell line (Ehrlich ascites tumor cells), depletion of polyamines by DFMO led to a 5.2-fold increase in SAMDC synthesis rate, but only 2-fold increase in mRNA level was observed, insufficient to account for the increase in the synthesis rate (39). These results suggest that increased translation efficiency plays a significant role in the observed increases of SAMDC in these cells with lowered polyamine levels.

3.4. Regulation of SAMDC Degradation

Both ODC and SAMDC have very short half-lives in many cell types. This rapid rate of turnover allows their activities to be regulated by changes in the amount of the enzyme protein and still respond dramatically within a few hours (23). The mechanism of ODC degradation is very well known. ODC is degraded by the 26S proteasome without ubiquitination [most proteins targeted for degradation by the 26S proteasome are first ubiquitinated (a 76 amino acid protein)]. Instead, antizyme protein binds to ODC monomers and causes it to be degraded by the 26S proteasome (40). On the other hand, the mechanism of SAMDC degradation remains ill-defined. Polyamines have been proposed to play roles in SAMDC degradation; for instance, inhibition of ODC by DFMO to deplete polyamines stabilizes SAMDC. In contrast, when the polyamine levels are high, there is generally more rapid degradation of SAMDC (41). Similarly, inhibition of spermidine and spermine synthases to decrease spermidine and spermine pools respectively stabilized SAMDC. However, since these inhibitors also cause accumulation of dcSAM in the cells, it is difficult to directly relate the stabilization of SAMDC in these experiments to the depletion of polyamine pools *per se*. In addition, the inhibitors may themselves cause the stabilization by binding to SAMDC as has been shown for SAMDC inhibitors [e.g., methylglyoxal bis (guanyl)hydrazone (MGBG), 4-amidinioindan-1-one 2'-amidinohydrazone (CGP48664), S-methyl-5'-methylthioadenosine, and aminoguanidine] (38, 42-45). These

inhibitors therefore lead directly to a major increase in the amount of enzyme protein in cells. It is possible that the binding of inhibitors at the active site changes the configuration of the protein to a form resistant to recognition by the degradation machinery (23).

As mentioned above, SAMDC undergoes substrate-mediated transamination in which pyruvate cofactor is converted to alanine. It has been previously suggested that the transaminated form of SAMDC may be the targeted for degradation (23). Therefore, a second explanation for the stabilization of SAMDC by the above mentioned inhibitors may be that they simply occupy the active site and prevent the transamination of SAMDC. Unlike many of the SAMDC inhibitors, in the presence of 5'[(Z)-4amino-2-butenyl]methylamino-5'-deoxyadenosine (AbeAdo), a substrate analog and its binding to the active site of SAMDC results in the transformation of pyruvate to alanine (46), the amount of SAMDC protein accumulated in cells was less than expected suggesting that the inhibitor increased the turnover rate (45). Similarly, depletion of SAM by SAM synthase inhibitor L-*cis*AMB increased the half-life of SAMDC 3-fold, suggesting that reduced rate of SAMDC transamination by SAM deprivation stabilized the enzyme (47). Therefore, all of these evidence support the hypothesis that the transamination plays a significant role in SAMDC degradation. The rapid turnover of SAMDC is therefore necessary to replace this pool of inactive enzyme (48). However, no study has yet shown directly that the transaminated form of SAMDC has faster half-life than the active form. And whether additional modifications following the transamination are required for SAMDC degradation remains to be determined. If so, how exactly the transamination or accompanying modifications target(s) the protein for rapid degradation is not known. The crystal structure of SAMDC indicated that the pyruvoyl cofactor is at a buried location between two b-sheets [Fig. 2 (Ref. 49)]. It is possible that the transamination or accompanying modifications cause(s) structural changes in the enzyme and exposes either alanine in place of pyruvate or a degradation signal near the active site for the recognition by the degradation machinery.

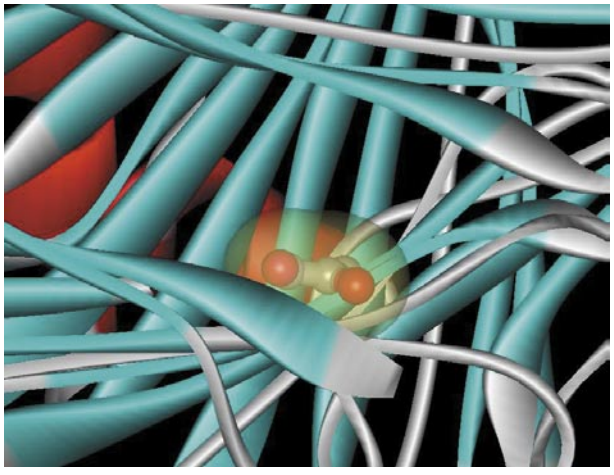

Figure 2 Three-dimensional structure of SAMDC in solid ribbon representation.

The processed SAMDC consists of a dimer (a_2b_2) of the two non-identical subunits. The pyruvate prosthetic group at the N-terminus of the large subunit (b) is shown in CPK model rendered transparent between two b-sheets (Ref. 49). The 3-D structure of SAMDC is viewed with WebLab Viewer software.

4. CONCLUSIONS

Polyamines have many roles in cellular physiology, including modulation of enzyme activities, altering transcription and translation and regulation of ion channels. Polyamines are essential for normal cell growth, and aberrant polyamine metabolism is known to cause neoplastic transformation (17). The two key factors in polyamine homeostasis are the rate-limiting enzymes of the biosynthetic pathway (i.e., ODC and SAMDC). Both have very short half-lives and are highly regulated. Especially, SAMDC has several unique features. For example, it is synthesized as a proenzyme, and processing reaction is stimulated by the interaction of putrescine with several negatively charged residues. Putrescine also stimulates the catalytic activity of the mature enzyme. Although most decarboxylases (e.g., ODC) use PLP as a cofactor, SAMDC uses a covalently bound pyruvate as a cofactor. Polyamines also influence the level of SAMDC through transcription, translation, and degradation. When the level of polyamines is high, SAMDC turns over more rapidly; however, no study has shown how exactly polyamines cause this rapid degradation of SAMDC. In the case of ODC, it is well known that polyamines induce the expression of antizyme which subsequently binds and targets ODC monomers to the 26S proteasome for degradation. As outlined above, studies have also implied that SAMDC is transaminated before complete degradation. Although other post-translation modifications are known to trigger degradation of other proteins, this-substrate-mediated transamination is a novel means of targeting the inactive form of SAMDC for rapid degradation (50). The exact mechanism of this targeting, give the site of transamination is in an essentially inaccessible interior site of SAMDC, remains to be determined, and should provide useful information for answering the general question of what structural features produce rapid degradation of only certain proteins, while other proteins apparently in the same intracellular compartment are degraded very slowly.

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