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MINIREVIEW ARTICLE

# Regulation of polyamine metabolism by translational control

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**Abstract** Polyamines are low molecular weight, positively charged compounds that are ubiquitous in all living cells. They play a crucial role in many biochemical processes including regulation of transcription and translation, modulation of enzyme activities, regulation of ion channels and apoptosis. A strict balance between synthesis, catabolism and excretion tightly controls the cellular concentration of polyamines. The concentrations of rate-limiting enzymes in the polyamine synthesis and degradation pathways are regulated at different levels, including transcription, translation and degradation. Polyamines can modulate the translation of most of the enzymes required for their synthesis and catabolism through feedback mechanisms that are unique for each enzyme. Translational control is associated with *cis*-acting and *trans*-acting factors that can be influenced by the concentration of polyamines through mechanisms that are not completely understood. In this review, we present an overview of the translational control mechanisms of the proteins in the polyamine pathway, including ornithine decarboxylase (ODC), ODC antizyme, *S*-adenosylmethionine decarboxylase and spermidine/spermine $N^1$ acetyltransferase, highlighting the areas where more research is needed. A better understanding of the translational control of these enzymes would offer the possibility of a novel pharmacological intervention against cancer and other diseases.

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**Abbreviations**

| | |
|---|---|
| ODC | Ornithine decarboxylase |
| dcAdoMet | Decarboxylated *S*-adenosylmethionine |
| AdoMetDC | *S*-Adenosylmethionine decarboxylase |
| SSAT | Spermidine/spermine $N^1$ acetyltransferase |
| uORF | Upstream open reading frame |
| DENSPM | $N^1$, $N^{11}$ Diethylnorspermine |

## Introduction

Polyamines are essential small molecules found in all cells (Agostinelli et al. 2010; Tabor and Tabor 1984). The most important polyamines are putrescine, spermidine and spermine. These molecules are known to be involved in the control of various biological processes, including transcription, translation, enzyme activities, regulation of ion channels, the response to oxidative stress and the formation of hypusine, which is an essential post-translational modification of eukaryotic translation initiation factor 5A (Cooper et al. 1983; Park et al. 1996; Pignatti et al. 2004; Wallace et al. 2003; Wang and Casero 2006). Polyamines are essential for cell growth (Porter and Bergeron 1983), and their rate of synthesis and total content increases proportionately with increases in cell proliferation. Because polyamines affect so many cell processes, intracellular pools are ordinarily maintained within a relatively narrow range through control of anabolism/catabolism and import/export (Alhonen-Hongisto et al. 1980; Porter and Bergeron 1988). Manipulation of polyamine metabolism has been

used as an anti-cancer strategy and to treat other diseases (Marton and Pegg 1995).

## Translational control

In order to respond to developmental and environmental stimuli in a precise and efficient manner, cells have developed mechanisms that allow control of protein translation without requiring the long process of mRNA transcription (Besse and Ephrussi 2008). Translational control is defined as changes in the translation efficiency of specific or multiple mRNA molecules that alter the amount of protein produced per unit of time. This process is mostly associated with translational repression, a mechanism that allows cells to maintain some mRNA molecules in a dormant state and permit translation only when the need occurs (Sonenberg et al. 2000).

Protein translation involves three complex steps: initiation, elongation and termination. Translational control occurs at translation initiation, which is the rate-limiting step of the process (Gingras et al. 1999). Translational control is mostly associated with translational repression and can occur on a global scale under specific circumstances (cellular stress, starvation or viral infections) or for specific transcripts that respond to intracellular environmental conditions (Gebauer and Hentze 2004).

Translation initiation can be inhibited by mechanisms that interfere with either of two crucial steps: ribosome subunit recruitment or the ribosome scanning process. Of these two processes, the latter is the most often studied because of the presence of RNA secondary structures on the 5′ untranslated region (UTR) of the mRNA and/or RNA-interacting proteins that act as translational repressors (Gebauer and Hentze 2004). Translational repressors have mainly been identified as interacting with 5′ UTR regions, but examples of translational repressors interacting with 3′ UTRs or within open reading frames of transcripts have also been reported (Chu et al. 1993; Fu and Benchimol 1997).

## Overview of the polyamine metabolism pathway

Cellular polyamine homeostasis is achieved through a strict balance between the synthesis, uptake and degradation of amines (Cohen 1998). The synthesis of putrescine, the simplest polyamine, occurs through decarboxylation of ornithine by ornithine decarboxylase (ODC). Formation of the two other polyamines, spermidine and spermine, requires a common precursor: decarboxylated *S*-adenosylmethionine (dcAdoMet), which is produced by *S*-adenosylmethionine decarboxylase. Spermidine is synthesized by spermidine synthase after fusing putrescine with the amino propyl group of dcAdoMet; subsequently spermine is synthesized by spermine synthase through the addition of another amino propyl group, dcAdoMet, to spermidine.

Spermidine and spermine are metabolized by spermidine/spermine $N^1$ acetyltransferase (SSAT), which inactivates these molecules by acetylation using acetyl-CoA as a donor. Acetylated polyamines can be excreted out of the cell or recycled by polyamine oxidase. Regulation of the concentration and activity of most of these enzymes occurs through transcriptional, translational and post-translational events.

In this mini-review, we will describe the events that regulate these proteins, emphasizing the translational control mechanisms that modulate their synthesis in response to cellular polyamine concentrations.

## Translational control of polyamine synthesis

### Ornithine decarboxylase

ODC is considered the rate-limiting enzyme of the polyamine pathway. It has a molecular weight of 51 kDa and is active only as a homodimer. ODC has a very short half-life of less than 20 min due to a strong interaction with ODC antizyme that prevents its homodimerization and promotes destruction of the monomer units by the 26S proteasome (Kahana 2007; Murakami et al. 1992).

Polyamines are required for cell growth; the ODC promoter contains transcription factor response elements that are activated upon stimulation with hormones or growth factors (Bellofernandez et al. 1993; Janne and Raina 1969). Transcription factors that promote ODC transactivation include the oncogene c-myc (Bellofernandez et al. 1993) and NFkappaB (Pfeffer et al. 2001); transcription is antagonized by PPAR-gamma (Takashima et al. 2001).

The ODC mRNA transcript contains a long 5′ UTR, a characteristic that is common in genes that regulate cell growth (Kozak 2005). The ODC 5′ UTR is CG-rich, conferring a strong secondary structure, and also contains an upstream open reading frame (uORF).

In vitro experiments have confirmed that both the strong stem loop structure and the uORF are able to repress translation when fused to reporter genes (Shantz et al. 1996). The scanning model of translation initiation indicates that translation usually starts at the first AUG codon (Kozak 2005). The presence of uORFs will prevent the ribosome machinery from initiating translation at the right codon in an efficient way; it has been shown that in transcripts with uORFs translation of the intended protein is reduced between 30 and 75% (Calvo et al. 2009).

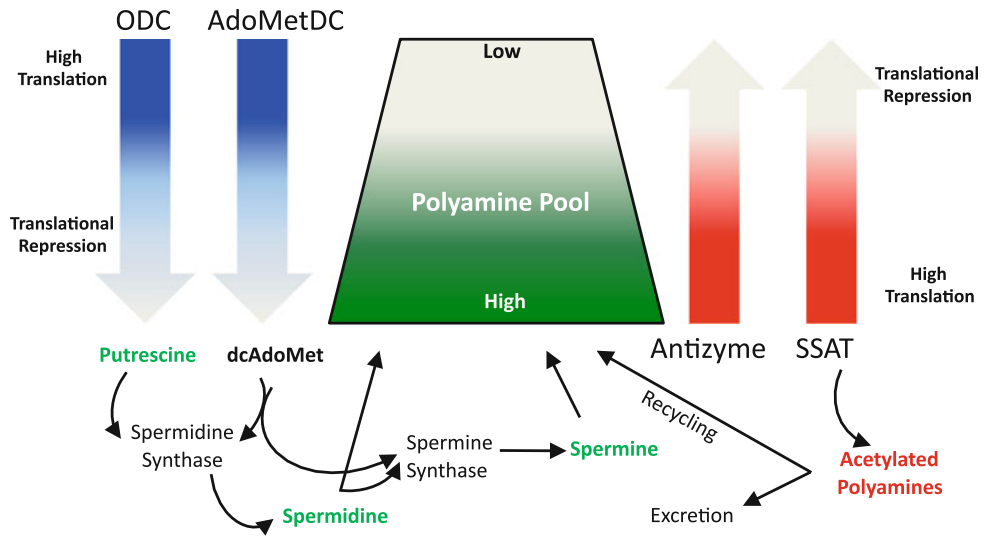


**Fig. 1** Polyamine-mediated translational control of enzymes in the polyamine pathway. *Gradient colors* indicate the levels of enzymes or polyamines. When polyamines levels are low, ODC and AdoMetDC translation are increased. The resulting increase in polyamine levels prevents the translation of these two enzymes. When polyamine levels are increased, translation of the antizyme and SSAT is enhanced, thus reducing the net amount of polyamines (i.e., negative feedback). Polyamine-mediated translational control and rapid degradation of the rate-limiting enzymes maintains tight control of polyamine levels

Studies in nude mice have shown that ODC overexpression is sufficient to induce tumorigenesis (Auvinen et al. 1997). Under normal circumstances this growth stimulation is prevented by the structural constraints in the 5′ UTR that allow only minimal translation of ODC, coupled with fast degradation of the ODC protein.

Polyamine requirements change according to the cell cycle stage (Tabor and Tabor 1984), indicating the presence of mechanisms that allow the cells to translate more ODC when needed. Regulation of the activity of translation initiation factors during the cell cycle may explain how increased translation of ODC is achieved. Specifically, overexpression of the translation initiation factor elF4E can increase translation of transcripts that have strong 5′ UTR secondary structure, including ODC (Shantz et al. 1996). The activity of eIF4E is normally inhibited through interaction with 4E-BP1. This interaction is blocked upon phosphorylation of 4E-BP1 by mTOR. Treatment of cells with growth factors (Insulin, EGF, and others) promotes the phosphorylation of 4E-BP1 by mTOR and increases both the activity of eIF4E and translation of ODC (Manzella et al. 1991; Proud and Denton 1997).

Characterization of the translation rate of ODC across the cell cycle identified G1/S and G2/M as the stages where ODC is translated (Pyronnet et al. 2000). It was also demonstrated that the increase in ODC in G1/S is mediated by cap-depended translation and requires eIF4E. Interestingly, the increase in ODC translation during G2/M does not require eIF4E. Instead, a different translation initiation event, mediated by an internal ribosome entry site (IRES) located between the CG-rich region and the AUG initiation codon, was suggested (Pyronnet et al. 2000).

ODC translation is heavily influenced by polyamine concentration (Fig. 1). An increase in polyamines promotes translational repression without affecting mRNA levels (Kahana and Nathans 1985), and a reduction in polyamines causes the converse effect. The exact molecular mechanism that allows polyamines to regulate ODC translation has not been determined. Attempts by different groups to identify the region of the ODC mRNA transcript that responds to polyamine levels and promotes translational repression have generated contradictory results. Some reports have suggested that the 5′ UTR of ODC is required for translational repression (Ito et al. 1990; Kashiwagi et al. 1991; Lovkvist et al. 1993), but others have found that the UTR regions are insignificant, and constructs with only the coding region can still be translationally repressed upon stimulation with polyamines (Wallstrom and Persson 1999; Wetters et al. 1989a, b). A possible explanation for such disparity comes from the fact that these reports have evaluated ODC translation in different expression systems, including reticulocytes, hamster cells, monkey cells, and human cells, using ODC transcripts from different origins.

RNA-interacting proteins that act as translational repressors to ODC have not been reported. Different studies have suggested that *trans*-acting factors regulate the interaction between the 5′ and 3′ UTR regions of ODC, and that this interaction could be significant for polyamine-mediated translational control of ODC (Lorenzini and Scheffler 1997). An unidentified ~58 kDa protein has

been shown to interact with the 5′ UTR of ODC (Manzella and Blackshear 1992). However, this protein remains bound to ODC mRNA regardless of polyamine stimulation; therefore, it is unknown if this interaction is of significance for polyamine regulated translational repression.

Characterization of polyamine-mediated translational repression of ODC is important because it offers the possibility of identification of drugs that inhibit ODC translation. Subsequently, these drugs might be used as anticancer agents.

### Antizyme

ODC activity is quickly inhibited by the monomeric 25 kDa inducible-protein, antizyme (Heller et al. 1976). Antizyme inhibits ODC by preventing its dimerization and promoting its ubiquitin-independent degradation by the 26S proteosome; in this process, antizyme itself is not degraded but rather is recycled to continue inhibiting more ODC molecules (Murakami et al. 1992). The efficiency of this process results in an extremely small half-life for ODC.

Antizyme levels are very low in most tissues (Heller et al. 1976; Kitani and Fujisawa 1984), but its concentration rises rapidly in response to an increase in polyamines through a process that is controlled at the level of translation (Fig. 1).

Antizyme mRNA is widely found in mammalian tissues, and its levels do not change with polyamine manipulation (Hayashi and Murakami 1995). It contains two ORFs: ORF1 encodes the first 68 amino acids, and ORF2 contains the rest but is in a +1 frame with respect to ORF1.

To produce a functional molecule of antizyme, a +1 ribosomal frameshift must occur before reading the stop codon of ORF1. In mammals there are three genes for ODC antizymes, and all of them require ribosomal frameshifting for the translation of antizyme. The frameshifting process is highly unusual in most organisms; in mammals, this translational control mechanism has been found exclusively in the three antizyme genes (Bekaert et al. 2010).

The exact mechanism through which polyamines promote this frameshifting has not been determined, but studies of the nucleotides surrounding the stop codon of ORF1 have identified an RNA stem loop and pseudoknot that are necessary for frameshifting to occur. Bioinformatic analysis has shown that these structures and nucleotide sequences surrounding the stop codon of ORF1 are conserved across hundreds of species (Ivanov and Atkins 2007; Matsufuji et al. 1995).

It has not been determined whether polyamines stimulate the frameshifting process by direct interaction with the mRNA, the ribosomes, or some other mediator proteins.

By regulating ODC activity, antizyme is considered a tumor suppressor gene (Fong et al. 2003). Therefore, the activation of translational frameshifting for antizyme using pharmacological compounds is a potential mechanism to treat or prevent cancer. Based on this principle, a reporter system has been used to detect molecules that promote ribosomal frameshifting, thus allowing the identification of compounds that increase antizyme and reduce the level of polyamines (Petros et al. 2006).

### *S*-Adenosylmethionine decarboxylase

Decarboxylated *S*-adenosylmethionine is an essential metabolite for spermidine and spermine synthesis. Approximately 1% of the cellular *S*-adenosylmethionine is decarboxylated by *S*-adenosylmethionine decarboxylase (AdoMetDC) for use in polyamine synthesis (Eloranta and Kajander 1984). This enzyme shares many characteristics with other polyamine pathway enzymes, including a short half-life mediated by 26S proteasomal degradation and being controlled at the translational level by polyamine concentration.

Polyamines negatively regulate the translation of AdoMetDC (Fig. 1). Translational repression mediated by polyamines requires the 5′ UTR region of AdoMetDC RNA. This region contains a uORF located 14 bp downstream from the 5′ cap and is necessary to maintain polyamine-dependent translational control. Interestingly, the sequence of the six amino acids (MAGDIS) encoded by this uORF is necessary for translational repression (Raney et al. 2000). It was shown that ribosomes that initiate translation of this peptide are prevented from releasing the short peptide before reaching the stop codon. It was further suggested that translation termination of the MAGDIS peptide is prevented by the interaction between serine-tRNA and the MAGDIS peptide, causing ribosomal stalling; the stability of the peptidyl-tRNA conjugate is increased by polyamines (Law et al. 2001; Raney et al. 2002).

## Translational control of polyamine catabolism

### Spermidine/spermine $N^1$-acetyltransferase

Spermidine/spermine $N^1$-acetyltransferase (SSAT) is the rate-limiting enzyme for polyamine catabolism. It is the smallest protein of the polyamine pathway, with only 171 amino acids, and possesses a very short half-life of approximately 15 min. SSAT acetylates spermidine and spermine at the $N^1$ position using acetyl-CoA as a substrate (Matsui and Pegg 1980; Matsui et al. 1981). Acetylation reduces the ability of polyamines to interact with their natural anionic binding sites and facilitates their cellular excretion (Seiler 1987).

SSAT levels are normally very low because of strong regulation at the transcriptional, translational and post-translational level (Seiler 2004). SSAT transcription is controlled by the transcription factor nuclear erythroid factor 2 (NRF2), which complexes with polyamine-modulated factor 1 (Wang et al. 1999, 2001). In response to an increase in polyamines, these factors interact with the polyamine-response element located in the promoter region of SSAT and transactivate this gene. Polyamines are not the only stimuli that can increase transcription of SSAT; others include hypoxia and non-polyamine small molecules like cisplatin and 5-fluorouracil. It is possible that these other effectors may disrupt the interaction between polyamines and macromolecules such as nucleic acids, resulting in an increase in the level of free polyamines (Casero and Pegg 1993). However, the exact molecular mechanism behind this transactivation is not known.

Interestingly enough, increasing the transcription of SSAT has very little effect on the expression of SSAT protein (FogelPetrovic et al. 1996; Parry et al. 1995; Suppola et al. 1999). Regulation at the level of translation is probably the most important factor for controlling how much SSAT protein will be produced (Butcher et al. 2007) (Fig. 1).

The translational control mechanism regulating SSAT expression is poorly understood. Two independent reports have shown that the translational repression mechanism is very unusual because it does not involve the 5′ or 3′ UTRs (Butcher et al. 2007; Parry et al. 1995). The same report has also suggested that an unidentified translational repressor protein interacts with the 5′ end of the ORF (Butcher et al. 2007). This repressor is unable to interact with SSAT mRNA when a polyamine analog is added (Butcher et al. 2007), suggesting that the level of free polyamines modulates SSAT translation by regulating the activity of the translational repressor.

Several polyamine-independent stimuli (heat shock, hypoxia, growth factors, NSAIDs and others) can increase SSAT activity by upregulating protein levels (Casero and Pegg 2009), but how these effectors are able to activate SSAT translation is unknown.

Increasing SSAT activity could be a new therapeutic option for multiple diseases, including cancer, obesity and Parkinson's disease (Jell et al. 2007; Kee et al. 2004; Lewandowski et al. 2010). Increasing SSAT activity to potentially treat obesity is suggested based on studies in which transgenic animals received more than 20 copies of the SSAT gene (Pietila et al. 1997). SSAT activity in these animals rose between 4 and 10 times in various tissues across their bodies. Interestingly, these animals were resistant to high-fat diet-induced obesity compared to wild type and knock out animals (Jell et al. 2007). The mechanism of obesity resistance involves an increase in consumption of acetyl-CoA, thus preventing lipogenesis (Jell et al. 2007).

A recent report showed that there are low levels of SSAT mRNA in specific areas of the brains of subjects with Parkinson's disease. Mechanistic studies in the same report suggested that polyamines accelerate the polymerization of alpha synuclein, a process implicated in Parkinson's disease. Using transgenic animals overexpressing alpha synuclein in the brain, they confirmed that increasing the activity of SSAT using $N^1$, $N^{11}$ diethylnorspermine (DENSPM) ameliorates the appearance of pathological changes related to Parkinson's disease (Lewandowski et al. 2010).

Preventing SSAT translation can also be a therapeutic opportunity for certain human diseases, including ischemia–reperfusion injury after liver or renal transplant, myocardial infarction (Han et al. 2009; Zahedi et al. 2009) and brain injury (Zahedi et al. 2010). In all of these conditions, ischemic injury has been suggested to increase SSAT activity to a level that causes cell toxicity. Studies with SSAT knockout animals have confirmed that renal ischemia–reperfusion injury is at least partially SSAT-dependent because SSAT knockout animals have very mild injury compared to wild type animals (Zahedi et al. 2009).

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