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Remaining Mysteries of Molecular Biology: The Role of Polyamines in the Cell

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Abstract

The polyamines (PAs) spermidine, spermine, putrescine and cadaverine are an essential class of metabolites found throughout all kingdoms of life. In this comprehensive review, we discuss their metabolism, their various intracellular functions and their unusual and conserved regulatory features. These include the regulation of translation via upstream open reading frames, the over-reading of stop codons via ribosomal frameshifting, the existence of an antizyme and an antizyme inhibitor, ubiquitin-independent proteasomal degradation, a complex bi-directional membrane transport system and a unique posttranslational modification—hypusination—that is believed to occur on a single protein only (eIF-5A). Many of these features are broadly conserved indicating that PA metabolism is both concentration critical and evolutionary ancient. When PA metabolism is disrupted, a plethora of cellular processes are affected, including transcription, translation, gene expression regulation, autophagy and stress resistance. As a result, the role of PAs has been associated with cell growth, aging, memory performance, neurodegenerative diseases, metabolic disorders and cancer. Despite comprehensive studies addressing PAs, a unifying concept to interpret their molecular role is missing. The precise biochemical function of polyamines is thus one of the remaining mysteries of molecular cell biology.
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Introduction

Polyamines (PAs) are small aliphatic polycations widely distributed in nature. They were first described in 1678 by Antonie van Leeuwenhoek in seminal fluid, resulting in naming two of its members spermine (Spm) and spermidine (Spd) (historical perspective was reviewed in Refs. [1] and [2]). PAs are present in all living organisms, with the most common PAs being Spm, Spd and putrescine (Put) [3], followed by cadaverine (Cad) and 1,3-diaminopropane (1,3-DAP) (Fig. 1). Between species, however, PA concentration and composition do vary. For instance, *Escherichia coli* contains high concentrations of Put, while in many other bacteria and eukaryotes, Spd and Spm are present at higher concentrations (reviewed in Refs. [4] and [5]). In fungi, Spm has not been detected, apart from in the *Saccharomycotina* subphylum [5]. Cad, despite being characterized in bacteria and plants, is of low to zero abundance in most other species (reviewed in Refs. [4], [6] and [7]). The ubiquity of PAs in cells implies that their existence is important; when PAs are depleted from the cell, an enormous number of biological processes have shown to be affected.

Biosynthesis of Polyamines

PAs are predominantly derived from the amino acids ornithine (Orn) and methionine, while arginine and lysine serve as alternative, secondary sources of these metabolites (Fig. 2). The canonical biosynthesis pathway begins with Orn decarboxylation, by

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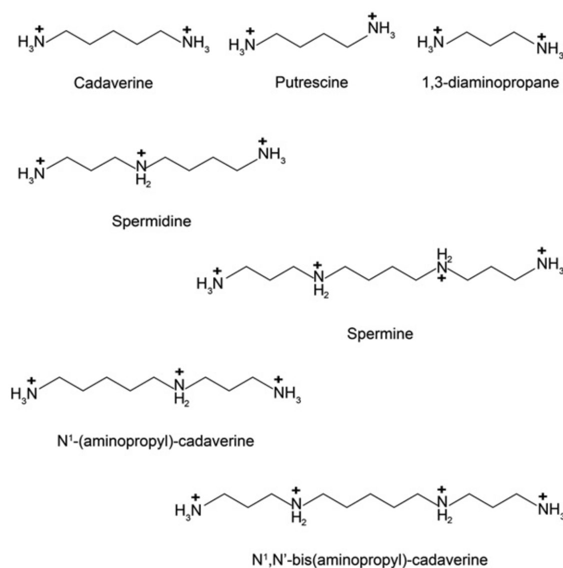

Fig. 1. Common and biologically relevant polyamines (PAs). Putrescine (Put), spermidine (Spd) and spermine (Spm) are the most common biological PAs followed by cadaverine (Cad) and 1,3-diaminopropane (1,3-DAP). Under physiological pH, PAs are present in a cationic form, a condition essential for function in cells.

ornithine decarboxylase (ODC), to form Put. Spd and Spm are formed from Put via addition of aminopropyl groups. These are donated by the methionine derivative: decarboxylated *S*-adenosylmethionine (dcAdoMet) produced by *S*-adenosylmethionine decarboxylase (AdoMetDC). The addition of aminopropyl groups is mediated by spermidine and spermine synthases (SpdS and SpmS), (reviewed in Refs. [4], [6] and [7]). Put can alternatively be synthesized from arginine via arginine decarboxylase (ADC) and agmatinase (Fig. 2) (reviewed in Refs. [4], [6] and [7]). There are exceptions in which the canonical pathway is not entirely present; here, organisms use alternative pathways to synthesize PAs. Such is the case for *Arabidopsis thaliana* and *Trypanosoma cruzi* that lack an *ODC* gene [8, 9]. *A. thaliana* synthesizes Put solely via the ADC route [9], whereas *T. cruzi* (the insect form) uptakes Put and Cad present in the excreta of its host insect [10, 11].

The less common PA, Cad, is the product of lysine decarboxylation. Lysine decarboxylases (LDCs) have been identified in bacteria (*E. coli*, *Vibrio sp.*, *Lactobacillus sp.*), cyanobacteria and plants (e.g. leguminosae, solanaceae and gramineae) [12–15], whereas for fungi and animal cells, no *LDC* gene has been described. Nonetheless, Cad has also been detected in some of these latter organisms [16, 17]. ODC was suggested as the enzyme responsible for synthesizing Cad in these cases [16, 18–20], but other biosynthesis pathways remain plausible. Cad could be the starting molecule for a parallel pathway to Put, Spd and Spm due to the fact that Cad derivatives N^1-(aminopropyl)-Cad and N^1,N'-(bis-aminopropyl)-Cad have been detected in *E. coli* and fungi [18, 19, 21].

The Intriguing Fine-Tuning of Polyamine Levels

Intracellular PA levels are tightly regulated in their biosynthesis, catabolism and/ or transport. The enzymes in PA metabolism are controlled via highly specialized and unconventional mechanisms at the level of transcription, translation and protein degradation, involving several feedback loops controlled by PA concentrations. These aforementioned features are highly conserved throughout all kingdoms of life, indicating that the regulation of PA levels is highly critical for the cell.

Transcriptional and translational control of ornithine decarboxylase (ODC)

ODC is in many species the limiting factor for the biosynthesis of Put, Spd and Spm and its intracellular concentrations are tightly controlled. ODC can alter its activity in response to many different types of cellular perturbation. For example, ODC activity is induced in response to growth stimuli and has elevated activity in cells infected by viruses and under conditions of disease such as cancer [22–28].

The regulation of ODC starts at transcription. Best studied in mammals, the Odc promoter contains various elements that respond to several stimuli, such as growth factors, hormones and tumor promoters [29–32]. For ODC translation, regulation is highly dependent on PA concentration (Fig. 3a). An increase in intracellular PA levels leads to ODC translation repression, whereas a decrease causes translation activation. So far, it is not well understood how this translation repression and activation by PAs occurs.

In mammals, ODC mRNAs have a long 5′ untranslated region (UTR) that contains a strong secondary structure (reviewed in Ref. [33]). The 5′ UTR contains two additional elements that cause a reduction in efficiency of ODC mRNA translation: a small functional upstream open reading frame (uORF) (Fig. 3a) and a GC-rich sequence [34–36]. Mammalian ODC mRNA translation can also be mediated by an internal ribosome entry site (IRES). This allows for translation initiation even when cap-dependent translation is blocked, as in mitosis for instance [37].

The turnover of ODC is also controlled. ODC is short-lived with a half-life of less than 1 h [38, 39]; in eukaryotes, ODC degradation occurs via the 26S proteasome; however, this process is independent of ubiquitination (Fig. 3b) [40]. As most proteins are

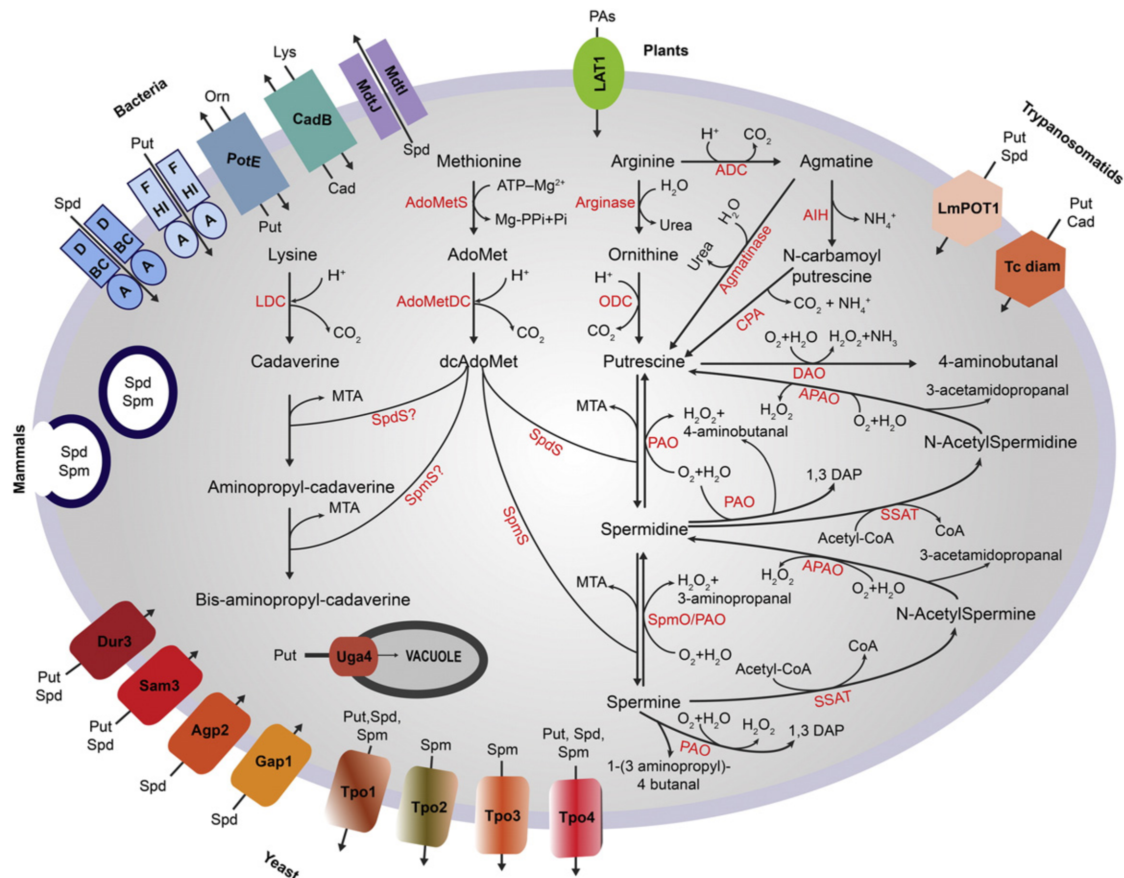

Fig. 2. Polyamine metabolism. PAs are synthesized, catabolized and transported according to the requirements of the cell. The main biosynthetic pathways of Spd and Spm involves formation of Put from Orn by ODC and the transfer of aminopropyl groups to Put from the methionine derivative, dcAdoMet, by SpdS and SpmS. Arginine can be used as a precursor of Put via its hydrolysis to Orn by arginase or alternatively, via its decarboxylation to agmatine by ADC. PAs can be acetylated by SSAT and/or oxidized by PAOs and APAOs producing a PA, an amino aldehyde and H_2O_2. In addition to the aforementioned PAs, Cad and 1,3-DAP are also produced. Cad is the product of lysine decarboxylation by LDC whereas 1,3-DAP is the product of Spm and Spd oxidation by PAO. The transport systems in mammals, bacteria, plants, yeast and trypanosomatids are shown. Abbreviations: Spd, spermidine; Spm, spermine; Put, putrescine; Orn, ornithine; ODC, ornithine decarboxylase; dcAdoMet, decarboxylated *S*-adenosyl-L-methionine; SpdS, spermidine synthase; SpmS, spermine synthase; ADC, arginine decarboxylase; PAs, polyamines; SSAT, spermidine/spermine acetyltransferase; PAOs, polyamine oxidases; APAO, acetylated polyamine oxidase; Cad, cadaverine; 1,3-DAP, 1,3-diaminopropane; LDC, lysine decarboxylase.

ubiquitinated prior to protein degradation, this feature of ODC degradation is relatively unusual [41]. Other proteins that are degraded in this ubiquitin-independent way in eukaryotes include thymidylate synthase, a human enzyme responsible for the conversion of deoxyuridine monophosphate into deoxythymidine monophosphate and Rpn4, a *Saccharomyces cerevisiae* transcription factor that activates proteasomal genes (reviewed in Ref. [41]). One similarity between these proteins that may explain their degradation independent of ubiquitin is the presence of an unstructured domain recognizable by the proteasome [41].

ODC degradation depends on a PA-activated protein: antizyme (AZ), an "antienzyme for ODC" [42–44]. AZ has high affinity for ODC monomers and the resulting interaction inhibits ODC dimerization and thus activity [43]. In addition, AZ causes a conformational change in ODC leading to exposure of ODC's unstructured C-terminus that is then recognized by the proteasome [43]. AZ can therefore be considered as a catalyst for ODC degradation [41, 45–47].

Unlike other organisms, the region of ODC exposed and recognized by the proteasome in *S. cerevisiae* is the N-terminus [48]. Despite sequence divergence across different species, the degradation of ODC continues to be independent of ubiquitination and accelerated by AZ. This would indicate that this type of regulation is optimal for ODC regulation [41].

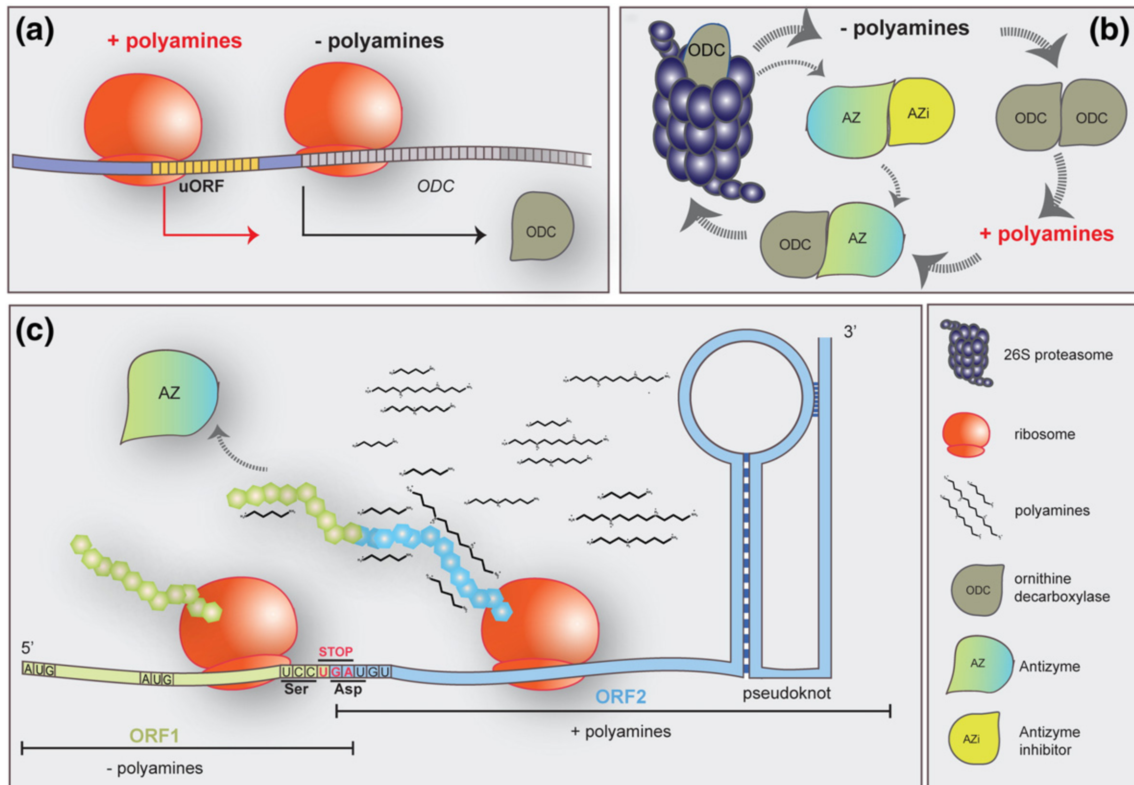

Fig. 3. Ornithine decarboxylase (ODC) and antizyme (AZ) regulation. (a) ODC translation is repressed in the presence of high levels of PAs. This is mediated by an uORF in the 5′ UTR of ODC mRNA that reduces ODC translation efficiency. (b) When cellular levels of PAs are low, ODC is in its active dimer form and produces additional Put. Upon increased levels of PAs, AZ binds to ODC and, as well as inactivating it, promotes ODC degradation via the 26S proteasome in an ubiquitin-independent manner. AZ is inactivated by binding to AZi. (c) Hypothetical model of AZ regulation. AZ is translated by two ORFs that are separated by a codon stop. The complete and functional AZ is translated by ribosomal frameshifting. This is achieved by shifting the reading frame by one nucleotide in the stop codon of the first ORF, which allows the translation of the second ORF. PAs promote an increase in ribosomal frameshifting efficiency. Downstream of the frameshift site is localized a pseudoknot that may stimulate frameshifting. Abbreviations: ODC, ornithine decarboxylase; PAs, polyamines; Put, putrescine; AZ, antizyme; AZi, antizyme inhibitor.

The regulation of polyamine synthesis through antizyme (AZ) levels

Apart from ODC, AZ facilitates the degradation of other proteins such as the human Aurora A kinase, via the proteasome in an ubiquitin-independent manner [49]. This enzyme is conserved from bacteria to humans but is not described in plants [50–52]. AZ levels are controlled by an unusual and highly conserved translational mechanism. It is encoded by two adjacent open reading frames (ORFs) and ribosomal frameshifting is required to generate a functional product. This frameshifting consists of ribosomes reaching the last codon of the first ORF (a stop codon), shifting one nucleotide and continuing to read the second ORF in the +1 frame. In this way, the UGA stop codon is over-read (Fig. 3c). The +1 ribosomal frameshifting at the stop codon is remarkably well conserved in many eukaryotes, while other features of the sequence evolved independently [51]. It is still unclear how this frameshift occurs mechanistically, how it is induced and, further, why such costly mechanisms are required to control AZ abundance.

The efficiency of ribosomal frameshifting is controlled by the levels of PAs and thus AZ is the center of a homeostatic feedback loop. When PA levels are high, the efficiency of ribosomal frameshifting increases, resulting in higher levels of AZ, an increased rate of ODC degradation and, finally, reduced biosynthesis of PAs [53–55]. In mammals, this feedback loop also leads to a lower PA uptake from the extracellular environment [53–55]. Whether PAs regulate the AZ ribosomal frameshift directly or indirectly is still not clear. A recent study in *S. cerevisiae* revealed that, in the absence of PAs, the nascent AZ polypeptide inhibits its own synthesis; furthermore, when PAs are present, they can interact with the nascent peptide and prevent AZ synthesis inhibition (Fig. 3c) [56]. PAs also bind to the mammalian AZ, suggesting that this is a conserved mechanism [56].

Furthermore, AZ is regulated by an AZ inhibitor (AZi) (Fig. 3b). AZi is similar to ODC but is catalytically inactive [57]. AZ has more affinity to the AZi than to ODC; their subsequent interaction allows ODC to dimerize, be activated and escape degradation (Fig. 3b). Both AZ and AZi are degraded by ubiquitin-dependent proteasome degradation; thus, ODC activity can be controlled by ubiquitination. Interestingly, in mammals, one of the three AZ present, AZ 1, has an additional characteristic: it possesses two alternative start codons. These two start codons result in two isoforms of varying length. Notably, the longer isoform which is expressed at low levels is targeted to the mitochondria [58] and the nucleus, where it concerts a yet unknown role [59, 60].

Polyamines and *S*-adenosylmethionine decarboxylase (AdoMetDC)

AdoMetDC catalyzes the formation of dcAdoMet [61] that acts as a donor of aminopropyl groups for the synthesis of Spd and Spm from Put. This enzyme is expressed at low levels and, in this way, does not deplete the concentration of *S*-adenosylmethionine (AdoMet) that is essential for methyl transfer reactions [61]. AdoMetDC is synthesized as an inactive proenzyme. To become active, the proenzyme undergoes an internal serinolysis, which causes cleavage of the proenzyme into two subunits (α and β) and also results in the formation of a pyruvoyl group at the N-terminus of the α-subunit (Fig. 4a) [62]. In mammals and yeast, Put stimulates AdoMetDC self-processing and activation [63–65].

The major regulators of AdoMetDC are PA levels. While Put positively regulates AdoMetDC, Spd and Spm negatively regulate the enzyme (reviewed in Ref. [61]). Increases in AdoMetDC levels have shown to be associated with growth stimulation, for example, during hormone treatment, tissue regeneration and cellular differentiation [66–68]. Although regulation of AdoMetDC transcription is not yet clear, translation is known to be mediated by uORFs. The mammalian uORF that precedes the ORF for AdoMetDC is located 14 nucleotides downstream of the 5′ cap and encodes a hexapeptide: MAGDIS [69]. During translation of MAGDIS, when the final tRNA (for serine) encounters the ribosome, it causes a ribosomal stall close to the uORF termination site, making the AdoMetDC start codon inaccessible (Fig. 4b) [70]. The stability of the bound tRNA-peptide is specific for the peptide sequence, and additionally, this stability increases with higher levels of Spd and Spm [70, 71].

In plants, there are two uORFs that overlap by one nucleotide, the 5′ "tiny" and the 3′ "small". The 3′ small uORF represses translation of the AdoMetDC ORF and is also affected by PA levels. It is hypothesized that, in low concentrations of PAs, the 5′ tiny uORF is translated and is able to inhibit translation of the 3′ small uORF. This inhibition would allow ribosomes to reach the initiation codon of AdoMetDC and initiate its translation [72]. In high concentrations of PAs, the 3′ small uORF is translated and subsequently blocks access to the AdoMetDC ORF. This is because the 5′ tiny uORF is bypassed by either the translation initiation complex or a ribosome -1 frameshifting that enables translation of the two ORFs [72].

Similar to ODC, AdoMetDC half-life is short (less than 1 h), and in extreme cases such as in *Crithidia fasciculata*, the turnover occurs in 3 min [73]. AdoMetDC turnover accelerates when concentrations of Spd and Spm are high [67]. Degradation of AdoMetDC by polyubiquitination via the proteasome is accelerated when its pyruvoyl group is transaminated and transformed into alanine by its substrate AdoMet [74]. This transformation is suggested to induce a conformational change in this enzyme, making its ubiquitination site more accessible and thus more prone for degradation [61, 74]. Additionally, besides transamination promoting AdoMetDC degradation, this reaction has also shown to inactivate its function [74].

Controlling Polyamine levels through catabolism

In addition to their synthesis, PAs can be oxidized and/or acetylated to maintain their cellular activity or concentration (Fig. 2). Regulation of PA concentration is mediated by PA oxidases (PAOs) that can be classified depending on their cofactor, flavin adenine dinucleotide (FAD) or copper. Within the FAD-containing enzymes fall acetylated polyamine oxidase (APAO) [75–77], the PA oxidase PAO [7, 78, 79] and the spermine oxidase SpmO [7, 80, 81]. The substrates of PAO and APAO are nonacetylated or acetylated PAs, respectively, O_2 and H_2O. Most PAOs produce smaller PAs, an amino aldehyde and H_2O_2 (Fig. 2). An exception is diamine oxidase (DAO), a copper-containing enzyme that produces ammonia in addition to H_2O_2 (Fig. 2) [82–85]. The amino aldehydes produced can then be precursors for amino acids such as β-alanine and gamma-aminobutyric acid (GABA) and for several different alkaloids (reviewed in Ref. [7]).

The acetylation of Spm or Spd is catalyzed by spermidine/spermine acetyltransferase (SSAT) [86–89]. When SSAT is activated, it leads to PA acetylation that subsequently reduces their positive charge, preventing their interaction with other molecules [90]. These acetylated metabolites are then excreted (reviewed in Ref. [90]) or oxidized by the above-mentioned FAD-dependent APAO. These reactions thus form a cycle that allows the cell to regulate Spd and Spm cellular concentrations quickly [90].

In addition, cells have adapted other mechanisms to regulate PA concentration at this stage [86, 90]. In

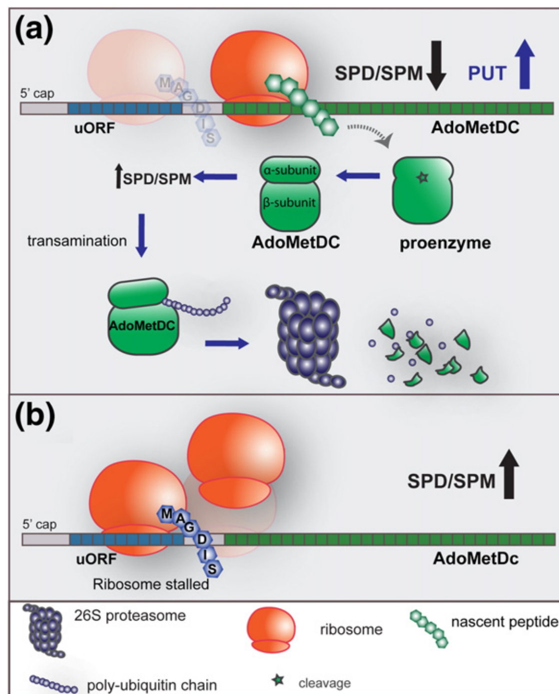

Fig. 4. Regulation of adenosylmethionine decarboxylase (AdoMetDC). (a) AdoMetDC is synthesized as an inactive proenzyme, which becomes active after an internal serinolysis and consequent cleavage into two subunits: α and β. AdoMetDC enzymes can be classified into different groups [64]. Class 1 comprises bacterial and archeal enzymes. Enzymes of this group have oligomeric α/β structures and are divided into two subgroups, depending on whether or not they require Mg^{2+} as a cofactor (1a and 1b, respectively). Class 2 AdoMetDCs include enzymes from plants, fungi and mammals and subdivides into three groups: group 2a comprises the mammalian and yeast dimeric α/β AdoMetDC. In this class, Put stimulates AdoMetDC self-processing, and although it is far from the catalytic domain, the binding of Put leads to its activation [66–68]. Group 2b includes plant monomeric enzymes that do not require Put but instead contain two arginine residues that mimic the role of Put. Group 2c includes the parasitic *Trypanosoma brucei* enzyme that is composed of the α/β subunits and a catalytically dead paralogue named prozyme that is required for AdoMetDC activity [246]. The species in which regulation of AdoMetDC processing and activity is made by Put (group 2a) have higher levels of Spd and Spm than Put, while in species in which this type of regulation is absent, Put is likely the most abundant PA [64]. Upon transamination, AdoMetDC loses its function and is more prone for degradation via the polyubiquitination/proteasome system. Degradation of AdoMetDC is accelerated when cellular levels of Spd and Spm increase. (b) Regulation of translation is known to be mediated by an uORF. The mammalian uORF is located 14 nucleotides downstream of the 5′ cap and encodes a hexapeptide: MAGDIS. When this peptide is being synthesized, ribosomes stall and block access to the AdoMetDC start codon. The duration of the ribosome stalls increases with increasing Spd and Spm levels. Abbreviations: AdoMetDC, adenosylmethionine decarboxylase; Put, putrescine; Spd, spermidine; Spm, spermine.

human cells, the SSAT gene contains a PA-responsive element (PRE) in the 5′ regulatory region that allows transcription to be regulated by PA concentration [91]. Moreover, it was found that Nrf-2 (*n*uclear factor erythroid 2–*r*elated *f*actor *2*) binds constitutively to PRE and when the levels of PAs are high this complex interacts with another protein, PA-modulated factor-1, to activate SSAT transcription [92, 93]. This mechanism was only found in tumor cells that are sensitive to synthetic PA analogues, that is, cells that respond to these compounds by upregulating SSAT and consequently increasing PA catabolism. This indicates that different cell types regulate SSAT dissimilarly [91–93].

SSAT expression can also be modulated during RNA processing by alternative splicing. During its splicing, the intron between exon 3 and exon 4 might be retained. This intron contains multiple codon stops, making this splice variant prone for degradation by nonsense-mediated mRNA decay [94]. There is evidence that this splice variant can give rise to a truncated SSAT protein. In the presence of high levels of PAs or its analogues, the formation of this alternative splice variant is decreased, leading to increased SSAT activity and therefore PA acetylation [86, 95].

SSAT translation can increase drastically in the presence of PAs or synthetic PA analogues [96, 97]. Contrary to other enzymes of the PA pathway, the 5′ or 3′ UTRs do not seem to have the same prominent role in the translational regulation of SSAT [96, 97]. Nonetheless, one or two uORFs can be found depending on the species [98]. Recently, a study using a human embryonic kidney cell line revealed that these uORFs were able to repress SSAT translation [99]. In addition, the initiation region of SSAT mRNA contains a stem–loop that is stabilized by a specific isoform of a protein called nucleolin [99]. This interaction subsequently results in SSAT translation repression (Fig. 5a). PAs at high levels promote the autocatalysis of nucleolin, which likely causes a reduction in the stability of the stem–loop of SSAT and in turn alleviates translation repression (Fig. 5b) [99]. This would then lead to an increase in PA catabolism and re-establishment of PA levels. Finally, for degradation, SSAT is polyubiquitinated and degraded by the 26S proteasome [100]. SSAT has a very short half-life of approximately 20 min [99], which can be extended in the presence of an Spm analogue, such as N^1N^{12}-bis(ethyl)spermine [99].

Controlling Polyamine levels through transport

PA transport has been detected in almost every model organism. In bacteria and single cellular eukaryotes, membrane transport systems are well described (Fig. 2). *E. coli* imports PAs mainly by two ABC (*A*TP *b*inding *c*assettes) type transporters,

PotABCD and PotFGHI, that are Spd preferential and Put specific, respectively [101, 102]. Moreover, there are two uptake/antiporters known as PotE (Orn or Lys/Put) and CadB (Lys/Cad) that uptake Orn or Lys and excrete Put or Cad, respectively [103–105]. These transporters are induced under acidic conditions and also have an important role in the cell's response to acidic stress [104, 105]. In *E. coli*, studies have also shown a Spd exporter (MdtJI) to be important for PA homeostasis since it is capable of rescuing a SSAT knockout strain from the toxicity caused by high levels of Spd [106].

Yeast, a model organism for single cell eukaryotes, has at least 10 transmembrane proteins capable of PA transport. There are four transporters in the plasma membrane involved in the PA uptake: Dur3, Sam3, Agp2 and Gap1 [107–109]. Dur3 and Sam3 are predominantly responsible for PA import [108, 110], while Uga4 dominates PA vacuolar transport [111]. Conversely, yeast has four transporters (Tpo1–Tpo4) that function as PA efflux pumps [7, 112–114]. Tpo1 and Tpo4 are responsible for the transport of Spd, Spm [115] and Put [116], while Tpo2 and Tpo3 only recognize Spm [115]. Deletion of Tpo1, the best-studied PA transporter, shows sensitivity toward high levels of PAs, while its overexpression increases tolerance to excess PA supplementation [117, 118]. Finally, there is also a fifth transporter, Tpo5, that is localized in the Golgi or post-Golgi secretory vesicles and is responsible for the excretion of Put and less effectively of Spd [114]. PA transporters have also been studied in *T. cruzi* and *Leishmania major*. Here, they transport Put, Cad and Spd and share 41.3% identity [9, 10, 119, 120]. As *T. cruzi* lacks ODC, import of PA from external sources is the only way *T. cruzi* can obtain Put or Spd, highlighting the essentiality of PA transport for such organisms.

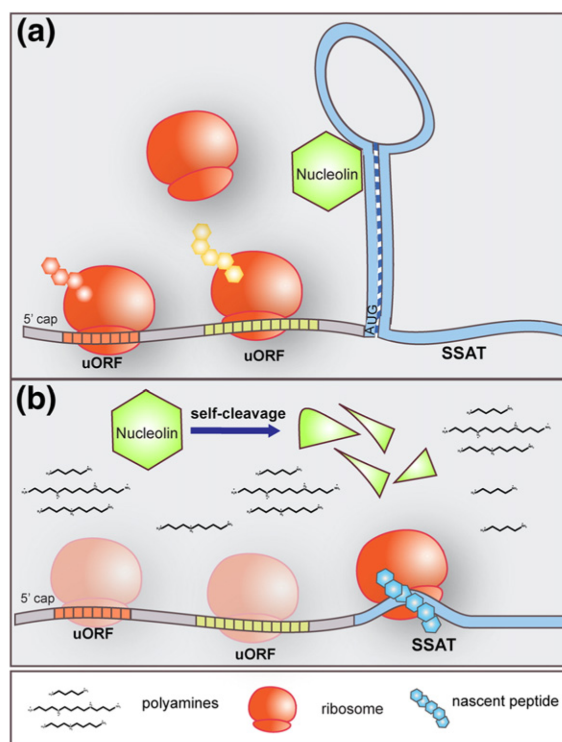

Fig. 5. Mammalian regulation of spermidine/spermine N^1-acetyltransferase (SSAT). (a) SSAT translation is repressed by one or two uORFs and a stem–loop in its mRNA. The stem-loop is stabilized by a specific isoform of nucleolin SSAT translation. (b) SSAT translation increases with an increase in the cellular concentration of PAs or PA analogues. As a consequence, nucleolin undergoes autocatalysis that destabilizes the stem–loop and releases translation repression. This causes an increase in PA catabolism and re-establishment of PA levels. Abbreviations: SSAT, spermidine/spermine N^1-acetyltransferase; PAs, polyamines.

PA-specific transport systems in mammals and plants are less well understood. In mammals, no PA transporter has yet been identified. It has been suggested that such a PA transport system would involve an endocytic mechanism (reviewed in Refs. [103] and [121]). Moreover, it has been proposed that transport systems with other functions such as SLC7 (Lys/Arg/Orn permeases), CCC9 (an inorganic ion transporter) and OCT6 (cation/anion/zwitterion transporter) could also be responsible for PA uptake (reviewed in Ref. [121]). In *Arabidopsis*, PA transport has been attributed to the LAT (*L*-type *a*mino acid *t*ransporter) family [122]. These LAT transporters, particularly RMV1/LAT1/AtPUT3, PAR1/AtLAT4/AtPUT2 and AtLAT3/AtPUT1, are 68–76% similar to each other and are localized in the plasma membrane, Golgi apparatus and endoplasmic reticulum, respectively [122].

The Role of Polyamines in the Cell

Polyamines in gene expression

PAs are important for gene expression due to their ability to bind to nucleic acids and proteins; thus, these molecules can stabilize and remodel the chromatin structure (reviewed in Ref. [123]). For example, the analysis of chromatin structure of nuclei isolated from U-87 MG human brain tumor cells revealed upon PA depletion by treatment with an ODC inhibitor [α-difluoromethylornithine (DFMO)] chromatin condensation is impaired [124].

DNA structural changes mediated by PAs have also shown to modulate the rate of transcription. For example, PAs enhance the affinity of the mammalian estrogenic receptor (ER) for its response elements (ERE) by promoting the transition of the B-DNA to the Z-DNA conformation [125]. PAs can further mediate the activation of c-MYC transcription by

modifying the quadruplex structure (present in the regulatory sequence of this gene) into an active conformation [126]. PAs additionally promote the binding between proteins and DNA. *In vitro* studies using the herpes simplex virus I DNA-binding protein ICP-4 demonstrated that physiological concentrations of Spd and Spm increase the rate of association of this protein to DNA [127].

Most PAs are bound to RNA as shown in bovine lymphocytes, rat liver and *E. coli* (57.2%, 78.3% and 89.7% respectively for Spd bound RNA; Spm: 65.2% and 85.2%, for rat liver and *E. coli*; Put: 47.9% for *E. coli*), suggesting that one of the major roles of PAs is related to structural changes in RNA [128]. It is therefore highly probable that PAs have an essential role in translation.

The "PA modulon" is comprised of a group of genes that increase their translation in the presence of PAs, which in certain cases is cased by an increase of their transcription factors [129, 130]. Members of this modulon have been identified in *E. coli* and eukaryotes in which intracellular PA concentrations have been modified [129–131]. The discovery and analysis of members of this modulon have provided information on mechanisms by which PAs can regulate translation. For example, in *E. coli*, PAs can promote the initiation of translation of mRNAs with distant Shine–Dalgarno sequences [e.g., *oppa*, *rpoN*, *FecI* σ factor (σ^{18}), *Fis*] by bringing the Shine–Dalgarno and the initial codon closer together enabling formation of the initiation complex. This was observed *in vitro* by measuring the fMet-tRNA bound to ribosomes and the sensitivity of synthesized RNAs to RNases in the presence and absence of PAs [131–133]. Moreover, PAs stimulate the interaction between inefficient initiation codons, UUG and GUG, and the fMet-tRNA, which enhance the translation of RNAs such as *cya* and *cra* [128, 131, 134]. In eukaryotes, PAs increase translation of *CCT2*, *HNRP1* and *PGAM1* in mammary carcinoma F3A cells, and *COX4* in yeast by "ribosome shunting" [130, 135]. In this translation mechanism the 40S ribosome bypasses 5′ UTR regions and secondary structures which usually interfere with translation, to reach the start codon [136].

PAs can also participate in the elongation of mRNAs with stop codons inside the coding sequence. Such is the case in *E. coli* for the σ factor regulating general stress response, *rpoS* (σ38). When the *rpoS* mRNA is mutated and has a (UAG) stop in the 33rd position PAs can stimulate the readthrough of this codon by increasing the incorporation of Gln-$tRNA^{supE}$ (a suppressor tRNA) [67, 137].

PAs can also regulate the phosphorylation of different factors involved in translation. Such is the case for NIH3T3 mammalian cells in which the ODC inhibitor, DFMO, promotes changes in the phosphorylation of the translation initiation factor eIF-2α and the translation repressor protein 4E-BP, subsequently leading to the gradual inhibition of translation initiation [138].

Polyamines in cell proliferation

The importance of PAs for cell growth and proliferation has been recognized for decades. In 1957, Kihara and Snell demonstrated that Spm and Spd promote growth of *Lactobacillus casei* [139]. Later in the 1970s, it was described that the concentration of PAs in sea urchin eggs can change cyclically and, further, egg cleavage is severely impaired when PA biosynthesis is inhibited [140, 141]. In bacteria, a decrease in Spd and Put concentrations leads to a reduction in growth rate [142, 143], while this causes a complete arrest of cell proliferation in eukaryotes [143–148]. Curiously, for *S. cerevisiae*, Spd or Spd is essential only under aerobic conditions, which may imply that different PAs are required under different metabolic conditions [147]. Although PA depletion leads to a similar outcome in cell proliferation for prokaryotes and eukaryotes, it seems that PAs affect this process in multiple ways. One explanation of PA involvement in bacterial growth is stimulation of the translation of transcription factors related to growth, such as OppA, Cya and RpoS, which belong to the "PA modulon" [129, 130, 132]. In eukaryotes, PAs play a putative role in cell cycle progression. Here, the PA concentrations and the activities of ODC and AdoMetDC change according to the phase of cell cycle [149–154]. Furthermore, PA-depleted cells are arrested in their cell cycle; however, it is still debated whether this occurs in G1, S or G2 or all of them [144, 145, 150, 155–160].

Another role of PAs in eukaryotic cell proliferation is related to the use of Spd as a substrate for an essential posttranslational modification named hypusination. So far, this modification has only been reported for one protein—the eukaryotic translation initiation factor eIF-5A—on a specific lysine residue [161–163] (reviewed in Ref. [164]). Hypusination involves two consecutive and highly conserved reactions. First, deoxyhypusine synthase (Dys1 in *S. cerevisiae* and DHPS in humans) transfers the 4-aminobutyl moiety of Spd to the ε-amino group of a specific lysine residue in the eIF-5A precursor protein, generating the intermediate deoxyhypusine. This is followed by conversion of deoxyhypusine into hypusine by deoxyhypusine hydroxylase (Lia1 in *S. cerevisiae* and DOHH in humans) activating eIF-5A [165].

Hypusine has been associated with cell proliferation since both eIF-5A and its hypusination are essential for eukaryotes. For instance, in budding yeast, deletion of both eIF-5A homologues (Hyp2 and Anb2) is lethal [164, 166, 167], as well as the deletion of the deoxyhypusine synthase [168, 169].

Expression of an unstable version of eIF-5A (prone for degradation) in a yeast strain deleted for both eIF-5A homologues showed that, upon eIF-5A depletion, cell cycle is arrested [170]. Mutating the eIF-5A lysine target of hypusination in yeast also leads to loss of viability, confirming that hypusine is required for the essential function of eIF-5A. It has been proposed that the major function of Spd in yeast is to serve as a substrate for hypusine modification [171, 172]. In *Caenorhabditis elegans* and *Drosophila melanogaster* the absence of DOHH is lethal. [173–175]. In mice, the homozygous deletion of eIF-5A-1 or DHPS is lethal [176]. Conversely, injection of a human liver cell line, LO2, transfected with eIF-5A in mice caused tumor formation [177]. Altogether, these observations indicate that deoxyhypusine modification of eIF-5A is essential for cell proliferation and survival of eukaryotes.

Role of Polyamines in cellular stress

Cells are continuously exposed to different types of stress, either by products of their own metabolism or by environmental changes in reactive oxygen species (ROS) levels, pH, osmotic pressure and temperature. Extensive literature has demonstrated that PAs are associated with the response and protection to different types of stress which might involve multiple PA properties. It is usually observed that PA intracellular concentrations change during exposure to stress. Moreover, modification of PA concentrations either by exogenous addition or chemical/ genetic methods can influence the sensitivity of cells to stress (reviewed in Refs. [5] and [6]). An example of this is the accumulation of Put during osmotic stress in rat hepatoma cell cultures and plants. In rats, this effect is due to an increase in ODC activity caused by a decrease in the stability of the regulatory enzyme of ODC, AZ [see The regulation of polyamine synthesis through antizyme (AZ) levels] [178]. In plants, when osmotic stress occurs, Put accumulates to toxic levels due to an increase in ADC activity [179, 180], resulting in chlorophyll loss and senescence [181]. Treatment with Spm protects cells from these toxic effects [181] by inhibiting ADC proenzyme posttranslational activation and therefore ADC activity [182]. This modification mediated by Spm suggests that ADC is regulated at the posttranslational level during osmotic stress [179, 181].

PAs have several other functions in the cell for stress protection. This includes scavenging of ROS [183–187], binding to membrane transport proteins [188–190] and regulating expression of proteins related to the stress response [191–196]. PAs can function as ROS scavengers as they are polycationic under physiological pH [183–185]. *In vitro* studies show that PAs can function as scavengers of alkyl, hydroxyl and peroxyl radicals (by Cad, Put, Spd and Spm) and superoxide (by Spd and Spm) using physiological concentrations [183–185]. Indeed, Spm was one of the most efficient ROS scavengers [183–185] for protecting DNA from oxidative stress [183].

Spm prevents the induction of the mitochondrial permeability transition in rat liver mitochondria, by maintaining the reduced state of glutathione (GSH) and the sulfhydryl groups of thiols responsible for the opening of the mitochondrial permeability pore [186]. Conversely, a study in fibroblasts lacking Spm suggests that this PA and Spd protect cells from H_2O_2, but by a different mechanism to GSH [187].

Another function of PAs during stress is to regulate the expression of genes associated with the cell's response and defense mechanisms. For example, in *E. coli*, Put and Spd positively regulate the transcription of stress-related transcription factors OxyR (peroxide detoxification), SoxRS (superoxide radical response) and RpoS (general stress) (reviewed in Ref. [197]). This leads to the expression of downstream targets such as *ahpC* (alkyl hydroperoxide reductase), *katG* (catalase/hydroperoxidase I) and *katE* (hydroperoxidase II) [192, 193]. In yeast, overexpression of the PA exporter, Tpo1, leads to sensitivity to H_2O_2 and prevents the induction of canonical stress proteins including Sod1, Hsp70, Hsp90 and Hsp104. In addition to this phenotype, Tpo1 -overexpressing cells have a prolonged oxidant-induced cell cycle arrest, supporting the hypothesis that these cells are less efficient in responding to stress. It thus appears that an exact concentration of PAs is critical for cells to mount the general stress response [191].

Consistently, Spm appears to protect *Arabidopsis* from heat stress by increasing the expression of stress response genes [194]. Transcriptomic analysis has revealed information on the targets of PAs during the stress response, suggesting new mechanisms by which PAs can protect cells from stress. For example, the pretreatment of tomatoes with Spd before heat shock promoted an increase in expression of signal transduction genes (e.g., calmodulin, serine/threonine protein kinase) along with genes related to PA biosynthesis pathway, hormone pathways, etc. [195]. Moreover, the analysis of transcriptome data from transgenic *Arabidopsis* containing different intracellular concentrations of Put and Spm, revealed that PAs are involved in stress signaling through Ca^{2+}, as well as through interactions with pathways related to abscisic acid [196].

PAs further contribute to osmotic stress protection, by functioning as “osmolytes” (reviewed in Ref. [198]). *E. coli* excrete Put to compensate for charge alterations during this type of stress [199]. Put treatment of tobacco plants 1 h before osmotic stress induced by polyethylene glycol, prevents water loss from cells [200]. PAs also contribute to

the homeostasis of Na^+/K^+ during osmotic stress by regulating the influx of Na^+ and the efflux of K^+ [201]. For example, in plants, the levels of Spm reached under salt stress modulate the activity of Ca^{2+} channels, avoiding changes in Na^+/K^+ balance [188].

Other function of PAs during stress can be related to their binding capacity to proteins. Put, Cad, Spd and Spm can bind to porins (OmpF and OmpC) in *E. coli*, which are membrane proteins that function as channels, inhibiting porin activity [189]. In particular, this inhibition helps cells counteract the acidic and osmotic stress conditions [190, 202].

Finally, a well-described mechanism in which a PA is involved in the stress response is the role of Cad in *E. coli* under acidic pH stress. This low pH causes an activation of the transcriptional factor, *cadC*, from the operon *cadAB*, which encodes for the inducible lysine decarboxylase, *cadA*, and the Lys/Cad antiporter, *cadB* [203]. The proposed mechanism involved in the acidic stress response includes (i) the consumption of a proton by lysine decarboxylase for the synthesis of Cad [4], (ii) the excretion of this diamine by *cadB* [105] and finally (iii) the partial inhibition of porins by Cad. This latter mechanism has been proposed to control the influx/efflux of substances to allow cells to adapt to the acidic stress [202].

Polyamines in human disease

Only one genetic disease, the Snyder-Robinson syndrome, has been directly linked to a genetic defect in the PA biosynthesis pathway [204]. This disease is a rare X-linked mental retardation disorder caused by mutations in the gene that encodes Spm synthase. Mutations in this enzyme reduce the levels of Spm in lymphocytes and fibroblasts, leading to deregulated Spd/Spm ratios. Further, apart from mental retardation, this PA imbalance causes many additional symptoms such as osteoporosis, facial asymmetry and hypotonia [204].

Due to the importance of PAs in so many molecular mechanisms, the number of human diseases that are associated with PAs is considerable. The list continuously increases as PAs are repeatedly found to be deregulated in metabolomics studies. PAs have known to be associated with cancer for more than 45 years, since Russel and Snyder observed increased ODC activity in tumors [205]. Since then, mounting evidence strongly supports the role of PAs in cancer. For example, PAs have increased abundance in urine and blood of many cancer patients relative to healthy individuals [206, 207]. Additionally, ODC is found increased in many cancers [208]. ODC is a target of the oncogene *MYC* [209] and is itself a potential oncogene as its overexpression can transform mammalian cell lines alone or together with other oncogenes [210–212]. Moreover, a polymorphism in intron 1 of ODC is considered a risk factor for colon cancer [213]. Transgenic mice models overexpressing ODC in skin showed that ODC can lead to the formation of spontaneous skin tumors, confirming *in vitro* cell results [214]. Studies with these models have also shown that reducing the levels of PAs may limit tumorigenesis [215, 216]. Other players of the PA pathway have also been associated with cancer. For example, high levels of SpmO were detected in several cancer types [217, 218], and *in vivo* studies in mice suggest that AZ (Fig. 3) can function as a tumor suppressor [219].

Despite the strong association of PAs with cancer, attempts to use this pathway as a therapeutic target have failed so far. Several drugs targeting different steps in the PA metabolic pathway have been developed, but their efficacy in treating cancer largely falls short of clinical success. Initial tests with DFMO, an inhibitor of ODC, were promising, appearing to be cytostatic or at least to slow down growth in mammalian cells; further, DFMO revealed anticancer activity in mice models [220, 221]. Conveniently, DFMO is approved by the Food and Drug Administration, to treat African *trypanosomiasis* (sleeping sickness), which has facilitated broader tests [222]. However, neither alone nor in combination with other agents was DFMO clinically effective. To overcome these caveats, an attempt is currently being undertaken to find synthetic PA analogues that (i) do not replace the natural PAs functionally, (ii) are taken up by cells competing with the import of natural PAs and (iii) have the capacity to decrease the PA levels by increasing their catabolism [223]. Moreover, despite observations that PA levels are higher in blood and urine in cancer patients, it has still not been confirmed whether PAs can be used as a prognostic marker [224]. Due to these setbacks, the authors speculate that, for developing a successful PA therapeutic agent, it will first be required to elaborate which biological role PAs play in cancer (and in cells in general) so that the cancer relevant functions can be specifically targeted.

Furthermore, PAs have been associated with aging and neurodegeneration. In several organisms, including yeast and humans, the levels of PAs decrease with age. Remarkably, restoring their levels is beneficial [225, 226]. Supplemented Spd increased the lifespan of *S. cerevisiae*, *D. melanogaster* and human peripheral blood mononuclear cells [225]. It was recently shown that feeding *D. melanogaster* with Spd prevents age-related memory decline, most likely as a result of enhanced autophagy [227]. In addition, Spm prevents lipopolysaccharide-induced memory deficit in mice via the ionotropic glutamate receptor GluN2B [228].

Unlike observations made for aging, in neurodegenerative diseases such as Parkinson's disease

(PD) and Alzheimer's disease (AD), certain PAs have increased levels. Metabolic profiling of serum samples of PD patients suggested that alteration of PA metabolism can be used to predict cases of rapid progression [229]. In another study, PD patients were found to have higher concentrations of Put, Cad, acetylated derivatives of Cad and Spd (N^1-acetyl-Cad and N^1-acetyl-Spd) and lower levels of Spd in the cerebrospinal fluid. In red blood cells of PD patients, Put levels are decreased and Spd and Spm levels are increased [230]. Similar to these results from PD, metabolic profiling of brains of AD patients revealed elevated levels of Put, Spd, Spm and acetylated Spd and Spm [231].

In *in vitro* studies, Spd accelerated misfolding and aggregation of α-synuclein (associated with PD [232]), while aggregates of amyloid-β (associated with AD) were potentiated by Put, Spd and Spm [233]. In addition, Spm enhanced α-synuclein toxicity in a PD yeast model [234]. Furthermore, PAs together with glutamyl residues can be incorporated into proteins, such as neuronal tubulin, by transglutaminases (TG) forming the irreversible posttranslational modification γ-glutamylamine [235–240]. Abnormal TG activity is hypothesized to contribute to the pathogenesis of neurodegenerative diseases, by contributing to formation and stabilization of proteinaceous aggregates [235–240].

Whether the increase in PA levels is a cause or consequence of these pathologies is still unclear. However, PAs have also shown to induce autophagy [225, 241] to protect cells from stress thus, potentially, they could be neuroprotective and this could be the reason why PAs are increased in neurodegenerative diseases. On the other hand, an increase in PAs is cytotoxic and can lead to increased formation of toxic metabolites including aldehydes and H_2O_2 [242, 243]. Lastly, the increase of PAs in PD and AD could simply be due to levels of their enzymes increasing as a result of proteasomal impairment, a hallmark of these diseases [244]. Despite these initial observations, additional studies, with *in vivo* models, are required to understand if aggregation promoted by PAs is neuroprotective or contributes to neurotoxicity.

Concluding Remarks

PAs are a fundamental class of positively charged metabolites ubiquitous in nature. PAs are involved in several cellular processes including transcription, translation, stress protection and metabolism; subsequently, they are found to be important for growth, aging and many diseases such as cancer and neurodegeneration. The role of PAs is ancient, and both metabolism and concentration levels are tightly regulated at distinct stages. The regulation of PA levels involves multiple, unique and unusual conserved mechanisms, implying a fundamental importance of maintaining PAs at the correct cellular balance and concentration. A general concept that would unify these findings, for instance, a common chemical or physical process that can only operate by the presence of a PA, has not yet been presented. Solving the puzzle about the role of PAs might thus reveal a key feature in cellular and molecular biology that for now remains to be discovered.

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Abbreviations used:
uORF, upstream open reading frame; ORF, open reading frame; UTR, untranslated region; FAD, flavin adenine dinucleotide; DFMO, α-difluoromethylornithine; ROS, reactive oxygen species; PD, Parkinson's disease; AD, Alzheimer's disease.

References

[1] H. Tabor, C.W. Tabor, Spermidine, spermine, and related amines, Pharmacol. Rev. 16 (1964) 245–300.
[2] U. Bachrach, The early history of polyamine research, Plant Physiol. Biochem. 48 (2010) 490–495.
[3] S.S. Cohen, A guide to polyamines, Oxford University Press, Oxford, United Kingdom, 1997.
[4] P. Shah, E. Swiatlo, A multifaceted role for polyamines in bacterial pathogens, Mol. Microbiol. 68 (2008) 4–16.
[5] L. Valdés-Santiago, J. Ruiz-Herrera, Stress and polyamine metabolism in fungi, Front. Chem. 1 (2013) 42.

[6] H.J. Rhee, E.-J. Kim, J.K. Lee, Physiological polyamines: simple primordial stress molecules, J. Cell. Mol. Med. 11 (2007) 685–703.

[7] T. Kusano, T. Berberich, C. Tateda, Y. Takahashi, Polyamines: essential factors for growth and survival, Planta 228 (2008) 367–381.

[8] C. Carrillo, S. Cejas, N.S. González, I.D. Algranati, *Trypanosoma cruzi* epimastigotes lack ornithine decarboxylase but can express a foreign gene encoding this enzyme, FEBS Lett. 454 (1999) 192–196.

[9] C. Hanfrey, S. Sommer, M.J. Mayer, D. Burtin, A.J. Michael, *Arabidopsis* polyamine biosynthesis: absence of ornithine decarboxylase and the mechanism of arginine decarboxylase activity, Plant J. 27 (2001) 551–560.

[10] M.P. Hasne, I. Coppens, R. Soysa, B. Ullman, A high-affinity putrescine-cadaverine transporter from *Trypanosoma cruzi*, Mol. Microbiol. 76 (2010) 78–91.

[11] S.A. Le Quesne, A.H. Fairlamb, Regulation of a high-affinity diamine transport system in *Trypanosoma cruzi* epimastigotes, Biochem. J. 316 (1996) 481–486.

[12] P.C. Tomar, N. Lakra, S.N. Mishra, Cadaverine: a lysine catabolite involved in plant growth and development, Plant Signal Behav. 8 (2013) 1–15.

[13] Y. Yamamoto, Y. Miwa, K. Miyoshi, J. Furuyama, H. Ohmori, The *Escherichia coli ldcC* gene encodes another lysine decarboxylase, probably a constitutive enzyme, Genes Genet. Syst. 72 (1997) 167–172.

[14] A. Romano, H. Trip, J.S. Lolkema, P.M. Lucas, Three-component lysine/ornithine decarboxylation system in *Lactobacillus saerimneri* 30a, J. Bacteriol. 195 (2013) 1249–1254.

[15] Y. Tanaka, B. Kimura, H. Takahashi, T. Watanabe, H. Obata, A. Kai, et al., Lysine decarboxylase of *Vibrio parahaemolyticus*: kinetics of transcription and role in acid resistance, J. Appl. Microbiol. 104 (2008) 1283–1293.

[16] A.E. Pegg, S. McGill, Decarboxylation of ornithine and lysine in rat tissues, Biochim. Biophys. Acta 568 (1979) 416–427.

[17] P.A. Whitney, D.R. Morris, Polyamine auxotrophs of *Saccharomyces cerevisiae*, J. Bacteriol. 134 (1978) 214–220.

[18] T.J. Paulus, P. Kiyono, R.H. Davis, Polyamine-deficient *Neurospora crassa* mutants and synthesis of cadaverine, J. Bacteriol. 152 (1982) 291–297.

[19] D. Walters, T. Cowley, Formation of cadaverine derivatives in *Saccharomyces cerevisiae*, FEMS Microbiol. Lett. 145 (1996) 255–259.

[20] U. Bachrach, A. Shtorch, Formation of cadaverine as an effect of alpha-difluoromethylornithine on chick embryo fibroblasts transformed with rous sarcoma virus, Cancer Res. 45 (1985) 2159–2164.

[21] K. Igarashi, K. Kashiwagi, H. Hamasaki, A. Miura, T. Kakegawa, S. Hirose, et al., Formation of a compensatory polyamine by *Escherichia coli* polyamine-requiring mutants during growth in the absence of polyamines, J. Bacteriol. 166 (1986) 128–134.

[22] A.E. Pegg, Polyamine metabolism and its importance in neoplastic growth and a target for chemotherapy, Cancer Res. 48 (1988) 759–774.

[23] M.S. Abrahamsen, D.R. Morris, Cell type-specific mechanisms of regulating expression of the ornithine decarboxylase gene after growth stimulation, Mol. Cell. Biol. 10 (1990) 5525–5528.

[24] G.D. Luk, S.B. Baylin, Ornithine decarboxylase as a biologic marker in familial colonic polyposis, N. Engl. J. Med. 311 (1984) 80–83.

[25] A.F. Gazdar, H.B. Stull, L.J. Kilton, U. Bachrach, Increased ornithine decarboxylase activity in murine sarcoma virus infected cells, Nature 262 (1976) 696–698.

[26] S. Don, U. Bachrach, Polyamine metabolism in normal and in virus-transformed chick embryo fibroblasts, Cancer Res. 35 (1975) 3618–3622.

[27] S.E. Patchett, P.H. Katelaris, Z.W. Zhang, E.M. Alstead, P. Domizio, M.J. Farthing, Ornithine decarboxylase activity is a marker of premalignancy in longstanding *Helicobacter pylori* infection, Gut 39 (1996) 807–810.

[28] R.B. Pillai, V. Tolia, R. Rabah, P.M. Simpson, R. Vijesurier, C.H. Lin, Increased colonic ornithine decarboxylase activity in inflammatory bowel disease in children, Dig. Dis. Sci. 44 (1999) 1565–1570.

[29] A.E. Pegg, Regulation of ornithine decarboxylase, J. Biol. Chem. 281 (2006) 14529–14532.

[30] A.J. Wagner, C. Meyers, L.A. Laimins, N. Hay, c-Myc induces the expression and activity of ornithine decarboxylase, Cell Growth Differ. 4 (1993) 879–883.

[31] B. Zhao, A.P. Butler, Core promoter involvement in the induction of rat ornithine decarboxylase by phorbol esters, Mol. Carcinog. 32 (2001) 92–99.

[32] C. Qin, I. Samudio, S. Ngwenya, S. Safe, Estrogen-dependent regulation of ornithine decarboxylase in breast cancer cells through activation of nongenomic cAMP-dependent pathways, Mol. Carcinog. 40 (2004) 160–170.

[33] L.M. Shantz, A.E. Pegg, Translational regulation of ornithine decarboxylase and other enzymes of the polyamine pathway, Int. J. Biochem. Cell Biol. 31 (1999) 107–122.

[34] L.M. Shantz, R.H. Hu, A.E. Pegg, Regulation of ornithine decarboxylase in a transformed cell line that overexpresses translation initiation factor eIF-4E, Cancer Res. 56 (1996) 3265–3269.

[35] S.H. Kwak, S.H. Lee, The regulation of ornithine decarboxylase gene expression by sucrose and small upstream open reading frame in tomato (*Lycopersicon esculentum* Mill), Plant Cell Physiol. 42 (2001) 314–323.

[36] I.P. Ivanov, G. Loughran, J.F. Atkins, uORFs with unusual translational start codons autoregulate expression of eukaryotic ornithine decarboxylase homologs, Proc. Natl. Acad. Sci. U. S. A. 105 (2008) 10079–10084.

[37] S. Pyronnet, L. Pradayrol, N. Sonenberg, A cell cycle-dependent internal ribosome entry site, Mol. Cell 5 (2000) 607–616.

[38] D.H. Russell, S.H. Snyder, Amine synthesis in regenerating rat liver: extremely rapid turnover of ornithine decarboxylase, Mol. Pharmacol. 5 (1969) 253–262.

[39] K. Iwami, J.Y. Wang, R. Jain, S. McCormack, L.R. Johnson, Intestinal ornithine decarboxylase: half-life and regulation by putrescine, Am. J. Physiol. 258 (1990) G308–G315.

[40] Y. Murakami, S. Matsufuji, T. Kameji, S. Hayashi, K. Igarashi, T. Tamura, et al., Ornithine decarboxylase is degraded by the 26S proteasome without ubiquitination, Nature 360 (1992) 597–599.

[41] J. Erales, P. Coffino, Ubiquitin-independent proteasomal degradation, Biochim. Biophys. Acta 2014 (1843) 216–221.

[42] J.E. Kay, V.J. Lindsay, Control of ornithine decarboxylase activity in stimulated human lymphocytes by putrescine and spermidine, Biochem. J. 132 (1973) 791–796.

[43] J.S. Heller, W.F. Fong, E.S. Canellakis, Induction of a protein inhibitor to ornithine decarboxylase by the end products of its reaction, Proc. Natl. Acad. Sci. U. S. A. 73 (1976) 1858–1862.

[44] Y. Miyazaki, S. Matsufuji, S. Hayashi, Cloning and characterization of a rat gene encoding ornithine decarboxylase antizyme, Gene 113 (1992) 191–197.
[45] X. Li, P. Coffino, Degradation of ornithine decarboxylase: exposure of the C-terminal target by a polyamine-inducible inhibitory protein, Mol. Cell. Biol. 13 (1993) 2377–2383.
[46] X. Li, B. Stebbins, L. Hoffman, G. Pratt, M. Rechsteiner, P. Coffino, The N terminus of antizyme promotes degradation of heterologous proteins, J. Biol. Chem. 271 (1996) 4441–4446.
[47] M. Zhang, C.M. Pickart, P. Coffino, Determinants of proteasome recognition of ornithine decarboxylase, a ubiquitin-independent substrate, EMBO J. 22 (2003) 1488–1496.
[48] D. Gödderz, E. Schäfer, R. Palanimurugan, R.J. Dohmen, The N-terminal unstructured domain of yeast ODC functions as a transplantable and replaceable ubiquitin-independent degron, J. Mol. Biol. 407 (2011) 354–367.
[49] S.K. Lim, G. Gopalan, Antizyme1 mediates AURKAIP1-dependent degradation of Aurora-A, Oncogene 26 (2007) 6593–6603.
[50] C.A. Panagiotidis, S.C. Huang, S.A. Tsirka, D.A. Kyriakidis, E.S. Canellakis, Regulation of polyamine biosynthesis in *Escherichia coli* by the acidic antizyme and the ribosomal proteins S20 and L34, Adv. Exp. Med. Biol. 250 (1988) 13–24.
[51] I.P. Ivanov, J.F. Atkins, Ribosomal frameshifting in decoding antizyme mRNAs from yeast and protists to humans: close to 300 cases reveal remarkable diversity despite underlying conservation, Nucleic Acids Res. 35 (2007) 1842–1858.
[52] E.E. Lioliou, D.A. Kyriakidis, The role of bacterial antizyme: from an inhibitory protein to A-to-C transcriptional regulator, Microb. Cell Factories 3 (2004) 8.
[53] R. Palanimurugan, H. Scheel, K. Hofmann, R.J. Dohmen, Polyamines regulate their synthesis by inducing expression and blocking degradation of ODC antizyme, EMBO J. 23 (2004) 4857–4867.
[54] K. Sakata, K. Kashiwagi, K. Igarashi, Properties of a polyamine transporter regulated by antizyme, Biochem. J. 347 (2000) 297–303.
[55] K. Hoshino, E. Momiyama, K. Yoshida, K. Nishimura, S. Sakai, T. Toida, et al., Polyamine transport by mammalian cells and mitochondria: role of antizyme and glycosaminoglycans, J. Biol. Chem. 280 (2005) 42801–42808.
[56] L. Kurian, R. Palanimurugan, D. Gödderz, R.J. Dohmen, Polyamine sensing by nascent ornithine decarboxylase antizyme stimulates decoding of its mRNA, Nature 477 (2011) 490–494.
[57] K. Fujita, Y. Murakami, S. Hayashi, A macromolecular inhibitor of the antizyme to ornithine decarboxylase, Biochem. J. 204 (1982) 647–652.
[58] S. Gandre, Z. Bercovich, C. Kahana, Mitochondrial localization of antizyme is determined by context-dependent alternative utilization of two AUG initiation codons, Mitochondrion 2 (2003) 245–256.
[59] N. Murai, Y. Murakami, S. Matsufuji, Identification of nuclear export signals in antizyme-1, J. Biol. Chem. 278 (2003) 44791–44798.
[60] A. Gritli-Linde, J. Nilsson, M. Bohlooly-Y, O. Heby, A. Linde, Nuclear translocation of antizyme and expression of ornithine decarboxylase and antizyme are developmentally regulated, Dev. Dyn. 220 (2001) 259–275.
[61] A.E. Pegg, *S*-Adenosylmethionine decarboxylase, Essays Biochem. 46 (2009) 25–45.
[62] S. Bale, S.E. Ealick, Structural biology of *S*-adenosylmethionine decarboxylase, Amino Acids 38 (2010) 451–460.
[63] W.D. Tolbert, J.L. Ekstrom, I.I. Mathews, J.A. Secrist, P. Kapoor, A.E. Pegg, et al., The structural basis for substrate specificity and inhibition of human *S*-adenosylmethionine decarboxylase, Biochemistry 40 (2001) 9484–9494.
[64] S. Bale, M.M. Lopez, G.I. Makhatadze, Q. Fang, A.E. Pegg, S.E. Ealick, Structural basis for putrescine activation of human *S*-adenosylmethionine decarboxylase, Biochemistry 47 (2008) 13404–13417.
[65] J.L. Ekstrom, W.D. Tolbert, H. Xiong, A.E. Pegg, S.E. Ealick, Structure of a human *S*-adenosylmethionine decarboxylase self-processing ester intermediate and mechanism of putrescine stimulation of processing as revealed by the H243A mutant, Biochemistry 40 (2001) 9495–9504.
[66] R. Dayoub, W.E. Thasler, A.K. Bosserhoff, T. Singer, K.-W. Jauch, H.J. Schlitt, et al., Regulation of polyamine synthesis in human hepatocytes by hepatotrophic factor augmenter of liver regeneration, Biochem. Biophys. Res. Commun. 345 (2006) 181–187.
[67] A.E. Pegg, Mammalian polyamine metabolism and function, IUBMB Life 61 (2009) 880–894.
[68] K. Lam, L. Zhang, M. Bewick, R.M. Lafrenie, HSG cells differentiated by culture on extracellular matrix involves induction of *S*-adenosylmethione decarboxylase and ornithine decarboxylase, J. Cell. Physiol. 203 (2005) 353–361.
[69] J.R. Hill, D.R. Morris, Cell-specific translational regulation of *S*-adenosylmethionine decarboxylase mRNA. Dependence on translation and coding capacity of the cis-acting upstream open reading frame, J. Biol. Chem. 268 (1993) 726–731.
[70] A. Raney, G.L. Law, G.J. Mize, D.R. Morris, Regulated translation termination at the upstream open reading frame in *S*-adenosylmethionine decarboxylase mRNA, J. Biol. Chem. 277 (2002) 5988–5994.
[71] G.L. Law, A. Raney, C. Heusner, D.R. Morris, Polyamine regulation of ribosome pausing at the upstream open reading frame of *S*-adenosylmethionine decarboxylase, J. Biol. Chem. 276 (2001) 38036–38043.
[72] C. Hanfrey, K.A. Elliott, M. Franceschetti, M.J. Mayer, C. Illingworth, A.J. Michael, A dual upstream open reading frame-based autoregulatory circuit controlling polyamine-responsive translation, J. Biol. Chem. 280 (2005) 39229–39237.
[73] S. Nasizadeh, L. Persson, Extremely rapid turnover of *S*-adenosylmethionine decarboxylase in *Crithidia fasciculata*, FEBS Lett. 553 (2003) 131–134.
[74] A. Yerlikaya, B.A. Stanley, *S*-Adenosylmethionine decarboxylase degradation by the 26S proteasome is accelerated by substrate-mediated transamination, J. Biol. Chem. 279 (2004) 12469–12478.
[75] T. Wu, V. Yankovskaya, W.S. McIntire, Cloning, sequencing, and heterologous expression of the murine peroxisomal flavoprotein, N1-acetylated polyamine oxidase, J. Biol. Chem. 278 (2003) 20514–20525.
[76] T. Murray-Stewart, Y. Wang, W. Devereux, R.A. Casero, Cloning and characterization of multiple human polyamine oxidase splice variants that code for isoenzymes with different biochemical characteristics, Biochem. J. 368 (2002) 673–677.
[77] J. Landry, R. Sternglanz, Yeast Fms1 is a FAD-utilizing polyamine oxidase, Biochem. Biophys. Res. Commun. 303 (2003) 771–776.
[78] P. Tavladoraki, M.N. Rossi, G. Saccuti, M.A. Perez-Amador, F. Polticelli, R. Angelini, et al., Heterologous expression and biochemical characterization of a polyamine oxidase from *Arabidopsis* involved in polyamine back conversion, Plant Physiol. 141 (2006) 1519–1532.

[79] M. Cervelli, A. Cona, R. Angelini, F. Polticelli, R. Federico, P. Mariottini, A barley polyamine oxidase isoform with distinct structural features and subcellular localization, Eur. J. Biochem. 268 (2001) 3816–3830.
[80] M. Cervelli, F. Polticelli, R. Federico, P. Mariottini, Heterologous expression and characterization of mouse spermine oxidase, J. Biol. Chem. 278 (2003) 5271–5276.
[81] P. Fincato, P.N. Moschou, V. Spedaletti, R. Tavazza, R. Angelini, R. Federico, et al., Functional diversity inside the *Arabidopsis* polyamine oxidase gene family, J. Exp. Bot. 62 (2011) 1155–1168.
[82] S.G. Møller, M.J. McPherson, Developmental expression and biochemical analysis of the *Arabidopsis atao1* gene encoding an H_2O_2-generating diamine oxidase, Plant J. 13 (1998) 781–791.
[83] H.M.A. Awal, E. Hirasawa, Diamine oxidase from millet catalyzes the oxidation of 1,3 diaminopropane, J. Plant Res. 108 (1995) 395–397.
[84] T. Biegański, J. Kusche, W. Lorenz, R. Hesterberg, C.D. Stahlknecht, K.D. Feussner, Distribution and properties of human intestinal diamine oxidase and its relevance for the histamine catabolism, Biochim. Biophys. Acta 756 (1983) 196–203.
[85] M.L. Di Paolo, F. Vianello, R. Stevanato, A. Rigo, Kinetic characterization of soybean seedling amine oxidase, Arch. Biochem. Biophys. 323 (1995) 329–334.
[86] A.E. Pegg, Spermidine/spermine-*N*(1)-acetyltransferase: a key metabolic regulator, Am. J. Physiol. Endocrinol. Metab. 294 (2008) E995–E1010.
[87] J.I. Fukuchi, K. Kashiwagi, K. Takio, K. Igarashi, Properties and structure of spermidine acetyltransferase in *Escherichia coli*, J. Biol. Chem. 269 (1994) 22581–22585.
[88] B. Liu, A. Sutton, R. Sternglanz, A yeast polyamine acetyltransferase, J. Biol. Chem. 280 (2005) 16659–16664.
[89] T. Cook, D. Roos, M. Morada, G. Zhu, J.S. Keithly, J.E. Feagin, et al., Divergent polyamine metabolism in the Apicomplexa, Microbiology 153 (2007) 1123–1130.
[90] N. Seiler, Functions of polyamine acetylation, Can. J. Physiol. Pharmacol. 65 (1987) 2024–2035.
[91] Y. Wang, The identification of a *cis*-element and a *trans*-acting factor involved in the response to polyamines and polyamine analogues in the regulation of the human spermidine/spermine N^1-acetyltransferase gene transcription, J. Biol. Chem. 273 (1998) 34623–34630.
[92] Y. Wang, W. Devereux, T.M. Stewart, R.A. Casero, Cloning and characterization of human polyamine-modulated factor-1, a transcriptional cofactor that regulates the transcription of the spermidine/spermine *N*(1)-acetyltransferase gene, J. Biol. Chem. 274 (1999) 22095–22101.
[93] Y. Wang, W. Devereux, T.M. Stewart, R.A. Casero, Characterization of the interaction between the transcription factors human polyamine modulated factor (PMF-1) and NF-E2-related factor 2 (Nrf-2) in the transcriptional regulation of the spermidine/spermine N^1-acetyltransferase (SSAT) gene, Biochem. J. 355 (2001) 45–49.
[94] M.T. Hyvönen, A. Uimari, T.A. Keinänen, S. Heikkinen, R. Pellinen, T. Wahlfors, et al., Polyamine-regulated unproductive splicing and translation of spermidine/spermine N^1-acetyltransferase, RNA 12 (2006) 1569–1582.
[95] K. Kim, J.-H. Ryu, J.-W. Park, M.-S. Kim, Y.-S. Chun, Induction of a SSAT isoform in response to hypoxia or iron deficiency and its protective effects on cell death, Biochem. Biophys. Res. Commun. 331 (2005) 78–85.
[96] N.J. Butcher, G.M. Broadhurst, R.F. Minchin, Polyamine-dependent regulation of spermidine-spermine N^1-acetyltransferase mRNA translation, J. Biol. Chem. 282 (2007) 28530–28539.
[97] L. Parry, R. Balaña Fouce, A.E. Pegg, Post-transcriptional regulation of the content of spermidine/spermine N^1-acetyltransferase by N^1N^{12}-bis(ethyl)spermine, Biochem. J. 305 (1995) 451–458.
[98] I.P. Ivanov, J.F. Atkins, A.J. Michael, A profusion of upstream open reading frame mechanisms in polyamine-responsive translational regulation, Nucleic Acids Res. 38 (2010) 353–359.
[99] O. Perez-Leal, C.A. Barrero, A.B. Clarkson, R.A. Casero, S. Merali, Polyamine-regulated translation of spermidine/spermine-N^1-acetyltransferase, Mol. Cell. Biol. 32 (2012) 1453–1467.
[100] C.S. Coleman, A.E. Pegg, Polyamine analogues inhibit the ubiquitination of spermidine/spermine N^1-acetyltransferase and prevent its targeting to the proteasome for degradation, Biochem. J. 358 (2001) 137–145.
[101] K. Kashiwagi, S. Miyamoto, E. Nukui, H. Kobayashi, K. Igarashi, Functions of PotA and PotD proteins in spermidine-preferential uptake system in *Escherichia coli*, J. Biol. Chem. 268 (1993) 19358–19363.
[102] K. Igarashi, K. Ito, K. Kashiwagi, Polyamine uptake systems in *Escherichia coli*, Res. Microbiol. 152 (2001) 271–278.
[103] K. Igarashi, K. Kashiwagi, Characteristics of cellular polyamine transport in prokaryotes and eukaryotes, Plant Physiol. Biochem. 48 (2010) 506–512.
[104] K. Kashiwagi, S. Shibuya, H. Tomitori, A. Kuraishi, K. Igarashi, Excretion and uptake of putrescine by the PotE protein in *Escherichia coli*, J. Biol. Chem. 272 (1997) 6318–6323.
[105] W. Soksawatmaekhin, A. Kuraishi, K. Sakata, K. Kashiwagi, K. Igarashi, Excretion and uptake of cadaverine by CadB and its physiological functions in *Escherichia coli*, Mol. Microbiol. 51 (2004) 1401–1412.
[106] K. Higashi, H. Ishigure, R. Demizu, T. Uemura, K. Nishino, A. Yamaguchi, et al., Identification of a spermidine excretion protein complex (MdtJI) in *Escherichia coli*, J. Bacteriol. 190 (2008) 872–878.
[107] T. Uemura, K. Kashiwagi, K. Igarashi, Uptake of putrescine and spermidine by Gap1p on the plasma membrane in *Saccharomyces cerevisiae*, Biochem. Biophys. Res. Commun. 328 (2005) 1028–1033.
[108] T. Uemura, K. Kashiwagi, K. Igarashi, Polyamine uptake by DUR3 and SAM3 in *Saccharomyces cerevisiae*, J. Biol. Chem. 282 (2007) 7733–7741.
[109] M. Aouida, A. Leduc, R. Poulin, D. Ramotar, AGP2 encodes the major permease for high affinity polyamine import in *Saccharomyces cerevisiae*, J. Biol. Chem. 280 (2005) 24267–24276.
[110] M. Aouida, M. Rubio-Texeira, J.M. Thevelein, R. Poulin, D. Ramotar, Agp2, a member of the yeast amino acid permease family, positively regulates polyamine transport at the transcriptional level, PLoS One 8 (6) (2013 Jun 3) e65717.
[111] T. Uemura, Y. Tomonari, K. Kashiwagi, K. Igarashi, Uptake of GABA and putrescine by UGA4 on the vacuolar membrane in *Saccharomyces cerevisiae*, Biochem. Biophys. Res. Commun. 315 (2004) 1082–1087.
[112] K. Igarashi, K. Kashiwagi, Polyamine transport in bacteria and yeast, Biochem J 344 (Pt 3) (1999) 633–642.
[113] K. Kashiwagi, K. Igarashi, Identification and assays of polyamine transport systems in *Escherichia coli* and

Saccharomyces cerevisiae, Methods Mol. Biol 720 (2011) 295–308.
[114] K. Tachihara, T. Uemura, K. Kashiwagi, K. Igarashi, Excretion of putrescine and spermidine by the protein encoded by YKL174c (TPO5) in *Saccharomyces cerevisiae*, J. Biol. Chem. 280 (2005) 12637–12642.
[115] H. Tomitori, K. Kashiwagi, T. Asakawa, Y. Kakinuma, A.J. Michael, K. Igarashi, Multiple polyamine transport systems on the vacuolar membrane in yeast, Biochem. J. 353 (2001) 681–688.
[116] L. Valdés-Santiago, J.A. Cervantes-Chávez, C.G. León-Ramírez, J. Ruiz-Herrera, Polyamine metabolism in fungi with emphasis on phytopathogenic species, J. Amino Acids 2012 (2012) 837932.
[117] M.C. Teixeira, T.R. Cabrito, Z.M. Hanif, R.C. Vargas, S. Tenreiro, I. Sá-Correia, Yeast response and tolerance to polyamine toxicity involving the drug: H+ antiporter Qdr3 and the transcription factors Yap1 and Gcn4, Microbiology 157 (2011) 945–956.
[118] M. Albertsen, I. Bellahn, R. Krämer, S. Waffenschmidt, Localization and function of the yeast multidrug transporter Tpo1p, J. Biol. Chem. 278 (2003) 12820–12825.
[119] V. Olin-Sandoval, R. Moreno-Sánchez, E. Saavedra, Targeting trypanothione metabolism in trypanosomatid human parasites, Curr. Drug Targets 11 (12) (2010 Dec) 1614–1630.
[120] M.P. Hasne, B. Ullman, Identification and characterization of a polyamine permease from the protozoan parasite *Leishmania major*, J. Biol. Chem. 280 (2005) 15188–15194.
[121] R. Poulin, R.A. Casero, D. Soulet, Recent advances in the molecular biology of metazoan polyamine transport, Amino Acids 42 (2012) 711–723.
[122] M.S.K. Fujita, Identification of polyamine transporters in plants:paraquat transport provides crucial clues, Plant Cell Physiol. 55 (2014) 855–861.
[123] A.C. Childs, D.J. Mehta, E.W. Gerner, Polyamine-dependent gene expression, Cell. Mol. Life Sci. 60 (2003) 1394–1406.
[124] H.S. Basu, M.C. Sturkenboom, J.G. Delcros, P.P. Csokan, J. Szollosi, B.G. Feuerstein, et al., Effect of polyamine depletion on chromatin structure in U-87 MG human brain tumour cells, Biochem. J. 282 (1992) 723–727.
[125] T. Thomas, M.A. Gallo, C.M. Klinge, T.J. Thomas, Polyamine-mediated conformational perturbations in DNA alter the binding of estrogen receptor to poly(dG-m5dC).poly(dG-m5dC) and a plasmid containing the estrogen response element, J. Steroid Biochem. Mol. Biol. 54 (1995) 89–99.
[126] N. Kumar, R. Basundra, S. Maiti, Elevated polyamines induce c- MYC overexpression by perturbing quadruplex-WC duplex equilibrium, Nucleic Acids Res. 37 (2009) 3321–3331.
[127] C.A. Panagiotidis, S. Artandi, K. Calame, S.J. Silverstein, Polyamines alter sequence-specific DNA-protein interactions, Nucleic Acids Res. 23 (1995) 1800–1809.
[128] K. Igarashi, K. Kashiwagi, Modulation of cellular function by polyamines, Int. J. Biochem. Cell Biol. 42 (2010) 39–51.
[129] M. Yoshida, K. Kashiwagi, A. Shigemasa, S. Taniguchi, K. Yamamoto, H. Makinoshima, et al., A unifying model for the role of polyamines in bacterial cell growth, the polyamine modulon, J. Biol. Chem. 279 (2004) 46008–46013.
[130] K. Nishimura, H. Okudaira, E. Ochiai, K. Higashi, M. Kaneko, I. Ishii, et al., Identification of proteins whose synthesis is preferentially enhanced by polyamines at the level of translation in mammalian cells, Int. J. Biochem. Cell Biol. 41 (2009) 2251–2261.
[131] K. Igarashi, K. Kashiwagi, Polyamine modulon in *Escherichia coli*: genes involved in the stimulation of cell growth by polyamines, J. Biochem. 139 (2006) 11–16.
[132] Y. Terui, K. Higashi, S. Taniguchi, A. Shigemasa, K. Nishimura, K. Yamamoto, et al., Enhancement of the synthesis of RpoN, Cra, and H-NS by polyamines at the level of translation in *Escherichia coli* cultured with glucose and glutamate, J. Bacteriol. 189 (2007) 2359–2368.
[133] M. Yoshida, D. Meksuriyen, K. Kashiwagi, G. Kawai, K. Igarashi, Polyamine stimulation of the synthesis of oligopeptide-binding protein (OppA). Involvement of a structural change of the Shine–Dalgarno sequence and the initiation codon aug in OppA mRNA, J. Biol. Chem. 274 (1999) 22723–22728.
[134] M. Yoshida, K. Kashiwagi, G. Kawai, A. Ishihama, K. Igarashi, Polyamine enhancement of the synthesis of adenylate cyclase at the translational level and the consequential stimulation of the synthesis of the RNA polymerase σ28 subunit, J. Biol. Chem. 276 (2001) 16289–16295.
[135] T. Uemura, K. Higashi, M. Takigawa, T. Toida, K. Kashiwagi, K. Igarashi, Polyamine modulon in yeast—stimulation of COX4 synthesis by spermidine at the level of translation, Int. J. Biochem. Cell Biol. 41 (2009) 2538–2545.
[136] A. Yueh, R.J. Schneider, Selective translation initiation by ribosome jumping in adenovirus- infected and heat-shocked cells, Genes Dev. 10 (1996) 1557–1567.
[137] M. Yoshida, K. Kashiwagi, G. Kawai, A. Ishihama, K. Igarashi, Polyamines enhance synthesis of the RNA polymerase σ38 subunit by suppression of an amber termination codon in the open reading frame, J. Biol. Chem. 277 (2002) 37139–37146.
[138] G. Landau, Z. Bercovich, M.H. Park, C. Kahana, The role of polyamines in supporting growth of mammalian cells is mediated through their requirement for translation initiation and elongation, J. Biol. Chem. 285 (2010) 12474–12481.
[139] H. Kihara, E.E. Snell, Spermine and related polyamines as growth stimulants for *Lactobacillus casei*, Proc. Natl. Acad. Sci. U. S. A. 43 (1957) 867–871.
[140] S. Kusunoki, I. Yasumasu, Cyclic change in polyamine concentrations in sea urchin eggs related with cleavage cycle, Biochem. Biophys. Res. Commun. 68 (1976) 881–885.
[141] S. Kusunoki, I. Yasumasu, Inhibitory effect of α-hydrazinoornithine on egg cleavage in sea urchin eggs, Dev. Biol. 67 (1978) 336–345.
[142] S. Cunningham-Rundles, W.K. Maas, Isolation, characterization, and mapping of *Escherichia coli* mutants blocked in the synthesis of ornithine decarboxylase, J. Bacteriol. 124 (1975) 791–799.
[143] Q.-W. Xie, C.W. Tabor, H. Tabor, Deletion mutations in the *speED* operon: spermidine is not essential for the growth of *Escherichia coli*, Gene 126 (1993) 115–117.
[144] R.M. Ray, B.J. Zimmerman, S.A. McCormack, T.B. Patel, L.R. Johnson, Polyamine depletion arrests cell cycle and induces inhibitors p21(Waf1/Cip1), p27(Kip1), and p53 in IEC-6 cells, Am. J. Physiol. 276 (1999) C684–C691.
[145] M. Odenlund, B. Holmqvist, B. Baldetorp, P. Hellstrand, B.-O. Nilsson, Polyamine synthesis inhibition induces S phase cell cycle arrest in vascular smooth muscle cells, Amino Acids 36 (2009) 273–282.
[146] M.K. Chattopadhyay, C.W. Tabor, H. Tabor, Absolute requirement of spermidine for growth and cell cycle progression of fission yeast (*Schizosaccharomyces pombe*), Proc. Natl. Acad. Sci. U. S. A. 99 (2002) 10330–10334.

[147] D. Balasundaram, C.W. Tabor, H. Tabor, Spermidine or spermine is essential for the aerobic growth of *Saccharomyces cerevisiae*, Proc. Natl. Acad. Sci. U. S. A. 88 (1991) 5872–5876.

[148] J. Pitkin, R.H. Davis, The genetics of polyamine synthesis in *Neurospora crassa*, Arch. Biochem. Biophys. 278 (1990) 386–391.

[149] D.H. Russell, P.J. Stambrook, Cell cycle specific fluctuations in adenosine 3′:5′-cyclic monophosphate and polyamines of Chinese hamster cells, Proc. Natl. Acad. Sci. U. S. A. 72 (1975) 1482–1486.

[150] O. Heby, G.P. Sarna, L.J. Marton, M. Omine, S. Perry, D.H. Russell, Polyamine content of AKR leukemic cells in relation to the cell cycle, Cancer Res. 33 (1973) 2959–2964.

[151] P.S. Sunkara, S. Ramakrishna, K. Nishioka, P.N. Rao, The relationship between levels and rates of synthesis of polyamines during mammalian cell cycle, Life Sci. 28 (1981) 1497–1506.

[152] S.J. Friedman, R.A. Bellantone, E.S. Canellakis, Ornithine decarboxylase activity in synchronously growing Don C cells, Biochim. Biophys. Acta 261 (1972) 188–193.

[153] J.O. Fredlund, M.C. Johansson, E. Dahlberg, S.M. Oredsson, Ornithine decarboxylase and *S*-adenosylmethionine decarboxylase expression during the cell cycle of Chinese hamster ovary cells, Exp. Cell Res. 216 (1995) 86–92.

[154] O. Heby, J.W. Gray, P.A. Lindl, L.J. Marton, C.B. Wilson, Changes in L-ornithine decarboxylase activity during the cell cycle, Biochem. Biophys. Res. Commun. 71 (1976) 99–105.

[155] B.F. Cheetham, An inhibitor of polyamine synthesis arrests cells at an earlier stage of G1 than does calcium deprivation, Mol. Cell. Biol. 3 (1983) 480–483.

[156] D.L. Kramer, S. Vujcic, P. Diegelman, J. Alderfer, J.T. Miller, J.D. Black, et al., Polyamine analogue induction of the p53-p21WAF1/CIP1-Rb pathway and G1 arrest in human melanoma cells, Cancer Res. 59 (1999) 1278–1286.

[157] O. Heby, G. Andersson, J.W. Gray, Interference with S and G2 phase progression by polyamine synthesis inhibitors, Exp. Cell Res. 111 (1978) 461–464.

[158] S. Anehus, P. Pohjanpelto, B. Baldetorp, E. Långström, O. Heby, Polyamine starvation prolongs the S and G2 phases of polyamine-dependent (arginase-deficient) CHO cells, Mol. Cell. Biol. 4 (1984) 915–922.

[159] F. Scorcioni, A. Corti, P. Davalli, S. Astancolle, S. Bettuzzi, Manipulation of the expression of regulatory genes of polyamine metabolism results in specific alterations of the cell-cycle progression, Biochem. J. 354 (2001) 217–223.

[160] R.M. Ray, S.A. McCormack, L.R. Johnson, Polyamine depletion arrests growth of IEC-6 and Caco-2 cells by different mechanisms, Am. J. Physiol. Gastrointest. Liver Physiol. 281 (2001) G37–G43.

[161] J. Schnier, H.G. Schwelberger, Z. Smit-McBride, H.A. Kang, J.W. Hershey, Translation initiation factor 5A and its hypusine modification are essential for cell viability in the yeast *Saccharomyces cerevisiae*, Mol. Cell. Biol. 11 (1991) 3105–3114.

[162] H.L. Cooper, M.H. Park, J.E. Folk, B. Safer, R. Braverman, Identification of the hypusine-containing protein Hy+ as translation initiation factor eIF-4D, Proc. Natl. Acad. Sci. U. S. A. 80 (1983) 1854–1857.

[163] H.L. Cooper, M.H. Park, J.E. Folk, Posttranslational formation of hypusine in a single major protein occurs generally in growing cells and is associated with activation of lymphocyte growth, Cell 29 (1982) 791–797.

[164] M.H. Park, K. Nishimura, C.F. Zanelli, S.R. Valentini, Functional significance of eIF5A and its hypusine modification in eukaryotes, Amino Acids 38 (2010) 491–500.

[165] M.H. Park, E.C. Wolff, J.E. Folk, Hypusine: its post-translational formation in eukaryotic initiation factor 5A and its potential role in cellular regulation, Biofactors 4 (1993) 95–104.

[166] M.H. Park, Y.A. Joe, K.R. Kang, Y.B. Lee, E.C. Wolff, The polyamine-derived amino acid hypusine: its post-translational formation in eIF-5A and its role in cell proliferation, Amino Acids 10 (1996) 109–121.

[167] E.C. Wolff, K.R. Kang, Y.S. Kim, M.H. Park, Posttranslational synthesis of hypusine: evolutionary progression and specificity of the hypusine modification, Amino Acids 33 (2007) 341–350.

[168] K. Sasaki, M.R. Abid, M. Miyazaki, Deoxyhypusine synthase gene is essential for cell viability in the yeast *Saccharomyces cerevisiae*, FEBS Lett. 384 (1996) 151–154.

[169] M.H. Park, Y.A. Joe, K.R. Kang, Deoxyhypusine synthase activity is essential for cell viability in the yeast *Saccharomyces cerevisiae*, J. Biol. Chem. 273 (1998) 1677–1683.

[170] H.A. Kang, J.W. Hershey, Effect of initiation factor eIF-5A depletion on protein synthesis and proliferation of *Saccharomyces cerevisiae*, J. Biol. Chem. 269 (1994) 3934–3940.

[171] M.K. Chattopadhyay, M.H. Park, H. Tabor, Hypusine modification for growth is the major function of spermidine in *Saccharomyces cerevisiae* polyamine auxotrophs grown in limiting spermidine, Proc. Natl. Acad. Sci. U. S. A. 105 (2008) 6554–6559.

[172] M.K. Chattopadhyay, C.W. Tabor, H. Tabor, Spermidine but not spermine is essential for hypusine biosynthesis and growth in *Saccharomyces cerevisiae*: spermine is converted to spermidine *in vivo* by the FMS1-amine oxidase, Proc. Natl. Acad. Sci. U. S. A. 100 (2003) 13869–13874.

[173] P.H. Patel, M. Costa-Mattioli, K.L. Schulze, H.J. Bellen, The Drosophila deoxyhypusine hydroxylase homologue nero and its target eIF5A are required for cell growth and the regulation of autophagy, J. Cell Biol. 185 (2009) 1181–1194.

[174] I. Maeda, Y. Kohara, M. Yamamoto, A. Sugimoto, Large-scale analysis of gene function in *Caenorhabditis elegans* by high-throughput RNAi, Curr. Biol. 11 (2001) 171–176.

[175] H. Sievert, N. Pällmann, K.K. Miller, I. Hermans-Borgmeyer, S. Venz, A. Sendoel, et al., A novel mouse model for inhibition of DOHH-mediated hypusine modification reveals a crucial function in embryonic development, proliferation and oncogenic transformation, Dis. Model. Mech. 7 (2014) 963–976.

[176] K. Nishimura, S.B. Lee, J.H. Park, M.H. Park, Essential role of eIF5A-1 and deoxyhypusine synthase in mouse embryonic development, Amino Acids 42 (2012) 703–710.

[177] X.-Y. Guan, J.M.-W. Fung, N.-F. Ma, S.-H. Lau, L.-S. Tai, D. Xie, et al., Oncogenic role of eIF-5A2 in the development of ovarian cancer, Cancer Res. 64 (2004) 4197–4200.

[178] J.L. Mitchell, G.G. Judd, A. Leyser, C. Choe, Osmotic stress induces variation in cellular levels of ornithine decarboxylase-antizyme, Biochem. J. 329 (1998) 453–459.

[179] M.B. Watson, R.L. Malmberg, Regulation of *Arabidopsis thaliana* (L.) Heynh Arginine decarboxylase by potassium deficiency stress, Plant Physiol. 111 (1996) 1077–1083.

[180] J. Legocka, A. Kluk, Effect of salt and osmotic stress on changes in polyamine content and arginine decarboxylase activity in *Lupinus luteus* seedlings, J. Plant Physiol. 162 (2005) 662–668.

[181] A. Borrell, R.T. Besford, T. Altabella, C. Masgrau, A.F. Tiburcio, Regulation of arginine decarboxylase by spermine in osmotically stressed oat leaves, Physiol. Plant. 98 (1996) 105–110.
[182] R.L. Malmberg, M.L. Cellino, Arginine decarboxylase of oats is activated by enzymatic cleavage into two polypeptides, J. Biol. Chem. 269 (1994) 2703–2706.
[183] H.C. Ha, N.S. Sirisoma, P. Kuppusamy, J.L. Zweier, P.M. Woster, R.A. Casero, The natural polyamine spermine functions directly as a free radical scavenger, Proc. Natl. Acad. Sci. U. S. A. 95 (1998) 11140–11145.
[184] K.C. Das, H.P. Misra, Hydroxyl radical scavenging and singlet oxygen quenching properties of polyamines, Mol. Cell. Biochem. 262 (2004) 127–133.
[185] S. Fujisawa, Y. Kadoma, Kinetic evaluation of polyamines as radical scavengers, Anticancer Res. 25 (2005) 965–969.
[186] I.G. Sava, V. Battaglia, C.A. Rossi, M. Salvi, A. Toninello, Free radical scavenging action of the natural polyamine spermine in rat liver mitochondria, Free Radic. Biol. Med. 41 (2006) 1272–1281.
[187] J.E. Rider, A. Hacker, C.A. Mackintosh, A.E. Pegg, P.M. Woster, R.A. Casero, Spermine and spermidine mediate protection against oxidative damage caused by hydrogen peroxide, Amino Acids 33 (2007) 231–240.
[188] K. Yamaguchi, Y. Takahashi, T. Berberich, A. Imai, A. Miyazaki, T. Takahashi, et al., The polyamine spermine protects against high salt stress in *Arabidopsis thaliana*, FEBS Lett. 580 (2006) 6783–6788.
[189] R. Iyer, A.H. Delcour, Complex inhibition of OmpF and OmpC bacterial porins by polyamines, J. Biol. Chem. 272 (1997) 18595–18601.
[190] A.L. Dela Vega, A.H. Delcour, Polyamines decrease *Escherichia coli* outer membrane permeability, J. Bacteriol. 178 (1996) 3715–3721.
[191] A. Krüger, J. Vowinckel, M. Mülleder, P. Grote, F. Capuano, K. Bluemlein, et al., Tpo1-mediated spermine and spermidine export controls cell cycle delay and times antioxidant protein expression during the oxidative stress response, EMBO Rep. 14 (2013) 1113–1119.
[192] A.G. Tkachenko, L.Y. Nesterova, Polyamines as modulators of gene expression under oxidative stress in *Escherichia coli*, Biochem 68 (2003) 850–856.
[193] I.L. Jung, I.G. Kim, Transcription of *ahpC*, *katG*, and *katE* genes in *Escherichia coli* is regulated by polyamines: polyamine-deficient mutant sensitive to H_2O_2-induced oxidative damage, Biochem. Biophys. Res. Commun. 301 (2003) 915–922.
[194] G.H.M. Sagor, T. Berberich, Y. Takahashi, M. Niitsu, T. Kusano, The polyamine spermine protects *Arabidopsis* from heat stress-induced damage by increasing expression of heat shock-related genes, Transgenic Res. 22 (2013) 595–605.
[195] L. Cheng, R. Sun, F. Wang, Z. Peng, F. Kong, J. Wu, et al., Spermidine affects the transcriptome responses to high temperature stress in ripening tomato fruit, J. Zhejiang Univ. Sci. B 13 (2012) 283–297.
[196] F. Marco, R. Alcázar, A.F. Tiburcio, P. Carrasco, Interactions between polyamines and abiotic stress pathway responses unraveled by transcriptome analysis of polyamine overproducers, OMICS 15 (2011) 775–781.
[197] S.M. Chiang, H.E. Schellhorn, Regulators of oxidative stress response genes in *Escherichia coli* and their functional conservation in bacteria, Arch. Biochem. Biophys. 525 (2012) 161–169.
[198] M.D.B.M. Groppa, Polyamines and abiotic stress: recent advances, Amino Acids 34 (2008) 35–45.
[199] D. Schiller, D. Kruse, H. Kneifel, R. Kramer, A. Burkovski, Polyamine transport and role of potE in response to osmotic stress in *Escherichia coli*, J. Bacteriol. 182 (2000) 6247–6249.
[200] C. Kotakis, E. Theodoropoulou, K. Tassis, C. Oustamanolakis, N.E. Ioannidis, K. Kotzabasis, Putrescine, a fast-acting switch for tolerance against osmotic stress, J. Plant Physiol. 171 (2014) 48–51.
[201] F. Zhao, C.-P. Song, J. He, H. Zhu, Polyamines improve K^+/Na^+ homeostasis in barley seedlings by regulating root ion channel activities, Plant Physiol. 145 (2007) 1061–1072.
[202] H. Samartzidou, M. Mehrazin, Z. Xu, M.J. Benedik, A.H. Delcour, Cadaverine inhibition of porin plays a role in cell survival at acidic pH, J. Bacteriol. 185 (2003) 13–19.
[203] N. Watson, D.S. Dunyak, E.L. Rosey, J.L. Slonczewski, E.R. Olson, Identification of elements involved in transcriptional regulation of the *Escherichia coli* cad operon by external pH, J. Bacteriol. 174 (1992) 530–540.
[204] A.L. Cason, Y. Ikeguchi, C. Skinner, T.C. Wood, K.R. Holden, H.A. Lubs, et al., X-linked spermine synthase gene (SMS) defect: the first polyamine deficiency syndrome, Eur. J. Hum. Genet. 11 (2003) 937–944.
[205] D. Russell, S.H. Snyder, Amine synthesis in rapidly growing tissues: ornithine decarboxylase activity in regenerating rat liver, chick embryo, and various tumors, Proc. Natl. Acad. Sci. U. S. A. 60 (1968) 1420–1427.
[206] B.G. Durie, S.E. Salmon, D.H. Russell, Polyamines as markers of response and disease activity in cancer chemotherapy, Cancer Res. 37 (1977) 214–221.
[207] D.H. RUSSELL, Increased polyamine concentrations in the urine of human cancer patients, Nature 233 (1971) 144–145.
[208] C.A. Elmets, M. Athar, Targeting ornithine decarboxylase for the prevention of nonmelanoma skin cancer in humans, Cancer Prev. Res. (Phila.) 3 (2010) 8–11.
[209] C. Bello-Fernandez, G. Packham, J.L. Cleveland, The ornithine decarboxylase gene is a transcriptional target of c-Myc, Proc. Natl. Acad. Sci. U. S. A. 90 (1993) 7804–7808.
[210] J.A. Moshier, J. Dosescu, M. Skunca, G.D. Luk, Transformation of NIH/3T3 cells by ornithine decarboxylase overexpression, Cancer Res. 53 (1993) 2618–2622.
[211] M. Auvinen, A. Paasinen-Sohns, H. Hirai, L.C. Andersson, E. Hölttä, Ornithine decarboxylase- and ras-induced cell transformations: reversal by protein tyrosine kinase inhibitors and role of pp130CAS, Mol. Cell. Biol. 15 (1995) 6513–6525.
[212] M. Auvinen, A. Laine, A. Paasinen-Sohns, A. Kangas, L. Kangas, O. Saksela, et al., Human ornithine decarboxylase-overproducing NIH3T3 cells induce rapidly growing, highly vascularized tumors in nude mice, Cancer Res. 57 (1997) 3016–3025.
[213] M.E. Martinez, T.G. O'Brien, K.E. Fultz, N. Babbar, H. Yerushalmi, N. Qu, et al., Pronounced reduction in adenoma recurrence associated with aspirin use and a polymorphism in the ornithine decarboxylase gene, Proc. Natl. Acad. Sci. U. S. A. 100 (2003) 7859–7864.
[214] L. Megosh, S.K. Gilmour, D. Rosson, A.P. Soler, M. Blessing, J.A. Sawicki, et al., Increased frequency of spontaneous skin tumors in transgenic mice which overexpress ornithine decarboxylase, Cancer Res. 55 (1995) 4205–4209.
[215] Y. Guo, J.L. Cleveland, T.G. O'Brien, Haploinsufficiency for ODC modifies mouse skin tumor susceptibility, Cancer Res. 65 (2005) 1146–1149.

[216] J.A. Nilsson, U.B. Keller, T.A. Baudino, C. Yang, S. Norton, J.A. Old, et al., Targeting ornithine decarboxylase in Myc-induced lymphomagenesis prevents tumor formation-Cancer Cell 7 (2005) 433–444.
[217] R. Chaturvedi, M. Asim, J. Romero-Gallo, D.P. Barry, S. Hoge, T. de Sablet, et al., Spermine oxidase mediates the gastric cancer risk associated with *Helicobacter pylori* CagA, Gastroenterology 141 (2011) 1696–1708.
[218] S.-K.S. Hong, R. Chaturvedi, M.B. Piazuelo, L.A. Coburn, C.S. Williams, A.G. Delgado, et al., Increased expression and cellular localization of spermine oxidase in ulcerative colitis and relationship to disease activity, Inflamm. Bowel Dis. 16 (2010) 1557–1566.
[219] D.J. Feith, L.M. Shantz, A.E. Pegg, Targeted antizyme expression in the skin of transgenic mice reduces tumor promoter induction of ornithine decarboxylase and decreases sensitivity to chemical carcinogenesis, Cancer Res. 61 (2001) 6073–6081.
[220] C.E. Weeks, A.L. Herrmann, F.R. Nelson, T.J. Slaga, alpha-Difluoromethylornithine, an irreversible inhibitor of ornithine decarboxylase, inhibits tumor promoter-induced polyamine accumulation and carcinogenesis in mouse skin, Proc. Natl. Acad. Sci. U. S. A. 79 (1982) 6028–6032.
[221] N.D. Nigro, A.W. Bull, M.E. Boyd, Inhibition of intestinal carcinogenesis in rats: effect of difluoromethylornithine with piroxicam or fish oil, J. Natl. Cancer Inst. 77 (1986) 1309–1313.
[222] F. Milord, J. Pépin, L. Loko, L. Ethier, B. Mpia, Efficacy and toxicity of eflornithine for treatment of *Trypanosoma brucei* gambiense sleeping sickness, Lancet 340 (1992) 652–655.
[223] S.L. Nowotarski, P.M. Woster, R.A. Casero, Polyamines and cancer: implications for chemotherapy and chemoprevention, Expert Rev. Mol. Med. 15 (2013) e3.
[224] E.W. Gerner, F.L. Meyskens, Polyamines and cancer: old molecules, new understanding, Nat. Rev. Cancer 4 (2004) 781–792.
[225] T. Eisenberg, H. Knauer, A. Schauer, S. Büttner, C. Ruckenstuhl, D. Carmona-Gutierrez, et al., Induction of autophagy by spermidine promotes longevity, Nat. Cell Biol. 11 (2009) 1305–1314.
[226] M. Vivó, N. de Vera, R. Cortés, G. Mengod, L. Camón, E. Martínez, Polyamines in the basal ganglia of human brain. Influence of aging and degenerative movement disorders, Neurosci. Lett. 304 (2001) 107–111.
[227] V.K. Gupta, L. Scheunemann, T. Eisenberg, S. Mertel, A. Bhukel, T.S. Koemans, et al., Restoring polyamines protects from age-induced memory impairment in an autophagy-dependent manner, Nat. Neurosci. 16 (2013) 1453–1460.
[228] P. Santana Frühauf, R. Porto Ineu, L. Tomazi, T. Duarte, C. Mello, M. Rubin, Spermine reverses lipopolysaccharide-induced memory deficit in mice, J. Neuroinflammation 12 (2015) 3.
[229] J.R. Roede, K. Uppal, Y. Park, K. Lee, V. Tran, D. Walker, et al., Serum metabolomics of slow vs. rapid motor progression Parkinson's disease: a pilot study, PLoS One 8 (2013) e77629.
[230] C. Gomes-Trolin, I. Nygren, S.-M. Aquilonius, H. Askmark, Increased red blood cell polyamines in ALS and Parkinson's disease, Exp. Neurol. 177 (2002) 515–520.
[231] K. Inoue, H. Tsutsui, H. Akatsu, Y. Hashizume, N. Matsukawa, T. Yamamoto, et al., Metabolic profiling of Alzheimer's disease brains, Sci. Rep. 3 (2013) 2364.
[232] A.V. Krasnoslobodtsev, J. Peng, J.M. Asiago, J. Hindupur, J.-C. Rochet, Y.L. Lyubchenko, Effect of spermidine on misfolding and interactions of alpha-synuclein, PLoS One 7 (2012) e38099.
[233] J. Luo, C.-H. Yu, H. Yu, R. Borstnar, S.C.L. Kamerlin, A. Gräslund, et al., Cellular polyamines promote amyloid-beta (Aβ) peptide fibrillation and modulate the aggregation pathways, ACS Chem. Neurosci. 4 (2013) 454–462.
[234] N.M. Lewandowski, S. Ju, M. Verbitsky, B. Ross, M.L. Geddie, E. Rockenstein, et al., Polyamine pathway contributes to the pathogenesis of Parkinson disease, Proc. Natl. Acad. Sci. U. S. A. 107 (2010) 16970–16975.
[235] J. Vowinckel, S. Stahlberg, N. Paulmann, K. Bluemlein, M. Grohmann, M. Ralser, et al., Histaminylation of glutamine residues is a novel posttranslational modification implicated in G-protein signaling, FEBS Lett. 586 (2012) 3819–3824.
[236] J.E. Folk, M.H. Park, S.I. Chung, J. Schrode, E.P. Lester, H.L. Cooper, Polyamines as physiological substrates for transglutaminases, J. Biol. Chem. 255 (1980) 3695–3700.
[237] Y. Song, L.L. Kirkpatrick, A.B. Schilling, D.L. Helseth, N. Chabot, J.W. Keillor, et al., Transglutaminase and polyamination of tubulin: posttranslational modification for stabilizing axonal microtubules, Neuron 78 (2013) 109–123.
[238] T.M. Jeitner, K. Battaile, A.J.L. Cooper, γ-Glutamylamines and neurodegenerative diseases, Amino Acids 44 (2013) 129–142.
[239] T.M. Jeitner, W.R. Matson, J.E. Folk, J.P. Blass, A.J.L. Cooper, Increased levels of gamma-glutamylamines in Huntington disease CSF, J. Neurochem. 106 (2008) 37–44.
[240] A. Martin, G. De Vivo, V. Gentile, Possible role of the transglutaminases in the pathogenesis of Alzheimer's disease and other neurodegenerative diseases, Int. J. Alzheimers Dis. 2011 (2011) 865432.
[241] F. Madeo, T. Eisenberg, S. Büttner, C. Ruckenstuhl, G. Kroemer, Spermidine: a novel autophagy inducer and longevity elixir, Autophagy 6 (2010) 160–162.
[242] A.E. Pegg, Toxicity of polyamines and their metabolic products, Chem. Res. Toxicol. 26 (2013) 1782–1800.
[243] P.L. Wood, M.A. Khan, J.R. Moskal, The concept of “aldehyde load” in neurodegenerative mechanisms: cytotoxicity of the polyamine degradation products hydrogen peroxide, acrolein, 3-aminopropanal, 3-acetamidopropanal and 4-aminobutanal in a retinal ganglion cell line, Brain Res. 1145 (2007) 150–156.
[244] N.P. Dantuma, L.C. Bott, The ubiquitin-proteasome system in neurodegenerative diseases: precipitating factor, yet part of the solution, Front. Mol. Neurosci. 7 (2014) 70.