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REVIEW

Polyamines: essential factors for growth and survival

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Abstract Polyamines are low molecular weight, aliphatic polycations found in the cells of all living organisms. Due to their positive charges, polyamines bind to macromolecules such as DNA, RNA, and proteins. They are involved in diverse processes, including regulation of gene expression, translation, cell proliferation, modulation of cell signalling, and membrane stabilization. They also modulate the activities of certain sets of ion channels. Because of these multifaceted functions, the homeostasis of polyamines is crucial and is ensured through regulation of biosynthesis, catabolism, and transport. Through isolation of the genes involved in plant polyamine biosynthesis and loss-of-function experiments on the corresponding genes, their essentiality for growth is reconfirmed. Polyamines are also involved in stress responses and diseases in plants, indicating their importance for plant survival. This review summarizes the recent advances in polyamine research in the field of plant science compared with the knowledge obtained in microorganisms and animal systems.

Keywords Polyamine · Metabolism · Homeostasis · Ion channel · Growth · Survival

Introduction

Polyamines are low molecular weight aliphatic cations that are ubiquitous to all living organisms. Their initial discovery was made as early as 1678, when "three-sided" crystals from human semen were first described (van Leeuwenhoek 1678). Because the described polyamine occurs in high concentration in sperm, the name spermine [*N*,*N*′-bis(3-aminopropyl)butane-1,4-diamine] was designated (Ladenburg and Abel 1888). The structure and chemical synthesis of this compound were not established until much later (1926) (Dudley et al. 1926; Wrede 1925). Accordingly, the name spermidine was given to a previously chemically synthesized bovine pancreatic polyamine [*N*-(3-aminopropyl)butane-1,4-diamine] (Dudley et al. 1927). Spermine and spermidine are responsible for the typical odor of semen. Two other naturally occurring polyamines, putrescine (butane-1,4-diamine) and cadaverine (pentane-1,5-diamine), are bacterial decomposition compounds that are also fragrant volatile compounds (Brieger 1885). Both contribute to the foul odor of the putrefying flesh of cadaver, which gives them their names. Their structures were established, as was spermidine, by comparison with the already synthesized molecules (Ladenburg 1886; von Udransky and Baumann 1888) (Fig. 1). Since their discovery, the cellular functions of the physiological polyamines putrescine, spermidine, and spermine have been the focus of much study. Due to their positive charge, these compounds can bind various cellular macromolecules, including DNA, RNA, chromatin and proteins by electrostatic linkages which can cause stabilization or destabilisation. Furthermore, covalent linkages can lead to cross-link formation of proteins forming cytotoxic derivatives. Thus, they have been implicated in myriad fundamental cellular processes, including regulation of gene expression, translation, cell proliferation, modulation of cell signaling, and membrane stabilization (Tabor and Tabor 1984; Cohen 1998; Igarashi and Kashiwagi 2000). Polyamines can also regulate cell death, particularly apoptosis (Thomas and Thomas 2001; Seiler and Raul 2005).

The most abundant polyamines in bacteria are putrescine and spermidine. Cadaverine is also present but is less

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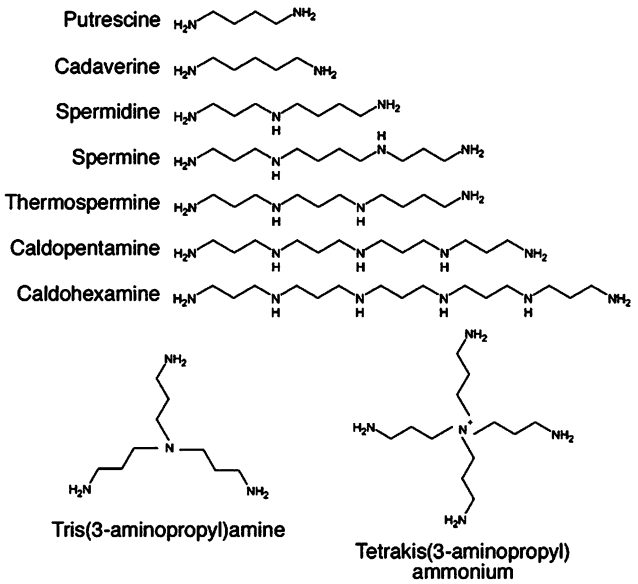

Fig. 1 Names and structures of polyamines. The common and unique polyamines described in this text are listed. Please see the references Cohen (1998) and Oshima (2007)

abundant. Various unique functions for bacterial polyamines have been uncovered (Wortham et al. 2007); they (1) are often components of outer membrane of gram-negative bacteria, (2) are involved in the biosynthesis of siderophores, (3) are important in acid resistance, (4) protect from oxygen toxicity, (5) play a potent role in signaling for cellular differentiation (as suggested through their action as an extracellular signal for swarming), and (6) are essential for plaque biofilm formation. Additionally, putrescine is known to activate the transcription of the genes involved in polyamine uptake and utilization. Thermophilic bacteria contain two additional categories of unique polyamines (Hamana et al. 1998; Oshima 2007). These include polyamines with longer chains such as caldopentamine and caldohexamine, and branched polyamines such as tris(3-aminopropyl)amine (so-called mitsubisine) and tetrakis(3-aminopropyl)ammonium (Fig. 1).

Intensive research on polyamine function in mammals has revealed that they are, as in bacteria, essential regulators of growth, gene transcription, and ribosome-mediated translation (Thomas and Thomas 2003; Childs et al. 2003; Umekage and Ueda 2006). Polyamines and their metabolism are of clear medical and pharmacological importance. They are present at relatively high concentrations in the mammalian brain and are believed to be involved in the pathophysiological processes underlying brain ischemia (Li et al. 2007). Owing to the high turnover of the intestinal mucosal cells, those cells have a high requirement for polyamines. They contribute to the maintenance of normal gut function, the maturation of the intestinal mucosa and its repair after injury (Seiler and Raul 2007). In addition, the polyamine metabolic pathway is a recognized drug target for cancer prevention, as there is a strong positive correlation between polyamine content and cancer cell growth (Saunder and Wallace 2007; Casero and Marton 2007).

In plants, the three major polyamines are putrescine, spermidine, and spermine. Cadaverine is also present in legumes. Plant polyamines have been suggested to play important roles in morphogenesis, growth, embryogenesis, organ development, leaf senescence, and abiotic and biotic stress response (Kumar et al. 1997; Walden et al. 1997; Malmberg et al. 1998; Bouchereau et al. 1999; Liu et al. 2000; Alcázar et al. 2006; Groppa and Benavides 2007; Kusano et al. 2007b). Plant polyamines are also responsible for characteristics of agro-economical importance, including phytonutrient content, fruit quality, and vine life (Mehta et al. 2002; Matto et al. 2006).

In this review, we summarize what is known about polyamine metabolism and function in plants, with particular emphasis on stress responses.

Polyamine biosynthesis

With some variations, the biosynthetic pathways for the polyamines are conserved from bacteria to animals and plants (Tabor and Tabor 1984). The synthesis essentially starts from the two amino acid precursor molecules, L-arginine and L-methionine. An overview of the general pathway is given in Fig. 2a.

In plants, polyamines have not only been localized in the cytoplasm but also in organelles such as vacuoles, mitochondria, and chloroplasts (Kumar et al. 1997). Two alternative synthesis pathways have been verified and the genes encoding enzymes for the polyamine biosynthesis pathway have been cloned and characterized from various plant species (Bell and Malmberg 1990; Michael et al. 1996; see also the reviews, Bagni and Tassoni 2001; Liu et al. 2007). Starting from arginine, the diamine putrescine is synthesized via ornithine by arginase (EC 3.5.3.1) and ornithine decarboxylase (ODC, EC 4.1.1.17). Putrescine can also be synthesized via agmatine by three sequential reactions catalyzed by arginine decarboxylase (ADC, EC 4.1.1.19), agmatine iminohydrolase (AIH, EC 3.5.3.12), and *N*-carbamoylputrescine amidohydrolase (CPA, EC 3.5.1.53), respectively. Putrescine is converted to spermidine by action of spermidine synthase (SPDS, EC 2.5.1.16). An aminopropyl group is transferred from the decarboxylated *S*-adenosylmethionine, which is synthesized from methionine in two sequential reactions of methionine adenosyltransferase (EC 2.5.1.6) and *S*-adenosylmethionine decarboxylase (SAMDC, EC 4.1.1.50), respectively. In legumes, where also cadaverine is present, this diamine is derived from lysine via a reaction of lysine decarboxylase (LDC, EC 4.1.1.18).

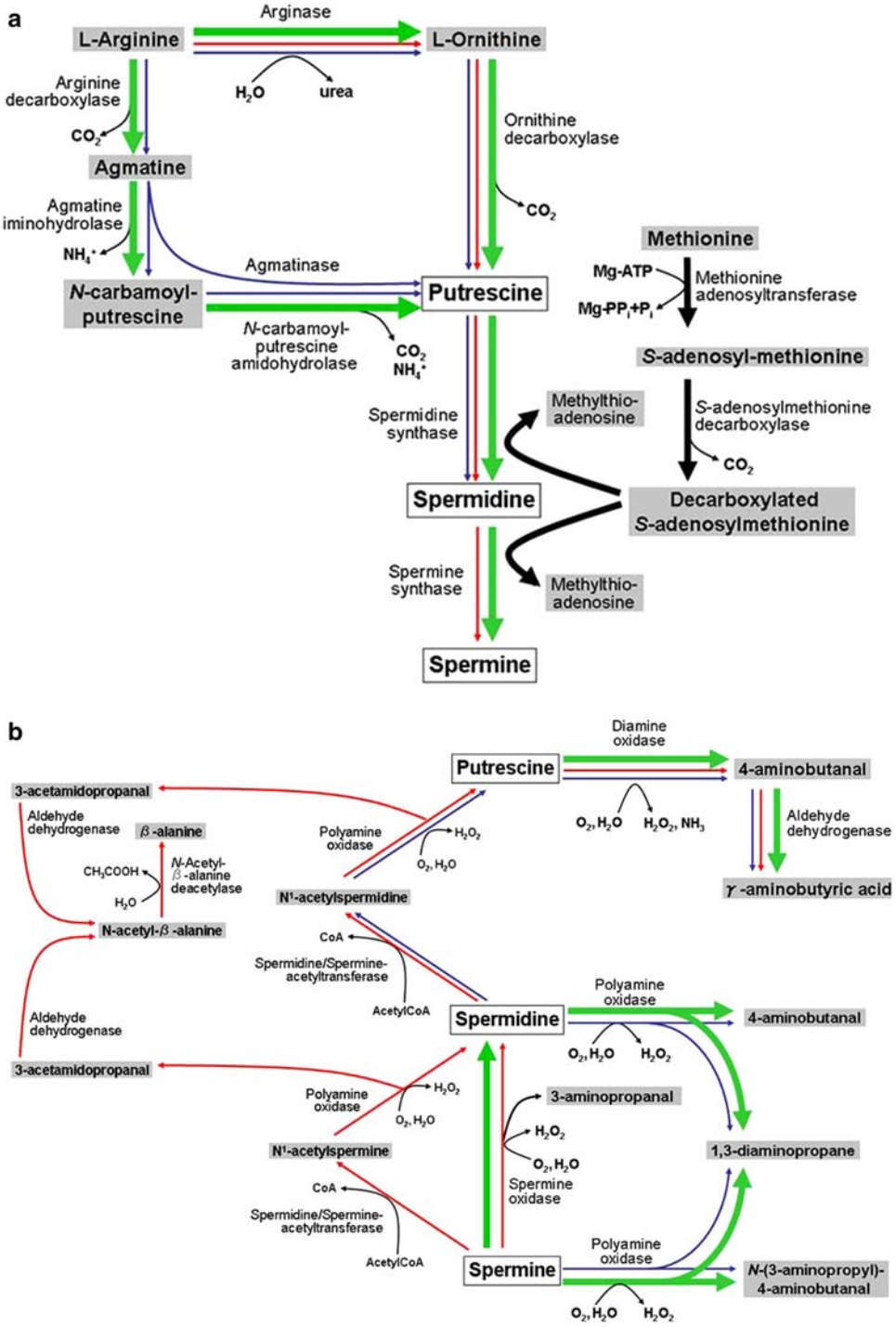

Fig. 2 Polyamine biosynthesis and degradation pathways. **a** Biosynthesis; **b** degradation. Plant pathways are indicated by *green bold arrows*. *Blue* and *red arrows* indicate bacterial and animal pathways, respectively

Interestingly, the sequenced genome of the model plant *Arabidopsis thaliana* does not contain a gene coding for ornithine decarboxylase (ODC) (Hanfrey et al. 2001). So far, absence of this enzyme has only been reported in one other organism, the protozoan eukaryote *Trypanosoma cruzi*. All other polyamine biosynthesis genes have been assigned in *A. thaliana*: there are two genes (*ADC1* and *ADC2*) for arginine decarboxylase (Watson and Malmberg 1996; Watson et al. 1997), and one each (*AIH* and *CPA*) for agmatine iminohydrolase and *N*-carbamoylputrescine amidohydrolase (Janowitz et al. 2003; Piotrowski et al. 2003). Spermidine synthase is encoded by two genes (*SPDS1* and *SPDS2*) (Hanzawa et al. 2002). *ACL5* and *SPMS* (formally *SPDS3*) were identified as the genes encoding spermine synthase (Hanzawa et al. 2000; Panicot et al. 2002; Clay and Nelson 2005; see also the next paragraph). There are at least four genes (*SAMDC1*, *SAMDC2*, *SAMDC3* and *SAMDC4*) for *S*-adenosylmethionine decarboxylase (Urano

et al. 2003; Ge et al. 2006). A study of the interactions of these gene products revealed that SPMS but not ACL5 associates with the spermidine synthases (SPDS1 and SPDS2) to form "polyamine metabolon complexes" (Panicot et al. 2002). The dynamics of these complexes during environmental changes have yet to be investigated.

In 2007, Knott et al. reported that a putative spermine synthase from the diatom *Thalassiosira pseudonana* has thermospermine synthase activity, and that *A. thaliana* ACL5 has the same enzymatic activity. Thermospermine is an isomer of spermine (Fig. 1). The substrate binding sites of spermidine synthases were identified by X-ray analysis (Korolev et al. 2002; Dufe et al. 2005). By sequence comparison, spermine and thermospermine synthases exhibit a similar spatial arrangement of these binding sites. The conserved amino acid sequence GGGDG constitutes the binding site for decarboxylated *S*-adenosylmethionine in spermidine synthase (Korolev et al. 2002), and this domain is also found in spermine synthase. The aspartate (D) residue in this sequence is responsible for an ionic interaction with the amino group of the aminopropyl moiety of decarboxylated *S*-adenosylmethionine (Dufe et al. 2005) and is replaced by a glutamate (E) in all ACL5 group sequences. Besides *ACL5* from *A. thaliana*, *MdACL5-1* and *-2* from apple (Kitashiba et al. 2005), and a number of other genes deposited in the DNA database are classified as thermospermine synthases (Knott et al. 2007). A knockout mutation on *ACL5* leads to defects in stem elongation (Hanzawa et al. 1997) and in vascular development (Clay and Nelson 2005). One (*sac51*) of the *acl5*-suppressor mutants, which recovers normal stem growth, was mapped to a gene encoding a bHLH-type transcription factor (Imai et al. 2006). Future work should uncover the physiological roles of thermospermine synthase in plants.

In bacteria, in addition to the pathways which are effective in plants putrescine can be synthesized directly from agmatine by agmatinase (EC 3.5.3.11). Spermine is not synthesized in *Escherichia coli* as its genome does not encode spermine synthase (SPMS, EC 2.5.1.22) (Wortham et al. 2007). Recent studies on polyamine biosynthesis in the extreme thermophile *Thermus thermophilus* revealed a new metabolic pathway for spermidine synthesis in this organism. *T. thermophilus* spermidine, the precursor for the unique polyamines described above, is derived from arginine but not putrescine (Oshima 2007).

Polyamine synthesis in animals also starts from ornithine, and can be formed directly from proline by ornithine aminotransferase (Wu et al. 2005). The arginine decarboxylase pathway via agmatine as described for bacteria and plants has not been demonstrated in animal cells. Ornithine decarboxylase, spermidine synthase, and spermine synthase accomplish the sequential synthesis of putrescine, spermidine, and spermine, respectively.

Polyamine catabolism

The major pathways of polyamine degradation are depicted in Fig. 2b. The enzyme polyamine oxidase (PAO, EC 1.5.3.11) has been characterized as a flavine adenine dinucleotide (FAD)-containing enzyme that uses N^1-acetyl derivatives as substrates (Bolenius and Seiler 1981). In plants, it was demonstrated that PAOs catalyze the conversion of spermidine and spermine to 4-aminobutanal and *N*-(3-aminopropyl)-4-aminobutanal, respectively, along with the production of 1,3-diaminopropane and H_2O_2 (Federico et al. 1990; Šebela et al. 2001; Cona et al. 2006). This means that plant PAOs are involved in the terminal catabolism of polyamines. The first described plant PAO was ZmPAO derived from the apoplast of maize cells. ZmPAO is a 53-kDa monomeric glycoprotein containing one molecule of FAD (Tavladoraki et al. 1998). Two isoforms, HvPAO1 and HvPAO2, have been isolated from barley; the latter targets to the vacuole. A C-terminal eight amino acid-extension observed only in HvPAO2 was identified as a sorting-signal for this organelle (Cervelli et al. 2001, 2004, 2006).

Spermine oxidase (SMO), a FAD-dependent amine oxidase that directs the back-conversion of spermine to spermidine with concomitant production of 3-aminopropanal and H_2O_2, was initially identified in mammalian cells (Wang et al. 2001; Vujcic et al 2002; Cervelli et al. 2003). An enzyme (Fms1) with the same enzymatic activity was found in yeast (Landry and Sternglanz 2003). The genome of the model plant *Arabidopsis* contains five PAO-like genes (see the review, Alcázar et al. 2006). Of those, AtPAO1 catalyzes the same reaction as SMO/Fms1 (Tavladoraki et al. 2006), indicating that a back-conversion pathway of polyamines also exists in plants. Whether any of the plant PAOs can convert spermidine to putrescine, thus completing a full back-conversion cycle should be assessed in the future.

The other class of enzymes that catabolizes polyamines is the copper-containing diamine oxidase (DAO, EC 1.4.3.6), which prefers diamines as substrates (Zeller 1938; Brazeau et al. 2004). DAO catalyzes the oxidation of putrescine to 4-aminobutanal with concomitant production of NH_3 and H_2O_2, and the resulting aldehyde is further metabolized to γ-aminobutyric acid via Δ^1-pyrroline (Bagni and Tassoni 2001). *Arabidopsis* contains 12 DAO-like genes (see review Alcázar et al. 2006). Among them, only ATAO1 is characterized biochemically (Møller and McPherson 1998). Thus, the functional analysis of the remaining 11 genes with sequence similarity to ATAO1 is awaiting. As has been demonstrated, all polyamine-oxidizing enzymes generate H_2O_2. The importance of this will be addressed later in the review.

Post-translational modification of histone N-terminal tails impacts chromatin structure, in which human LSD1

(lysine-specific demethylase 1), a nuclear homolog of amine oxidase, is involved. LSD1 protein consists of three major domains, and, of these, the C-terminal domain has significantly high sequence homology to polyamine oxidases that belong to the FAD-dependent enzyme family (Binda et al. 2002; Anand and Marmostein 2007). LSD1 functions as a transcriptional corepressor through histone demethylase activity specifically to histone H3 lysine 4, which is linked to active transcription. The protein is evolutionarily conserved from yeast (*Schizosaccharomyces pombe*) to animals and plants (Shi et al. 2004; Culhane and Cole 2007). *A. thaliana* homologs of LSD1 promote floral transition through repressing the expression of floral repressor genes (Jiang et al. 2007). In this context, again, the functional characterization of the members whose sequences have enough homology either to *ATAO1* or to *AtPAO1* might be informative.

Plant polyamines serve as substrates for secondary metabolites. Putrescine, for instance, is a common precursor of nicotine and tropane alkaloids, which are present abundantly in the Solanaceae (Leete 1980). In the first step of the pathway, putrescine is methylated by *N*-methyltransferase (Hibi et al. 1994). This methyl derivative is then deaminated oxidatively to 4-methylaminobutanal, which spontaneously cyclizes to give the *N*-methylpyrrolinium cation. This reaction is catalyzed by *N*-methylputrescine oxidase (MPO) (Katoh et al. 2007; Heim et al. 2007). Tobacco plants have two *MPO* genes (*MPO1* and *MPO2*) that share 88% identity (Katoh et al. 2007). MPO1 has 43% homology each to *Pisum sativum* amine oxidase (Tipping and McPherson 1995) and to *A. thaliana* amine oxidase1 (Møller and McPherson 1998).

In animals, polyamine catabolism starts with the inducible enzyme spermidine/spermine N^1-acetyltransferase (SSAT, EC 2.3.1.57) (Casero and Pegg 1993; Seiler 2004), which catalyzes the formation of N^1-acetyl derivatives by the transfer of the acetyl group from acetyl-coenzyme A to the N^1 position of spermine/spermidine. The acetyl derivatives are then converted to spermidine or putrescine along with the production of 3-aceto-aminopropanal and hydrogen peroxide (H_2O_2) by the peroxisomal and constitutive PAO (Bolenius and Seiler 1981). The aldehyde can be further catabolized to β-alanine by sequential reactions of aldehyde dehydrogenase and *N*-acetyl-β-alanine deacetylase. Mice chronically treated with the PAO inhibitor MDL72527 [N^1,N^4-bis(2,3-butadienyl)-1,4-butanediamine] die, due to spermine accumulation in red blood cells and blood plasma. This result indicates that blockage of polyamine catabolism, especially spermine catabolism, can be fatal in these animals (Seiler et al. 2002), and symbolizes the importance of polyamine catabolism.

Polyamine transport

Polyamine transport systems in plant and animal cells have been proposed, but none have been identified at the molecular level. Results from uptake-experiments of putrescine and spermidine into carrot cells suggested that the entry of polyamines into the cells is driven by a transmembrane electrical gradient, with a possible antiport mechanism between external and internal polyamines (Pistocchi et al. 1987). Other results suggested that in maize roots the bulk of exogenously applied putrescine is transported across the plasmalemma by a carrier-mediated process, similar to that proposed for animal systems (DiTomaso et al. 1992).

In mammalian cells, two transport systems for polyamines have been suggested. In one model, polyamines are transported into cells through unidentified membrane transporters/carriers driven by a membrane potential. The polyamines then are sequestered into vesicles by proton exchange over a pH gradient built by a vacuolar ATPase (Soulet et al. 2004; Casero and Marton 2007). The second model proposes a role for the heparin sulphate side chains of recycling glypican 1 (GPC1) in the transport of spermine, and assumes that GPC1 recycling is a basis of polyamine transport (Belting et al. 2003). In addition to these suggested transport mechanisms that also act as control points for the adjustment of intracellular polyamine levels, two additional mammalian mechanisms have also been proposed (Wallace et al. 2003). For plant cells a model for a polyamine transport system is yet not available.

In microorganisms such as *E. coli* and yeast polyamine transport systems have been investigated in-depth. In *E. coli*, four systems, (1) spermidine-preferential uptake system (PotABCD), (2) putrescine-specific uptake system (PotFGHI), (3) putrescine transport system (PotE), and (4) cadaverine transport system (CadB), have been identified (Igarashi and Kashiwagi 1999; Igarashi 2006). Of those, the former two uptake systems are ATP-binding cassette transporters. Recently, a novel putrescine utilization pathway in *E. coli* was identified (Kurihara et al. 2005). The pathway components are encoded by the *ycj* gene cluster, and include a novel putrescine importer gene, *ycjJ* (now renamed *puuP*). In yeast, nine proteins were identified as polyamine transport proteins: TPO1–5, UGA4, GAP1, DUR3, and SAM3. TPO1–4 are efflux-pumps for xenobiotics that also recognize polyamines. TPO5, which localizes in the post-Golgi complex, is an efflux-pump for polyamines. UGA4, which resides in vacuoles, takes up putrescine along with γ-aminobutyric acid. The cytoplasmic membrane protein GAP, takes up polyamines into the cytoplasm along with amino acids. DUR3 and SAM3 also carry polyamines preferentially into the cytoplasm (Igarashi 2006).

Polyamine homeostasis

The overall intracellular concentration of polyamines is in the range of several hundred micromolar to a few millimolars and is tightly regulated, as higher levels of polyamines are toxic to cells and lead to cell death. Polyamine levels are elegantly regulated at various steps including de novo synthesis, degradation, and transport.

S-adenosylmethionine decarboxylase (SAMDC) was found to be an important enzyme in regulation of polyamine homeostasis in all organisms. *E. coli* SAMDC is first synthesized as a proenzyme, and thereafter cleaved post-translationally to form α and β subunits (Li et al. 2001). The former subunit is modified by covalent attachment of a pyruvoyl group derived from serine, which is essential for enzyme activity. The mature enzyme takes $(\alpha\beta)_4$ configuration. Subsequent work revealed that SAMDC enzymes from other organisms including plants are also synthesized as a proenzyme and then processed to form the active pyruvoyl-containing enzyme (Kashiwagi et al. 1990). The processing and activity of SAMDC are increased by putrescine, indicating that the increased concentration of putrescine raises the formation of decarboxylated SAM which is required for the spermidine synthase (Pegg 1986; Kameji and Pegg 1987; Xiong et al. 1997). The active enzyme is further modified irreversibly at the cysteine residue of α subunit by the product of enzyme reaction, decarboxylated *S*-adenosylmethionine (Li et al. 2001). This modification causes the inactivation of the enzyme and contributes to polyamine homeostasis.

A further regulation mechansim for SAMDC has been uncovered. For the plant model it is outlined in Fig. 3. First it was shown for the mammalian *SAMDC* transcript that it contains a small open reading frame (ORF) encoding the hexapeptide MAGDIS upstream of the main ORF. This type of ORF is termed an upstream ORF (uORF). *SAMDC* is regulated at the translation level in response to cellular polyamine levels through interactions between the peptide product and polyamines. These interactions results in ribosomal stalling near the stop codon of the uORF (Ruan et al 1996). Plant *SAMDC* genes have an unusually long 5′-UTR where two uORFs are well conserved (Franceschetti et al. 2001). The first uORFs (termed tiny uORFs) distal to the 5′ end are 3–4 codons long, while the second (termed small uORFs) encode 50–54 peptides. The small uORF-encoded peptide sequences are conserved among different plant species (Hanfrey et al. 2002, 2003, 2005). The small uORF-encoded peptide is responsible for translational repression of the main ORF under conditions of excess polyamine concentration; while the tiny uORF is required for induced translation of the main ORF during conditions of low polyamine concentration (Hanfrey et al. 2002, 2005) (Fig. 3). Interestingly, this tiny/small uORFs' configuration with

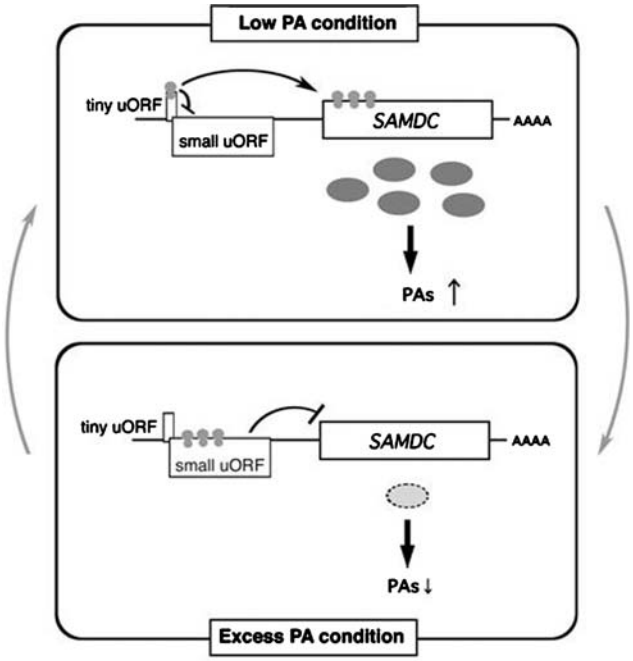

Fig. 3 Regulation of the translation of plant *SAMDC* main ORF mediated by the dual uORFs. This circuit model is based on the reference by Hanfrey et al. (2005)

one-nucleotide-overlap is highly conserved from *Chlamydomonas reinhardtii*, to *Physcomitrella patens*, to higher plants. These results demonstrate two things: first, that the dual uORF-based control mechanism of *SAMDC* has been maintained during plant evolution; and second, that the translational regulation of *SAMDC* mRNA is critically important for plant polyamine homeostasis.

A main modulator of polyamine concentration, antizyme, although it is generally presumed that it does not exist in plants, should be briefly described in this review. The antizyme proteins are encoded by a small gene family and details of the individual members are known but will not be touched upon here (see reviews, Mangold 2005; Pegg 2006). In response to increasing polyamine levels, antizyme binds to ODC, the key enzyme of polyamine biosynthesis. Besides non-competitively inhibiting ODC activity, antizyme recruits ODC to the 26S proteasome for destruction without ubiquitin-modification. Antizyme transcription is not modulated by polyamine concentration, however, higher concentrations of polyamine cause a +1 programmed frameshift of the antizyme mRNA, resulting in decoding of a full-length antizyme mRNA and production of the mature antizyme protein (Matsufuji et al. 1995; Hayashi et al. 1996; Ivanov et al. 2000). Antizyme also regulates polyamine transport (Mitchell et al. 1994; He et al. 1994). The bacterial ODC is also regulated by an antizyme-like molecule, AtoC (Canellakis et al. 1993; Lioliou and Kyriakidis 2004). Putrescine induces *atoC* expression, and

the resulting AtoC protein inhibits ODC activity. Although antizyme-like properties of AtoC have been demonstrated, its expression is not regulated by frameshifting. An antizyme-like protein of 22 kDa has been identified in the anaerobic, gram-negative bacterium *Selenomonas ruminantium* (Yamaguchi et al. 2002) that contains cadaverine as a membrane component (Kamio et al. 1981). The lysine decarboxylase of *S. ruminantium* has ODC activity and is completely inhibited by the ODC inhibitor 2-difluoromethylornithine. Furthermore, the antizyme-like protein is induced upon addition of putrescine and is able to bind to lysine decarboxylase. Interestingly, this protein has sequence similarity to the ribosomal L10 protein of Gram-positive bacteria (Yamaguchi et al. 2006).

As mentioned, at the moment, it is generally presumed that plants do not have antizyme-type proteins. The model plant *Arabidopsis* lacks the antizyme target, ODC (Hanfrey et al. 2001); and other plants possess two alternative biosynthetic pathways. These results suggest that plants are equipped with distinct but still veiled mechanism(s) to control intracellular polyamine levels. At least plant PAO and DAO activities contribute to the regulation of polyamine homeostasis (Šebela et al. 2001).

Polyamines as regulators of ion channels

In mammals, polyamines have direct effects on several ion channels and receptors, resulting in the regulation of Ca^{2+}, Na^{+}, and K^{+} homeostasis (Li et al. 2007; Johnson 1996; William 1997a, b). Intracellular polyamines are involved in the regulation of intrinsic gating and rectification of inward rectifier K^{+} channels (Ficker et al. 1994; Lopatin et al. 1994; Oliver et al. 2000). Furthermore, they are responsible for inward rectification of AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) and kainite receptors through blocking the pore of the receptor channel, thus preventing Na^{+} or Ca^{2+} influx. Extracellular polyamines, particularly spermine, have stimulatory effects on the NMDA (*N*-methyl-D-aspartate) receptor, which is a glutamate receptor (William 1997a, b). Polyamines also interact with voltage-activated Ca^{2+}-channels (Li et al. 2007) and cyclic nucleotide-gated channels (Lu and Ding 1999). Therefore, changes in intracellular or extracellular levels of polyamines could alter K^{+}, Na^{+}, or Ca^{2+} trafficking.

Studies of the effects of polyamines on ion channels have been extended to plants. Intracellular polyamines block a fast-activating vacuolar (FV) cation channel from barley (Brüggemann et al. 1998, 1999). FV and slow-activating channels in red beet vacuoles are also inhibited by polyamines (Dobrovinskaya et al. 1999a, b). Cytoplasmic polyamines block the inward K^{+} currents across the plasma membrane of guard cells (Liu et al. 2000). Non-selective cation channels are another target of polyamines, and channel blockage by polyamines leads to the prevention of K^{+} efflux from pea mesophyll cells (Shabala et al. 2007). Cyclic nucleotide-gated channels and glutamate receptor-like proteins are the major candidates for non-selective cation channels in plants (Davenport 2002). In addition to the direct effect of polyamines on the ion channels, it has also been reported that polyamines, particularly spermine, enhance the activity of plasma membrane H^{+}-ATPase through increased associations between the 14-3-3 protein and the enzyme (Garufi et al. 2007). More detailed analyses of polyamine action on ion channels in plants will be one of the most challenging and fruitful targets in polyamine research, and may uncover how these cationic molecules modulate ion cross-networks in plant cells.

Polyamines for growth

Polyamines are considered to be essential for life, as inhibition of polyamine biosynthesis blocks cell growth (Cohen 1998; Igarashi and Kashiwagi 2000; Thomas and Thomas 2001; Hanfrey et al. 2001). Early evidence for this comes from data on sea urchin eggs (Kusunoki and Yasumasu 1978). When the egg cells are treated with an ODC inhibitor, egg cleavage is significantly blocked, which inhibition is reversed in the presence of polyamines. Current genetic data now substantiates this notion: deletion of either the *ODC* gene or the *SAMDC* gene prevents spermidine synthesis and is lethal at very early embryonic stages in mice (Wang et al. 2004). Thus, spermidine is essential for eukaryotic viability.

Most bacteria do not contain a gene encoding spermine synthase (Wortham et al. 2007); and although yeast cells carry genes for the synthase, spermine is not essential for their growth (Hamasaki-Katagiri et al. 1998). The same is also the case in mice (Lorenz et al. 1998; Mackintosh and Pegg 2000). These findings suggest that spermine is not essential in all mammals or all prokaryotes. Recent evidence indicates that this is also the case in plants (Fig. 4). Urano et al. (2005) isolated T-DNA insertional mutants for two *ADC* genes, *ADC1* and *ADC2*. After crossing, these researchers generated an *Arabidopsis* double mutation on *ADC1* and *ADC2* that was found to cause a lethal defect in embryo development. A double mutation on two spermidine synthase-encoded genes, *SPDS1* and *SPDS2*, leads to a similar developmental defect in the embryo (Imai et al. 2004b). Furthermore, a dual mutation on *SAMDC1* and *SAMDC4* is embryonic lethal (Ge et al. 2006).

One molecular basis of the spermidine requirement for eukaryotic viability is that spermidine is a precursor of the unusual amino acid hypusine. Hypusine is involved in post-translational modification of the epsilon-amino group of

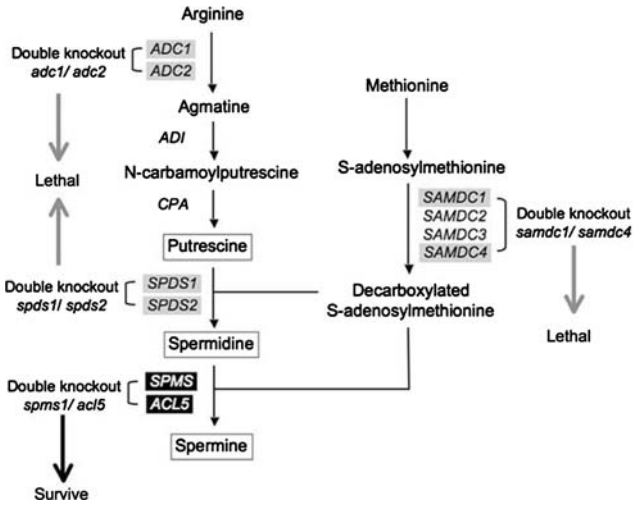

Fig. 4 Putrescine and spermidine, but not spermine, are essential for normal growth of *Arabidopsis*. Polyamine biosynthesis pathway in *A. thaliana* and the genes involved are depicted

one specific lysine residue of the eukaryotic translational initiation factor 5A (eIF5A) (Park 2006). In contrast with spermidine requirements, an *acl5*/*spms* double knockout mutant plant that cannot produce spermine grows well and sets fertile seeds (Imai et al. 2004a). Collectively, these data indicate that putrescine and spermidine are essential for plant embryogenesis and possibly for further growth, but that spermine is not essential for normal growth in *Arabidopsis* (Fig. 4).

These results raise the question of what role spermine has in growth and development. Interestingly, the above mentioned mice lacking spermine synthase have a variety of defects, including severe growth retardation, inner ear abnormalities, very short life spans, deafness, sterility, and neurological defects reflecting to abnormal behavior such as circling (Lorenz et al. 1998; Mackintosh and Pegg 2000). It has also been reported that Snyder–Robinson syndrome, an X-linked mental retardation disorder, is caused by a deficiency in spermine synthase (Cason et al. 2003). It is likely, therefore, that spermine is required not only for growth (Wang et al. 2004) but also for functionality of organs such as the brain in mammals. It is possible that the role of spermine in growth can be substituted by spermidine, whereas spermine is essential for organ functionality. This topic will be touched upon later in this review.

Polyamines can act as intracellular growth factors by increasing the rate of cell growth. The molecular mechanism underlying polyamine-enhanced growth has been discovered gradually. Igarashi et al. proposed a "polyamine modulon" theory to explain how polyamines enhance bacterial cell growth (Yoshida et al. 2004; Terui et al. 2004; Igarashi and Kashiwagi 2006): polyamines stimulate the synthesis of several key factors including oligopeptide binding protein (a periplasmic substrate-binding protein of the oligopeptide uptake system), adenylate cyclase, RNA polymerase sigma subunit (for transcription of stationary-phase genes), and several transcription factors. With the use of microarray analysis, these researchers further found that the expression of about 300 genes in *E. coli* are enhanced more than 2-fold by polyamines, and that 97 of those genes were under the control of transcription factors from the polyamine modulon (Terui et al. 2004).

Polyamines in plant survival

Mutants of *E. coli* and yeast strains with reduced levels of polyamines are more sensitive to oxidative damage (Chattopadhyay et al. 2003, 2006; Jung et al. 2003). Polyamines protect DNA from damage caused by alkylating reagents and from free radical attack in mammals (Ha et al. 1998; Mackintosh and Pegg 2000). Rider et al. (2007) used spermine synthase-deficient mouse fibroblast cells to demonstrate the protective potential of polyamines against oxidative damage caused by H_2O_2. A recent review summarizes that polyamines have a protective role against various stresses, including oxidative, acidic, osmotic, and neuronal stresses, and pathogen attacks (Rhee et al. 2007).

Plant polyamines frequently accumulate in response to abiotic and biotic stresses (Bouchereau et al. 1999; Urano et al. 2003; Walters 2003a, b). There is an extensive literature describing the correlation of changes in polyamine levels and physiological perturbations and on the protective effect of polyamines on environmental stresses (see reviews Alcázar et al. 2006; Groppa and Benavides 2007; Liu et al. 2007, and references therein). It was initially observed that exogenously applied polyamines protect plants from abiotic stress (Chattopadhayay et al. 2002). The improvement of stress tolerance in the transgenic plants overexpressing polyamine biosynthetic genes was then demonstrated; for instance, overexpression of *Cucurbita ficifolia SPDS* gene confers multi-stress tolerance to *Arabidopsis* and sweet potato (Kasukabe et al. 2004, 2006). Rice plants overexpressing *Datura stramonium ADC* gene are tolerant to drought (Capell et al. 2004). Even in woody plants, the enhancement of polyamine synthesis via a transgenic approach confers multi-stress tolerance (Wen et al. 2007). Data obtained by loss-of-function experiments also support the above notions; i.e., deletion of Arabidopsis *ADC2* results in host plants that are more sensitive to salt stress relative to control plants (Urano et al. 2004). The *Arabidopsis acl5/spms* mutant plant, which is unable to produce spermine, is hypersensitive to salt and drought stresses relative to wild type plant (Yamaguchi et al. 2006, 2007). These stress-sensitive phenotypes were reversed by the addition of exogenous polyamines, putrescine in the former case and spermine in the latter.

Curiously, the *acl5*/*spms* mutant plant is hypersensitive to KCl, but no difference in sensitivity to $MgCl_2$ or high osmoticum is observed. This mutant plant is also Ca^{2+} deficient (Yamaguchi et al. 2006). The overall phenotypes of ion sensitivity and Ca^{2+} deficiency were similar to those of transgenic plants overexpressing *AtGluR2* and *CAX1*, which encode a Ca^{2+} influx channel at the plasma membrane and a vacuolar Ca^{2+}/H^+ exchanger, respectively (Hirschi 1999; Kim et al. 2001). The *acl5*/*spms* plant also loses more water compared to control plants, due to a failure of stomatal closure upon onset of drought (Yamaguchi et al. 2007). It is known that changes in free Ca^{2+} concentrations in the cytoplasm of guard cells are involved in stomatal aperture/closure (Ward and Schroeder 1994; Allen and Sanders 1996; Rob et al. 2005). Taken together, these results suggest that the absence of spermine may cause deregulation of Ca^{2+} trafficking, resulting in a lack of proper adaptation to high NaCl or drought stresses (Kusano et al. 2007a, b). As mentioned above, it is proven that *ACL5* encodes thermospermine synthase (Knott et al. 2007). Therefore, the experiments using the *spms* single mutant plant are currently underway.

Consistent with the above data, it has been reported that polyamines including spermine inhibit stomatal opening and induce closure by regulating KAT1-like voltage-dependent inward K^+ channels of *Vicia faba* guard cells (Liu et al. 2000). Recently, Shabala et al. (2007) reported that polyamines prevent NaCl-induced K^+ efflux from pea leaf mesophyll cells by the inhibition of non-selective cation channels. Zhao et al. (2007) showed that polyamines improve barley root K^+/Na^+ homeostasis by regulating ion channel activities. It is plausible that one of the tasks of stress-induced polyamines is to modulate the activity of a certain set of ion channels to adapt ionic fluxes in response to environmental changes. To substantiate the above hypothesis, concerted research that includes many areas of science, including electrophysiology, genetics, and molecular biology, will be required.

Plant polyamines are also proposed to play a defensive role during biotic stress responses (Walters 2003a, b). One defense mechanism, the hypersensitive response (HR), which consists of rapid cell death at the sight of pathogen entry, typically develops in the interaction between tobacco mosaic virus (TMV) and *N* resistance gene carrying *Nicotiana tabacum*. Enhanced polyamine synthesis and accumulation was reported in this interaction (Torrigiani et al. 1997; Marini et al. 2001). Using a similar experimental system, it was discovered that apoplast-accumulated spermine is an endogenous inducer of the expression of the pathogenesis-related (PR) protein-genes (Yamakawa et al. 1998). Exogenous application of spermine to tobacco leaves, which mimics a situation of apoplastic accumulation upon incompatible pathogen attacks, induces a pathway involving mitochondrial dysfunction, activation of mitogen-activated protein kinases, increased expression of HR marker genes (including transcription factors), and caused defense responses and HR-like cell death (Takahashi et al. 2003, 2004a, b; Uehara et al. 2005; Mitsuya et al. 2007). It is likely, therefore, that spermine transmits a signal to activate defense pathways against pathogens (Takahashi et al. 2003). This pathway has been designated the "spermine-signaling pathway".

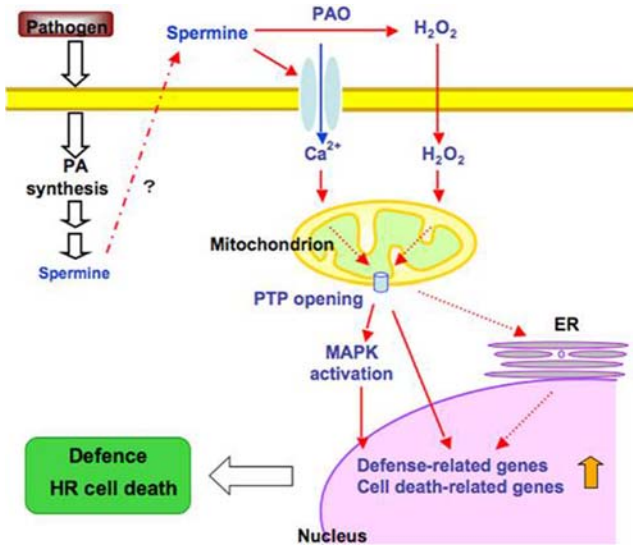

Fig. 5 A hypothetical role for spermine in plant survival against pathogens

To lead to mitochondrial malfunction, at least two events, activation of Ca^{2+} influx and the production of reactive oxygen species, are prerequisite (Takahashi et al. 2003) (Fig. 5). Mitochondrial involvement in biotic stress responses and programmed cell death has been reviewed (Amirsadeghi et al. 2007). Apolastic spermine may directly affect cation channel(s) and/or be catabolized by polyamine oxidase. These combined reactions would result in changes in K^+/Ca^{2+} trafficking and in generation of H_2O_2, both of which may trigger the downstream reaction of the spermine-signaling pathway (Kusano et al. 2007a). Polyamine catabolism in plants is associated with cell survival and cell growth, such as cell wall stiffening and lignification (Šebela et al. 2001; Cona et al. 2006). Yoda et al. (2003, 2006) demonstrated that HR cell death caused by TMV infection or cryptogein, an oomycete-originated elicitor, is partly mediated by H_2O_2 production through polyamine catabolism. These authors suggest that the polyamine substrate for H_2O_2 production is spermidine, since during HR elicitation spermidine but not spermine accumulates in the apoplasts. The idea that plants employ polyamine-catabolized H_2O_2 as a defensive tool upon exposure to biotic stresses has been reviewed by other groups (Cona et al. 2006; Walters 2003a, b).

Tobacco *ZFT1* is a spermine-responsive gene encoding a zinc-finger type transcriptional repressor, and is positioned in the spermine-signaling pathway (Uehara et al. 2005). Tobacco plants overexpressing *ZFT1* are more resistant to TMV compared with control plants (Uehara et al. 2005). Transgenic pine plants overexpressing the gene *CaPF1*, which encodes the ERF (ethylene responsive factor)/AP2-type transcription factor, have dramatically increased tolerances to drought, freezing, and salt stress (Tang et al. 2005). Curiously, in control pine plants, the levels of polyamines decrease upon exposure to stresses, whereas in the transgenics plants the polyamine levels remain constant. This result suggests that enhanced stress tolerance in transgenic pines expressing *CaPF1* is associated with polyamine biosynthesis (Tang et al. 2007). These studies suggest that the expressional modulation of key factors which are positioned upstream of polyamine biosynthesis or the polyamine-induced signaling pathway could make the host organisms resistant to abiotic and biotic stresses.

Tun et al. (2006) reported that spermine and spermidine are potent inducers of nitric oxide (NO) in *Arabidopsis*, but putrescine and its biosynthetic precursor arginine are not. NO has the potential to inhibit oxidative phosphorylation in plant mitochondria (Yamasaki et al. 2001) and plays an important signaling role in plant–pathogen interactions (Romero-Puertas et al. 2004); therefore, further research on the role of polyamine-mediated NO production is justified (Yamasaki and Cohen 2006).

Rhee et al. (2007) mentioned that the basic principle underlying polyamine adaptive responses appears to be shared by the prokaryotic stringent response and the eukaryotic unfolded protein response (UPR). UPR is triggered when unfolded proteins and uncharged tRNAs accumulate in the endoplasmic reticulum (ER) due to ER stress or nutrient starvation. Cap-dependent translation of many mRNAs is suppressed and the expression of a certain set of genes including the luminal binding protein gene *BiP* is induced. The underlying mechanisms of UPR in yeasts and mammals have been well researched (Rutkowski and Kaufman 2004), although those in plants have not (Kamauchi et al. 2005; Urade 2007).

Recently, Iwata and Koizumi (2005) reported that AtbZIP60, which belongs to a basic leucine zipper protein family, is a key transcription factor involved in *Arabidopsis* UPR. In relation to this, we have identified *NtbZIP60*, an orthologue of *AtbZIP60*, via screening of the spermine-responsive genes in tobacco (Tateda et al. 2008). We also confirmed that *AtbZIP60* is responsive to spermine and that some of the UPR-responsive genes are modulated by spermine (Y. Takahashi, unpublished data). This indicates that the cross-talk between polyamine function in survival and the UPR/stringent response warrants further investigation.

As described in this section, polyamines are involved in the defense response during interaction of resistant NN tobacco plants and TMV. By means of this interaction another effect of polyamines has been investigated. Polyamines can affect the conformation and function of specific proteins, by forming covalent linkages mediated by the activity of transglutaminase (TGase, EC 2.3.2.13) enzymes (Griffin et al. 2002). TGases catalyze the formation of a covalent bond between a free amine group, like protein-bound lysine and the γ-carboxamide group of protein-bound glutamine resulting in protein cross-links. Polyamines also act as physiological substrates. The terminal amino group binds one or two glutamyl residues, producing either mono-(γ-glutamyl)-polyamines or bis-(γ-glutamyl)-polyamines (Folk et al. 1980). TGase activity has also been identified in plants (Della Mea et al. 2004). It has now been shown that TGase activity is enhanced during the HR in tobacco/TMV interaction and that mono- and bis-glutamyl-polyamines were formed (Del Duca et al. 2007). The authors suggest that the latter polyamine derivatives may either induce conformational changes or intra- or intermolecular cross-links of proteins. Further investigations will show what kind of role these modified polyamines play in the defense response of plants.

Perspectives

Because of the pharmaceutical interest, intense research on polyamines has been done in animal fields. In bacteria, a variety of phenomena have been reported that confirm the importance of these molecules. As these ‘mysterious’ molecules are versatile players, most plant biologists have put them aside. But currently, as summarized in this review, their importance for growth and survival has been appreciated in plants. However, the knowledge on plant polyamines is still behind compared to the one of animals and prokaryotes. For example, the molecules involved in intracellular, extracellular and intercellular transport of polyamines remain unknown. Are there any mechanisms to regulate the polyamine levels in plants except the translational control of SAMDC mRNA? The cross-talk between the spermine-signal pathway and the signaling pathways triggered by plant hormones has not been examined well. To understand the role of polyamines in growth and differentiation, a plant version of the ‘polyamine modulon’ has to be clarified. To get a deeper insight into the defensive role of polyamines in abiotic and biotic stresses, investigations on how polyamines modulate ion channels will be required.

Intensive research using many modern biological disciplines including electrophysiology, genetics, molecular biology and metabolomics on the functions of polyamines

in plants will lead to fruitful results in basic and applied plant sciences.

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