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REVIEW

# Spermine synthase

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**Abstract** Spermine is present in many organisms including animals, plants, some fungi, some archaea, and some bacteria. It is synthesized by spermine synthase, a highly specific aminopropyltransferase. This review describes spermine synthase structure, genetics, and function. Structural and biochemical studies reveal that human spermine synthase is an obligate dimer. Each monomer contains a C-terminal domain where the active site is located, a central linking domain that also forms the lid of the catalytic domain, and an N-terminal domain that is structurally very similar to *S*-adenosylmethionine decarboxylase. Gyro mice, which have an X-chromosomal deletion including the spermine synthase (*SMS*) gene, lack all spermine and have a greatly reduced size, sterility, deafness, neurological abnormalities, and a tendency to sudden death. Mutations in the human *SMS* lead to a rise in spermidine and reduction of spermine causing Snyder-Robinson syndrome, an X-linked recessive condition characterized by mental retardation, skeletal defects, hypotonia, and movement disorders.

**Keywords** Polyamines · *S*-adenosylmethionine · Spermine · Spermidine · Aminopropyltransferase

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## Introduction

Polyamines are formed in eukaryotes and in many, but not all, prokaryotes by the action of aminopropyltransferase enzymes. The aminopropyltransferases form a class of enzymes that use decarboxylated *S*-adenosylmethionine (dcAdoMet) as a substrate and transfer the aminopropyl group to an amine acceptor molecule forming 5′-deoxy-5′-methylthioadenosine (MTA) as a byproduct. Agmatine, putrescine, cadaverine, spermidine, 1,3-diaminopropane, and *sym*-norspermidine are known to be substrates [1–4]. Spermidine, which is an unsymmetrical molecule, can be aminopropylated at either end forming spermine or thermospermine [1, 5]. It is likely that some longer polyamines may also be substrates since polyamines with more than three aminopropyl units have been identified in some thermophiles and in the walls of siliceous diatoms, but the responsible aminopropyltransferases have not yet been characterized [6–8].

Some aminopropyltransferases such as human spermidine synthase and spermine synthase are highly specific for their amine acceptors while others such as those from acute thermophiles, which contain a variety of polyamines not found in mammals, are less discriminating. Although the first crystal structure of an aminopropyltransferase was reported only in 2002, there are now numerous published structures including those for spermidine synthases from *Thermotoga maritima* [9], *Caenorhabditis elegans* [10], *Plasmodium falciparum* [11], *Helicobacter pylori* [12], human [3], *Arabidopsis thaliana* (PDB code 2Q41) and *Trypanosoma cruzi* (PDB code 3BWC), aminopropylagmatine synthases from *Thermus thermophilus* (PDB code 1UIR), *Pyrococcus horikoshii* (PDB code 2ZSU), and *Pyrococcus furiosus* [4], and spermine synthase from humans [13]. A general mechanism for aminopropyl

transfer has been proposed based on human and *T. maritima* spermidine synthase structures bound to substrates and inhibitors and the results of site-directed mutagenesis of key residues [3, 9].

This brief article focuses on spermine synthase (EC: 2.5.1.22), which catalyzes the reaction:

$$H_2N(CH_2)_3NH(CH_2)_4NH_2 + \text{dcAdoMet} \rightarrow H_2N(CH_2)_3NH(CH_2)_4NH(CH_2)_3NH_2 + \text{MTA}$$

## Distribution, genetics and function

Although many organisms contain spermidine, the distribution of spermine is more limited. Only in tissues from animals does the content of spermine equal or exceed that of its precursor spermidine. A highly specific spermine synthase enzyme has been characterized from a variety of sources including animals, plants, and *S. cerevisiae* (reviewed in [1]). It should be pointed out that earlier contentions that bacteria do not contain spermine, which are repeated in a recent review article [14], are an incorrect generalization. In bacteria, spermine is found in species of the Actinobacteria [15, 16], in thermophilic members of the orders Clostridiales, Bacilliales, and the family Peptococcoceae of the Firmicutes [8], in *Thermus* species [17], and in the α-Proteobacterium *Paracoccus denitrificans* [18]. Spermine is also found in diverse thermophilic and acidothermophilic members of the crenarchaeota and euryarchaeota phyla of the archaea [19]. It is not established that these species contain a specific spermine synthase. It is certainly possible that spermine is made by a non-specific aminopropyltransferase using a minor substrate.

Yeast and plants do contain spermine synthase enzymes, although, as discussed below, these seem to be derived from a modification of a spermidine synthase. However, yeast does not require spermine synthase since mutants in which this enzyme is deleted are viable and grow at a normal rate [20, 21].

It is also likely that plants do not require spermine for normal growth since mutants where the *SPMS* gene that encodes spermine synthase is inactivated are viable but contain no spermine [22]. The absence of spermine may lead to a hypersensitivity to drought [23]. There is a second gene in plants (*ACL5*) that was originally identified erroneously as encoding a spermine synthase. Mutations inactivating this gene product lead to developmental defects [22–24]. However, it has now been clarified that *ACL5* actually encodes an aminopropyltransferase which attacks the $N^1$ atom at the aminopropyl end of spermidine to form thermospermine, $H_2N(CH_2)_3NH(CH_2)_3NH(CH_2)_4NH_2$ [5], and it is thermospermine rather than spermine that rescues the dwarf phenotype of the mutants [25]. Most of the published papers in which measurements of plant polyamines are given do not distinguish between spermine and thermospermine. However, their total amount is much less than that of spermidine.

## Snyder-Robinson syndrome

In contrast, spermine synthase is clearly essential for normal development in humans and other mammals. Alterations in the human *SMS* gene, which is located at Xp22.1, are the cause of the X-linked recessive condition termed Snyder-Robinson syndrome (SRS) [26–28]. These mutations drastically reduce spermine synthase activity and cause mild-to-moderate mental retardation, and may lead to a variety of other characteristics including a marfanoid habitus, skeletal defects, osteoporosis, and facial asymmetry, as well as hypotonia and movement disorders. Changes in the brain of SRS patients have been identified by using volumetric neuroimaging analyses [29].

The first mutation causing SRS that was identified is at position +5 of the 5′ splice site of intron 4 of the *SMS* gene. This splice variant leads to the loss of exon 4 and inserts a premature stop codon resulting in a truncated protein containing only the first 110 amino acids. Enzyme activity in cells derived from these was reduced by 85–90%. This residual activity is due to a small level of correct splicing [26]. More recently, point mutations in the coding region of the *SMS* gene have been identified (Gly56 to Ser, Val132 to Gly, and Ile150 to Thr [27, 28]). Cells from individuals with these mutations have greatly reduced spermine synthase activity and protein content. Studies with the purified recombinant spermine synthase mutants show that these alterations lead to a large loss of spermine synthase activity, an inability to form dimers, and greatly reduced protein stability (Nadaraia-Hoke S., Kanugula S., Pegg A.E., and Schwartz C.E., unpublished).

## Mice lacking spermine synthase

Attempts to generate mice with a specific inactivation of the *SMS* gene have not led to viable progeny in the 129/SVJ strain tested [30], but male gyro (Gy) mice, which have an X-chromosomal deletion that includes the *SMS* gene, do survive. These mice whose tissues contain no spermine are only viable on the B6C3H background [31, 32], and it is possible that some compensatory variation in other gene(s) allows survival. Gy mice have a greatly reduced size, sterility, deafness, neurological abnormalities, and a propensity to sudden death causing a very short life span [31–33]. All these defects are abolished by the provision of spermine via breeding with a transgenic

mouse line CAG/SpmS that expresses spermine synthase from a ubiquitous and unregulated promoter [34–36].

The Gy mouse was isolated from a female offspring of an irradiated mouse and was termed Gy based on a circling behavior pattern in affected males [37]. These mice have a deletion of part of the X chromosome that inactivates both *Phex,* a gene that regulates phosphate metabolism, and *SpmS* [31, 38]. The lack of the *Phex* gene product causes hypophosphatemia and abnormal bone development that is not reversed by the restoration of spermine synthase activity [35]. This greatly complicates experiments using Gy mice to address the critical question of whether spermine deficiency affects bone development in mice as might be expected from the phenotype of the SRS patients.

## Polyamine content and function in spermine synthase deficiency

It should be pointed out that all the known SRS patients have alterations that greatly reduce but do not abolish spermine synthase activity. In cultured cells (fibroblast or lymphoblast) from such patients, there is only a modest reduction in spermine but a greatly increased spermidine content, and thus a major decrease in the spermine:spermidine ratio as well as an increase in the total polyamine content [26–28]. This is presumably also the case in tissues from these patients. In cultured mouse embryonic cells from *SMS* knockouts or embryonic or skin fibroblasts from Gy mice, as well as in the Gy mouse tissues, there is no spermine, but spermidine is increased by an even greater amount so that total polyamines are increased here as well [30, 32, 39]. It is therefore possible that the altered total polyamine content and/or the changed spermine:spermidine ratio is the underlying reason for the phenotypic effects in the whole organism. The cultured cells lacking spermine grow at a normal rate [30, 32, 39] although they differ in sensitivity to some antiproliferative agents and UV radiation, and the skin fibroblasts were more resistant to oxidative stress.

One possible explanation for the contrast between the lack of effect on cultured cells and severe phenotype of the spermine synthase-deficient mammals is that polyamines play important roles as regulators of ion channels. These include: NMDA, AMPA, and kainate receptors, which mediate excitatory synaptic transmission in the mammalian brain; inwardly rectifying potassium channels (Kir), which control membrane potential and potassium homeostasis in many cell types; certain connexin-linked gap junctions; and some other channels that affect intracellular calcium signaling or $Na^+$ transport (see [40–42] and references therein). These effects are brought about by binding of the amine to the channel/receptor. In general, spermine is more potent than spermidine in interacting with these channels. It is possible that the increased spermidine level can compensate for other functions of polyamines including their key role as regulators of gene expression allowing for growth, but the altered spermine:spermidine ratio and change in total polyamine content may lead to incorrect signaling at these channels and/or to alterations in ion flux and membrane potential that have profound effects on the whole organism. Some support for this hypothesis is provided by studies of the deafness in Gy mice in which there is an almost complete collapse of the endocochlear potential, which is known to be controlled via the mouse cochlear lateral wall-specific Kir4.1 channel, whose internal rectification is highly polyamine dependent [36]. The steepness of rectification of cardiac Kir channels was reduced in myocytes from Gy mice [43]. Such changes could contribute to arrhythmias leading to the sudden death syndrome in these mice [33].

One other consequence of the absence of spermine synthase is a large rise in the content of dcAdoMet. In heart and kidney of Gy mice, the content of dcAdoMet exceeds or equals that of AdoMet whereas in normal tissues only a small fraction (c. 1–2%) of the AdoMet pool is in the form of dcAdoMet. The dcAdoMet content increased by 150-fold (heart), 27-fold (kidney), 20-fold (brain), and 10-fold (liver) in Gy mice (McCloskey D.E., Keefer K., Wang X., and Pegg A.E., unpublished). Although AdoMet synthetase is able to keep up with the demand for AdoMet, which decreased only slightly in these mice, it is possible that the increased dcAdoMet level interferes with other critical functions of AdoMet such as acting as a methyl donor for the synthesis of many key metabolites. Previous studies have demonstrated dcAdoMet is a potent inhibitor of DNA methylation [44].

## Regulation and overproduction of spermine synthase

The formation of the products of the aminopropyltransferases in mammals is usually determined by the availability of the substrates rather than by fluctuations in the levels of spermidine synthase or spermine synthase. There are only a few reports describing physiological alterations in spermine and spermidine synthase activity (reviewed in [1]). However, such changes may have been overlooked since the aminopropyltransferases are seldom measured in experiments on polyamine metabolism. Recent studies suggest both aminopropyltransferase genes are targets for increased transcription by *Myc* [45, 46] (Nillson J.A., personal communication).

Transgenic overexpression of high levels of spermine synthase has been achieved in mice by placing the spermine synthase cDNA under the control of a composite

CMV-I.E. enhancer/chicken β-actin promoter [34]. This promoter has been claimed to lead to ubiquitous high levels of expression, and several lines of CAG/SpmS mice were obtained in which spermine synthase was increased in all tissues examined. However, there was a much higher level of expression in some tissues than in others with heart and skeletal muscle showing greatest activity. This may be related to the actin promoter in the expression construct. In two well-characterized CAG/SpmS lines, in heart, muscle, and liver (which has a very low endogenous spermine synthase activity), the increase in spermine synthase was >500-fold, and it was >50-fold in many other tissues. Despite this huge increase, the rise in spermine was quite small or non-existent although there was a drop in spermidine levels. No evidence for increased polyamine degradation was observed in these mice [34]. However, there was a substantial fall in dcAdoMet levels (McCloskey D.E., Keefer K., Wang X., and Pegg A.E., unpublished), and it is very likely that the availability of dcAdoMet limits polyamine synthesis. There was no adverse phenotype in the CAG/SpmS mice.

## Spermine synthase structure and function

Recently, the structure of human spermine synthase has been solved in complexes with products and substrates [13]. This structure has a number of interesting features (Fig. 1a). The enzyme is a dimer of two identical subunits of 41 kDa. Each monomer has three domains: an N-terminal domain, which contains most of the dimer contacts; a central domain made up of four β-strands that serves as a lid for the C-terminal domain; and a C-terminal catalytic domain. All known aminopropyltransferases are either dimeric or tetrameric with two pairs of dimers.

## Function of the N-terminal domain

The N-terminal domain forms the bulk of the dimerization interface (Fig. 1b). Although each active site appears to be formed within the dimer with no obvious input from the N-terminal domain, dimerization appears to be essential for activity since deletion of part or all of this domain led to the protein behaving as a monomer and to a complete loss of activity [13]. This is consistent with the low activity of the point mutations causing SRS syndrome that are described above. Mutation Gly56Ser is located in this domain, and mutation Val132Gly is located at the join between the N-terminal and central domain and is likely to alter their relative positioning. As described above, none of the mutant proteins that are associated with SRS dimerize.

Remarkably, the N-terminal domain has strong structural homology to the proenzyme form of *S*-adenosylmethionine decarboxylase (AdoMetDC), which is the preceding enzyme in the polyamine biosynthetic pathway responsible for forming the aminopropyl donor dcAdoMet (Fig. 1c). AdoMetDC is synthesized as an inactive proenzyme (π chain). This spontaneously undergoes an internal autoprocessing reaction generating the α and β subunits of the active enzyme with the essential pyruvate prosthetic group, which is formed from an internal Ser residue located at the N-terminus of the chain [47, 48]. The spermine synthase N-terminal domain has no AdoMetDC activity since it lacks this essential Ser residue but can be superimposed with *T. maritima* AdoMetDC with RMSD of 2.8 Å and with human AdoMetDC with an RMSD of 3.0 Å. Although the function is not yet understood, it is very possible that this structural similarity indicates that the N-terminal domain has some regulatory importance outside a role in maintaining the dimer structure of spermine synthase. It may be relevant to this that trypanosomatids contain a paralog of the AdoMetDC π chain, which has a high affinity for the processed AdoMetDC forming a heterodimer with it. This complex increases activity by >1,000-fold, and it makes up the active form of AdoMetDC in these species [49, 50]. The possibility that spermine synthase in some way alters the function of AdoMetDC in mammalian cells should definitely be investigated.

## Function of the central and C-terminal domains

The N-terminal domain is connected by a long loop to the central β-strand domain (amino acids 138–172) consisting of four anti-parallel β-strands that serves as a lid for the C-terminal catalytic domain (amino acids 173–366). The structure made up by the central and C-terminal domains is very similar to human spermidine synthase (RMSD of 1.9 Å for all Cα atoms) (Fig. 1c). Structures with MTA and spermidine or spermine bound define the active site of spermine synthase [13]. The overall structure of the spermine and spermidine synthase catalytic domains is analogous to the canonical AdoMet-methyltransferase fold [51]. Alterations in the nucleoside binding site allow dcAdoMet to bind but not AdoMet itself. A key factor is the presence of a charged acidic residue (Asp201 in spermine synthase; Asp104 in human spermidine synthase) which would be incompatible with the binding of AdoMet. All aminopropyltransferases contain the sequence (V/I)(I/V/L)GGG(**D/E**)G(G/A) surrounding this acidic residue.

The amine substrate is positioned by interactions between its terminal nitrogen atoms and acidic residues in the protein and by hydrophobic interactions of the enzyme

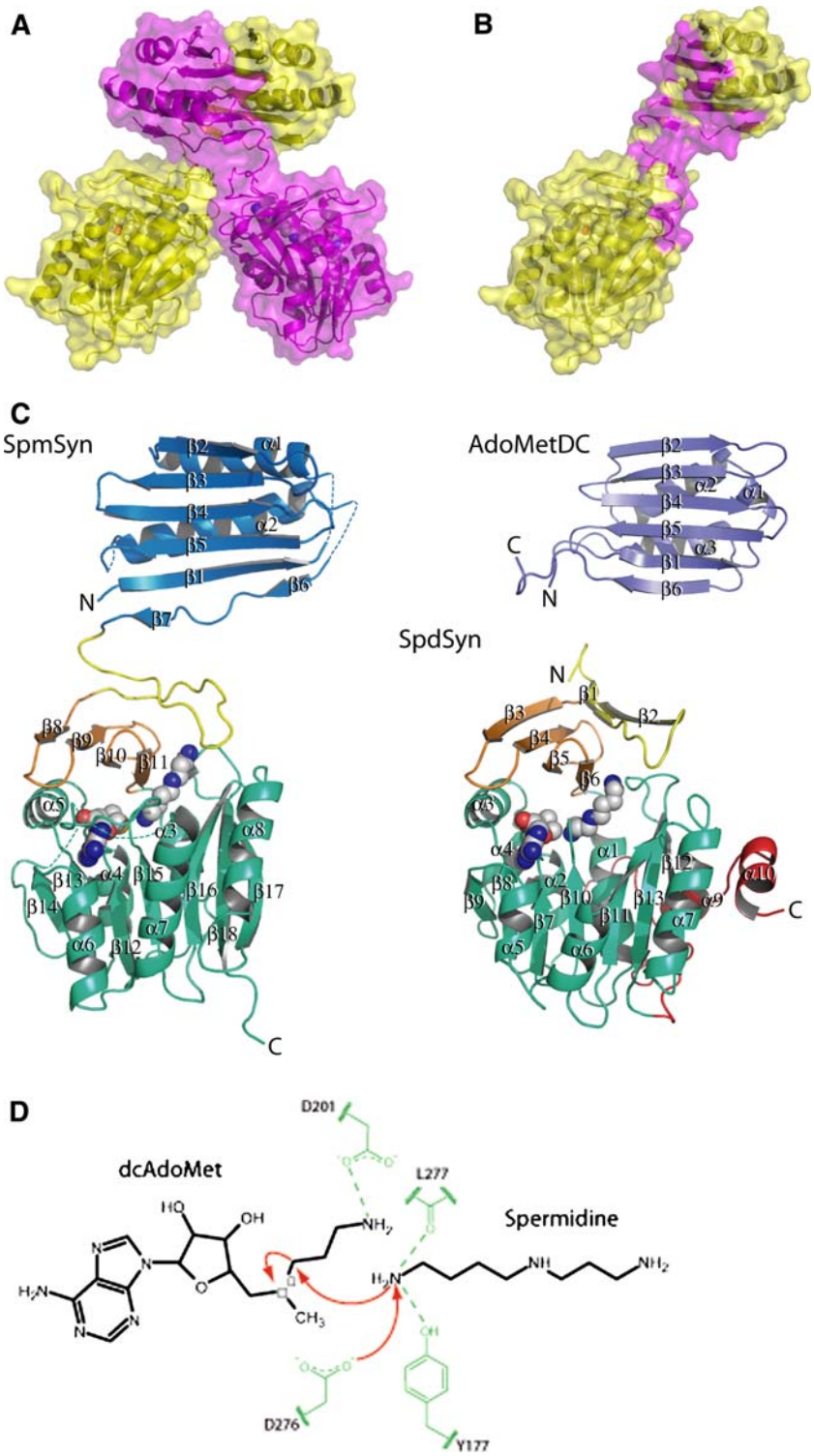



**Fig. 1** Spermine synthase structure and function. **a** The dimeric structure of spermine synthase. The bound molecules of spermidine and MTA are shown in *sphere* representation with carbon atoms in *gray*. **b** A monomer of spermine synthase with the dimerization interface in magenta. **c** Comparison of structures of monomers of human spermine synthase (*SpmSyn*), human spermidine synthase (*SpdSyn*), and *T. maritima* AdoMetDC proenzyme. **d** The postulated reaction mechanism. The spermidine and dcAdoMet substrates are shown in *black* and the key protein residues in *green*. A *red arrow* indicates the proposed attack by the spermidine amino group on the methylene carbon of the aminopropyl group. This figure is derived (with permission) from Figs. 2 and 7 in [13]

with the alkane portions of the polyamine. The major difference with spermidine synthase is in the active site pocket, which is larger and can accommodate spermidine as a substrate. The Trp residue that forms a steric block in spermidine synthase is replaced by a less bulky Ala residue. For catalysis, a key residue, which is conserved in all aminopropyltransferases, is Asp276, which acts to deprotonate the $N^{10}$-amino group of spermidine to allow attack on the C$\alpha$ atom of the aminopropyl group of dcAdoMet. This action is reinforced by interactions with the hydroxyl group of Tyr177 and the backbone carbonyl of Leu227 (Fig. 1d). Spermidine synthases have been

shown to have a similar mechanism for attack by putrescine [3, 9, 11].

Spermine synthase is strongly inhibited by the MTA product ($K_i$ about 0.3 μM) [1, 13]. Excretion or degradation of MTA by MTA phosphorylase is therefore needed to allow spermine synthesis to continue. The inhibition by MTA is due to the strong hydrophobic interactions of its adenine ring with the enzyme where it is stacked between Ile221, Ile282, and Leu227.

## Spermine synthase genes

The animal (metazoan) spermine synthase is distinguished by the N-terminal extension domain that is essential for enzymatic activity as described above. Some nematode worms such as *Caenorhabditis elegans* and the cnidarian *Hydra magnipapillata* have lost their spermine synthase, but it is clear that the ancestral animal lineage contained spermine synthase because it is present in the genome of *Monosiga brevicollis*, which belongs to the close sister group of animals, the choanoflagellatea (Fig. 2). Thus, the animal spermine synthase is considerably more ancient than the plant or fungal spermine synthases. Within the eukaryota, spermine synthase appears to be limited to animals and the choanoflagellate sister group, flowering plants and yeasts, and has evolved independently in each case. In contrast, thermospermine synthase appears to have disseminated from green algae and plants (Archaeplastidia) to other eukaryotic groups by serial endosymbiotic gene transfer and was probably initially acquired as a relaxed specificity aminopropyltransferase from the cyanobacterial progenitor of the primary chloroplast.

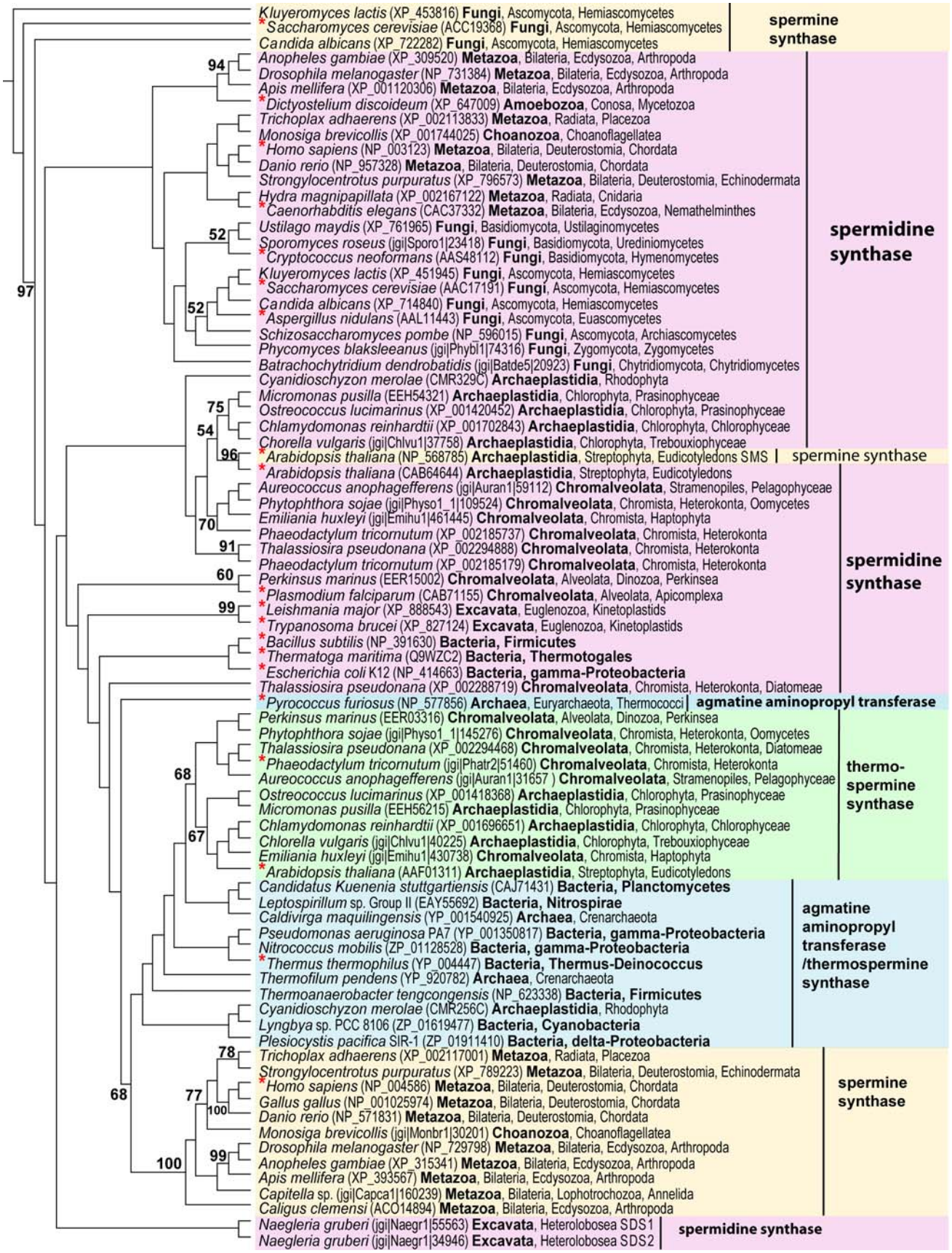
Unlike spermidine synthase and its product spermidine, which are ubiquitous in fungi, spermine synthase and spermine have a very limited distribution in fungi [52]. Of the four traditionally recognised fungal phyla, the monophyletic Ascomycota and Basidiomycota and the more basal and paraphyletic Zygomycota and Chytridiomycota, spermine synthase orthologues are found only in the Saccharomycotina class of the Ascomycota, which consists of the true yeasts (Fig. 2). The rest of the fungi contain only a spermidine synthase orthologue, which in the Basidiomycota is fused to saccharopine dehydrogenase [53]. Spermine synthase in yeasts appears to have arisen from a recent gene duplication of spermidine synthase.

Orthologues of spermine synthase in plants appear to be limited to the flowering plants (angiosperms). The characterized spermine synthase of *Arabidopsis thaliana* is closely related to the spermidine synthases of the same species, including conserved intron sites [14, 54], and would appear to be another case of a recent gene duplication of spermidine synthase followed by functional diversification. In contrast, orthologues of thermospermine synthase are found in all plants and green algae (Fig. 2). Thermospermine synthase orthologues are also found in members of the eukaryotic supergroup Chromalveolata (Fig. 2), including photosynthetic species such as diatoms (*Thalassiosira pseudonana* and *Phaeodactylum tricornutum*), coccolithophores (*Emiliania huxleyi*), and pelagophytes (*Aureococcus anophagefferens*), as well as species that are no longer photosynthetic but which are thought to have retained nuclear genes acquired from a lost red algal endosymbiont (*Perkinsus marinus* and *Phytophthora sojae*).

**Fig. 2** Neighbor-joining tree of amino acid sequences of diverse aminopropyltransferases. Trimming eliminated the extended N-terminal domain of metazoan spermine synthases and the saccharopine dehydrogenase C-terminal domain of Basidiomycota spermidine synthases. Alignment and neighbor-joining tree construction was performed as described [13]. Sequence names preceded by a *red asterisk* indicate aminopropyltransferase activities functionally confirmed. GeneBank protein sequence accession numbers are given in *parentheses*, numbers preceded by *JGI* indicate sequences from the Department of Energy Joint Genome Institute Genome Portal (http://genome.jgi-psf.org/) and the *Cyanidioschyzon merolae* sequences are from the corresponding *Cyanidioschyzon merolae* genome project (http://merolae.biol.s.u-tokyo.ac.jp/blast/blast.html). Figures represent percent value for 1,000 bootstrap replicates. The alignment upon which the tree is based is provided as an on-line supplementary figure ▶

## Conclusions

Spermine is essential for normal growth and development in animals, and their highly specific spermine synthase plays a key role in maintaining normal spermine levels. Although no unique role for spermine has been defined, the difference in potency between spermidine and spermine in effects on key cellular processes, such as ion channel regulation, transcription, translation, and enzyme activities, requires maintenance of a discrete spermine:spermidine ratio. The relative activities of the two aminopropyltransferases, spermidine synthase and spermine synthase, are important contributors to this regulation. Recent structure/function studies on these enzymes have provided a good understanding of their reaction mechanism and a basis for inhibitor design. Further work is needed to determine why the dimeric structure of spermine synthase is essential for activity and whether the N-terminal AdoMetDC-like domain has additional regulatory functions. The importance of spermine (and spermine synthase) in plants and those bacteria and fungi that contain this polyamine is not yet clearly established. Even though their growth does not appear to require the spermine synthase gene, the existence of a discrete spermine synthase in some


Kluyeromyces lactis (XP_453816) Fungi, Ascomycota, Hemiascomycetes
*Saccharomyces cerevisiae (ACC19368) Fungi, Ascomycota, Hemiascomycetes
Candida albicans (XP_722282) Fungi, Ascomycota, Hemiascomycetes
spermine synthase
Anopheles gambiae (XP_309520) Metazoa, Bilateria, Ecdysozoa, Arthropoda
Drosophila melanogaster (NP_731384) Metazoa, Bilateria, Ecdysozoa, Arthropoda
Apis mellifera (XP_001120306) Metazoa, Bilateria, Ecdysozoa, Arthropoda
*Dictyostelium discoideum (XP_647009) Amoebozoa, Conosa, Mycetozoa
Trichoplax adhaerens (XP_002113833) Metazoa, Radiata, Placezoa
Monosiga brevicollis (XP_001744025) Choanozoa, Choanoflagellatea
*Homo sapiens (NP_003123) Metazoa, Bilateria, Deuterostomia, Chordata
Danio rerio (NP_957328) Metazoa, Bilateria, Deuterostomia, Chordata
Strongylocentrotus purpuratus (XP_796573) Metazoa, Bilateria, Deuterostomia, Echinodermata
Hydra magnipapillata (XP_002167122) Metazoa, Radiata, Cnidaria
*Caenorhabditis elegans (CAC37332) Metazoa, Bilateria, Ecdysozoa, Nemathelminthes
Ustilago maydis (XP_761965) Fungi, Basidiomycota, Ustilaginomycetes
Sporomyces roseus (jgi|Sporo1|23418) Fungi, Basidiomycota, Urediniomycetes
*Cryptococcus neoformans (AAS48112) Fungi, Basidiomycota, Hymenomycetes
Kluyeromyces lactis (XP_451945) Fungi, Ascomycota, Hemiascomycetes
*Saccharomyces cerevisiae (AAC17191) Fungi, Ascomycota, Hemiascomycetes
Candida albicans (XP_714840) Fungi, Ascomycota, Hemiascomycetes
*Aspergillus nidulans (AAL11443) Fungi, Ascomycota, Euascomycetes
Schizosaccharomyces pombe (NP_596015) Fungi, Ascomycota, Archiascomycetes
Phycomyces blaksleeanus (jgi|Phybl1|74316) Fungi, Zygomycota, Zygomycetes
Batrachochytridium dendrobatidis (jgi|Batde5|20923) Fungi, Chytridiomycota, Chytridiomycetes
Cyanidioschyzon merolae (CMR329C) Archaeplastidia, Rhodophyta
spermidine synthase
Micromonas pusilla (EEH54321) Archaeplastidia, Chlorophyta, Prasinophyceae
Ostreococcus lucimarinus (XP_001420452) Archaeplastidia, Chlorophyta, Prasinophyceae
Chlamydomonas reinhardtii (XP_001702843) Archaeplastidia, Chlorophyta, Chlorophyceae
Chorella vulgaris (jgi|Chlvu1|37758) Archaeplastidia, Chlorophyta, Trebouxiophyceae
*Arabidopsis thaliana (NP_568785) Archaeplastidia, Streptophyta, Eudicotyledons SMS
spermine synthase
*Arabidopsis thaliana (CAB64644) Archaeplastidia, Streptophyta, Eudicotyledons
Aureococcus anophagefferens (jgi|Auran1|59112) Chromalveolata, Stramenopiles, Pelagophyceae
Phytophthora sojae (jgi|Physo1_1|109524) Chromalveolata, Chromista, Heterokonta, Oomycetes
Emiliania huxleyi (jgi|Emihu1|461445) Chromalveolata, Chromista, Haptophyta
Phaeodactylum tricornutum (XP_002185737) Chromalveolata, Chromista, Heterokonta
Thalassiosira pseudonana (XP_002294888) Chromalveolata, Chromista, Heterokonta
Phaeodactylum tricornutum (XP_002185179) Chromalveolata, Chromista, Heterokonta
Perkinsus marinus (EER15002) Chromalveolata, Alveolata, Dinozoa, Perkinsea
*Plasmodium falciparum (CAB71155) Chromalveolata, Alveolata, Apicomplexa
*Leishmania major (XP_888543) Excavata, Euglenozoa, Kinetoplastids
*Trypanosoma brucei (XP_827124) Excavata, Euglenozoa, Kinetoplastids
*Bacillus subtilis (NP_391630) Bacteria, Firmicutes
*Thermatoga maritima (Q9WZC2) Bacteria, Thermotogales
*Escherichia coli K12 (NP_414663) Bacteria, gamma-Proteobacteria
Thalassiosira pseudonana (XP_002288719) Chromalveolata, Chromista, Heterokonta, Diatomeae
spermidine synthase
*Pyrococcus furiosus (NP_577856) Archaea, Euryarchaeota, Thermococci
agmatine aminopropyl transferase
Perkinsus marinus (EER03316) Chromalveolata, Alveolata, Dinozoa, Perkinsea
Phytophthora sojae (jgi|Physo1_1|145276) Chromalveolata, Chromista, Heterokonta, Oomycetes
Thalassiosira pseudonana (XP_002294468) Chromalveolata, Chromista, Heterokonta, Diatomeae
*Phaeodactylum tricornutum (jgi|Phatr2|51460) Chromalveolata, Chromista, Heterokonta
Aureococcus anophagefferens (jgi|Auran1|31657 ) Chromalveolata, Stramenopiles, Pelagophyceae
Ostreococcus lucimarinus (XP_001418368) Archaeplastidia, Chlorophyta, Prasinophyceae
Micromonas pusilla (EEH56215) Archaeplastidia, Chlorophyta, Prasinophyceae
Chlamydomonas reinhardtii (XP_001696651) Archaeplastidia, Chlorophyta, Chlorophyceae
Chlorella vulgaris (jgi|Chlvu1|40225) Archaeplastidia, Chlorophyta, Trebouxiophyceae
Emiliania huxleyi (jgi|Emihu1|430738) Chromalveolata, Chromista, Haptophyta
*Arabidopsis thaliana (AAF01311) Archaeplastidia, Streptophyta, Eudicotyledons
thermo-spermine synthase
Candidatus Kuenenia stuttgartiensis (CAJ71431) Bacteria, Planctomycetes
Leptospirillum sp. Group II (EAY55692) Bacteria, Nitrospirae
Caldivirga maquilingensis (YP_001540925) Archaea, Crenarchaeota
Pseudomonas aeruginosa PA7 (YP_001350817) Bacteria, gamma-Proteobacteria
Nitrococcus mobilis (ZP_01128528) Bacteria, gamma-Proteobacteria
*Thermus thermophilus (YP_004447) Bacteria, Thermus-Deinococcus
Thermofilum pendens (YP_920782) Archaea, Crenarchaeota
Thermoanaerobacter tengcongensis (NP_623338) Bacteria, Firmicutes
Cyanidioschyzon merolae (CMR256C) Archaeplastidia, Rhodophyta
Lyngbya sp. PCC 8106 (ZP_01619477) Bacteria, Cyanobacteria
Plesiocystis pacifica SIR-1 (ZP_01911410) Bacteria, delta-Proteobacteria
agmatine aminopropyl transferase /thermospermine synthase
Trichoplax adhaerens (XP_002117001) Metazoa, Radiata, Placezoa
Strongylocentrotus purpuratus (XP_789223) Metazoa, Bilateria, Deuterostomia, Echinodermata
*Homo sapiens (NP_004586) Metazoa, Bilateria, Deuterostomia, Chordata
Gallus gallus (NP_001025974) Metazoa, Bilateria, Deuterostomia, Chordata
Danio rerio (NP_571831) Metazoa, Bilateria, Deuterostomia, Chordata
Monosiga brevicollis (jgi|Monbr1|30201) Choanozoa, Choanoflagellatea
Drosophila melanogaster (NP_729798) Metazoa, Bilateria, Ecdysozoa, Arthropoda
Anopheles gambiae (XP_315341) Metazoa, Bilateria, Ecdysozoa, Arthropoda
Apis mellifera (XP_393567) Metazoa, Bilateria, Ecdysozoa, Arthropoda
Capitella sp. (jgi|Capca1|160239) Metazoa, Bilateria, Lophotrochozoa, Annelida
Caligus clemensi (ACO14894) Metazoa, Bilateria, Ecdysozoa, Arthropoda
spermine synthase
Naegleria gruberi (jgi|Naegr1|55563) Excavata, Heterolobosea SDS1
Naegleria gruberi (jgi|Naegr1|34946) Excavata, Heterolobosea SDS2
spermidine synthase
94
52
97
52
75
54
96
70
91
60
99
68
67
68
78
77
100
100
99

of these species suggests that spermine may have a function that would be revealed only in certain environmental conditions.

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