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Polyamines in Eukaryotes, Bacteria, and Archaea*

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Polyamines are primordial polycations found in most cells and perform different functions in different organisms. Although polyamines are mainly known for their essential roles in cell growth and proliferation, their functions range from a critical role in cellular translation in eukaryotes and archaea, to bacterial biofilm formation and specialized roles in natural product biosynthesis. At first glance, the diversity of polyamine structures in different organisms appears chaotic; however, biosynthetic flexibility and evolutionary and ecological processes largely explain this heterogeneity. In this review, I discuss the biosynthetic, evolutionary, and physiological processes that constrain or expand polyamine structural and functional diversity.

The common feature of diverse polyamines found in eukaryotes, bacteria, and archaea is that they are all derived from amino acids and are positively charged at physiological pH. Structurally, they are mostly linear and flexible aliphatic chains containing two or more amine groups. They include the diamines 1,3-diaminopropane (Dap),[2] 1,4-diaminobutane (putrescine, Put), and 1,5-diaminopentane (cadaverine, Cad), triamines *sym*-norspermidine (Nspd), spermidine (Spd), and *sym*-homospermidine (Hspd), the uncommon triamines aminopropylcadaverine and aminobutylcadaverine, the tetraamines norspermine (Nspm), spermine (Spm), and thermospermine (Tspm), and the uncommon tetraamine aminopropyl homospermidine (Fig. 1), and a wide range of longer chain polyamines and branched polyamines. This review will cover the distribution and biosynthesis of different polyamines in the three domains of life and will discuss the mechanisms underlying this biosynthetic diversity.

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[2] The abbreviations used are: Dap, 1,3-diaminopropane; Cad, cadaverine; Put, putrescine; Spd, spermidine; Hspd, *sym*-homospermidine; Nspd, *sym*-norspermidine; SpdSyn, spermidine synthase; Spm, spermine; Nspm, norspermine; SpmSyn, spermine synthase; Tspm, thermospermine; TspmSyn, thermospermine synthase; AdoMetDC, *S*-adenosyl-L-methionine; dcAdoMet, decarboxylated *S*-adenosyl-L-methionine; ADC, arginine decarboxylase; Agm, agmatine; AIH, agmatine iminohydrolase/deiminase; AUH, agmatine ureohydrolase/agmatinase; CASDC, carboxyspermidine decarboxylase; CASDH, carboxyspermidine dehydrogenase; DABA AT, L-2,4-diaminobutyrate:2-ketoglutarate 4-aminotransferase; DABA DC, L-2,4-diaminobutyrate decarboxylase; DHS, deoxyhypusine synthase; HSS, homospermidine synthase; LCPA, long chain polyamine; NCPAH, *N*-carbamoylputrescine amidohydrolase/amidase; ODC, ornithine decarboxylase; L/ODC, bifunctional lysine/ornithine decarboxylase.

Polyamines in Eukaryotes

Eukaryotic Diversity

When considering the distribution of different polyamines in eukaryotes, it is worth considering two major factors. Firstly, the aminobutyl group of Spd is required for the hypusine post-translational modification of translation factor eIF5A, which is required for the translation of mRNAs encoding polyproline tracts (1–6). The enzyme deoxyhypusine synthase (DHS) transfers the aminobutyl group of Spd to eIF5A and is encoded in all eukaryotic genomes, including some intracellular parasites that have lost their polyamine biosynthetic pathway (7). Thus, the aminobutyl group of Spd is very probably universally required for eukaryotic life, although some single-celled eukaryotes appear to have replaced Spd with Hspd, which has two aminobutyl groups (7). The second factor to consider is the evolutionary events that have driven eukaryotic diversification, and that in large part underpin polyamine biosynthetic diversification. Current consensus about eukaryotic diversity from a phylogenomic point of view is that there are five supergroups and some unaligned groups (8). These are: the Opisthokonta, containing animals (Metazoa), Fungi, Choanoflagellida, and Microsporidia; the Amoebozoa, consisting of mostly single-celled amoeboid species and slime molds; the Archaeplastida, including plants, green and red algae, and also glaucocystophytes; the Excavata, encompassing heterotrophic and parasitic single-celled species; and the newly designated and large SAR group, assembled from stramenopiles, alveolates, and Rhizaria (8). Other major groups that are outside the supergroups include the cryptomonads and haptophytes.

A key evolutionary development in the diversification of eukaryotes, which is of profound relevance to the diversification of polyamine metabolism, was the assimilation of an endosymbiotic cyanobacterium in the heterotrophic ancestor of Archaeplastida, which then became the chloroplast (a large literature reviewed in Ref. 9). Furthermore, heterotrophic single-celled eukaryotes subsequently took up and assimilated red or green algal cells in independent secondary endosymbioses (10), and even tertiary endosymbioses in dinoflagellates (11). The nuclear genomes of the original heterotrophic host cells that have undergone these serial endosymbioses have acquired genes of cyanobacterial origin.

The Core Polyamine Biosynthetic Pathway

What was the likely ancestral polyamine biosynthetic pathway in the Last Eukaryotic Common Ancestor? As putrescine and spermidine are the only polyamines produced in all eukaryotes that synthesize polyamines, the ancestral pathway was almost certainly the extant core eukaryotic polyamine biosynthetic pathway depicted in Fig. 2. Ornithine decarboxylase (ODC) produces Put from ornithine (12), and Spd is formed by spermidine synthase (SpdSyn) through the aminopropylation of Put (13) using an aminopropyl group donated by decarboxy-

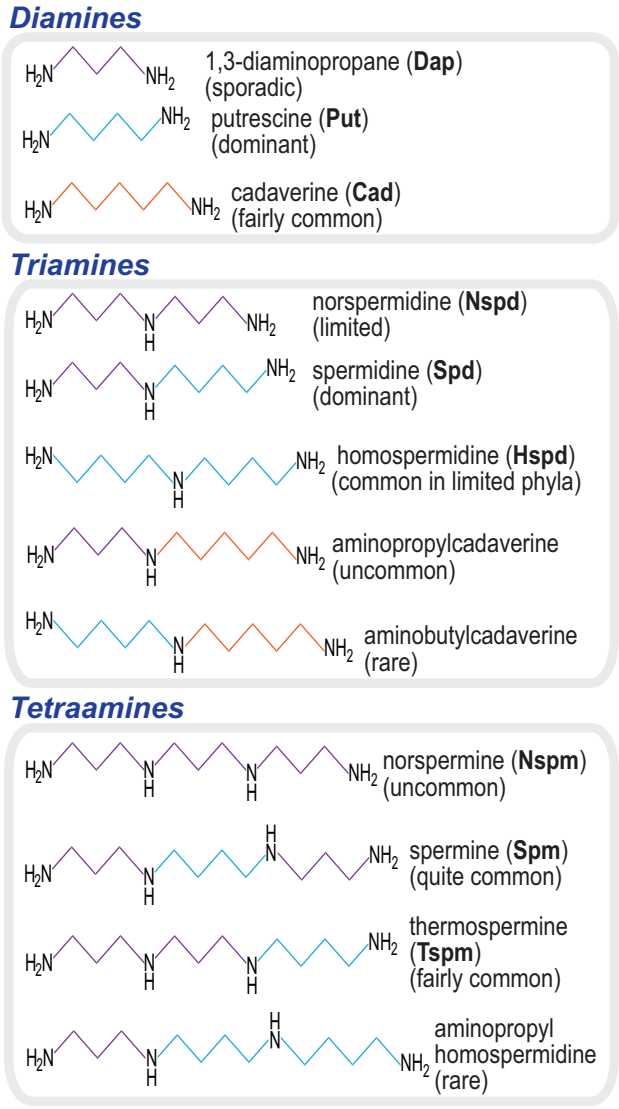

FIGURE 1. **Polyamines of the diamine, triamine, and tetraamine classes found in eukaryotes, bacteria, and archaea.** The aminopropyl and aminobutyl groups transferred to diamines or triamines to form triamines or tetraamines are shown in *purple* and *blue*, respectively. At physiological pH, these molecules are fully protonated. Approximate relative distributions of the polyamines are indicated in *parentheses*.

lated *S*-adenosylmethionine (dcAdoMet). The dcAdoMet is formed by the decarboxylation of AdoMet performed by *S*-adenosylmethionine decarboxylase (AdoMetDC) (14, 15). ODC, AdoMetDC, and SpdSyn are the universal pathway for spermidine biosynthesis in eukaryotes, and the pathway has been characterized in trypanosomes (16), *Leishmania* (17), *Plasmodium falciparum* (18), and filamentous fungus *Neurospora crassa* (19, 20), among others. Thus, the core pathway producing the triamine Spd has been characterized in the Excavata, SAR, and Opisthokonta supergroups.

The ancestral pathway did not synthesize the tetraamine Spm; however, Spm biosynthesis (Fig. 2) has evolved independently in the recent common ancestor of metazoans (21), in flowering plants (22), and in Saccharomycotina yeasts (23), although Spm is not present in the rest of the fungi including filamentous fungi (24). In the case of flowering plants and yeasts, the aminopropyltransferase spermine synthase (SpmSyn) evolved independently in each case by duplication of the gene encoding SpdSyn and subsequent change of substrate specificity (25), whereas the metazoan SpmSyn appears to have been acquired by horizontal gene transfer from a bacterial gene encoding an AdoMetDC-SpdSyn fusion protein that evolved to exhibit SpmSyn activity and lose AdoMetDC activity (21, 25). The core eukaryotic polyamine biosynthetic pathway can be seen to have diversified through biosynthetic extension in different phyla by evolution of a second aminopropylation step to produce Spm.

Biosynthetic Diversification via Endosymbiotic and Horizontal Gene Transfer

An additional and fundamental biosynthetic diversification step occurred when the Archaeplastida (glaucocystophytes, red and green algae, and plants) evolved from a heterotrophic single-celled eukaryote through the assimilation of a cyanobacterial endosymbiont that became the chloroplast. It has been determined, by analysis of the genome of the flowering plant *Arabidopsis thaliana*, that about 4,000 genes were transferred from the chloroplast progenitor to the host nucleus, and some 2,000 proteins encoded by those genes are now relocalized to the chloroplast (26). In the algal and plant lineage, an alternative Put biosynthetic pathway (Fig. 2) was acquired from the chloroplast cyanobacterial progenitor, consisting of arginine decarboxylase (ADC), which produces agmatine (Agm) from arginine, agmatine iminohydrolase/deiminase (AIH), which produces *N*-carbamoylputrescine from Agm, and *N*-carbamoylputrescine amidohydrolase (NCPAH), which produces Put from *N*-carbamoylputrescine (27–30). In addition, the same endosymbiotic source appears to have been the origin of the aminopropyltransferase thermospermine synthase (TspmSyn) (25, 31), which produces the tetraamine Tspm (Fig. 2), an isomer of Spm, and because of the identical masses of spermine and thermospermine, was originally misidentified as a SpmSyn (32). Homologues encoding TspmSyn-like proteins are found throughout the plant and algal lineage (25, 33) and also in members of the SAR supergroup that have undergone secondary endosymbiosis events (25), including some species that are no longer photosynthetic, such as oomycetes. It is not known whether the TspmSyn-like proteins produce Tspm in these species.

An additional, and phylogenetically more limited, polyamine biosynthetic diversity in eukaryotes is found mainly in plants. Some plants decarboxylate lysine to form the diamine Cad (Fig. 1), destined for quinolizidine alkaloid biosynthesis (34). The enzyme responsible for lysine decarboxylation in quinolizidine-producing plants is an alanine racemase fold bifunctional lysine/ornithine decarboxylase (L/ODC) that has coevolved with alkaloid production in leguminous plants (35). This bifunctional L/ODC has evolved independently in plants from ODC, and has acquired a chloroplast-targeting sequence to localize it in the plastid where lysine is produced (35). Plants have also evolved an alternative homospermidine synthase (DHS-like HSS) to produce Hspd (Fig. 1) used in pyrrolizidine alkaloid biosynthesis (36, 37). This enzyme has evolved independently several times in flowering plants through duplication of the gene encoding DHS (38), and unlike the bacterial HSS,

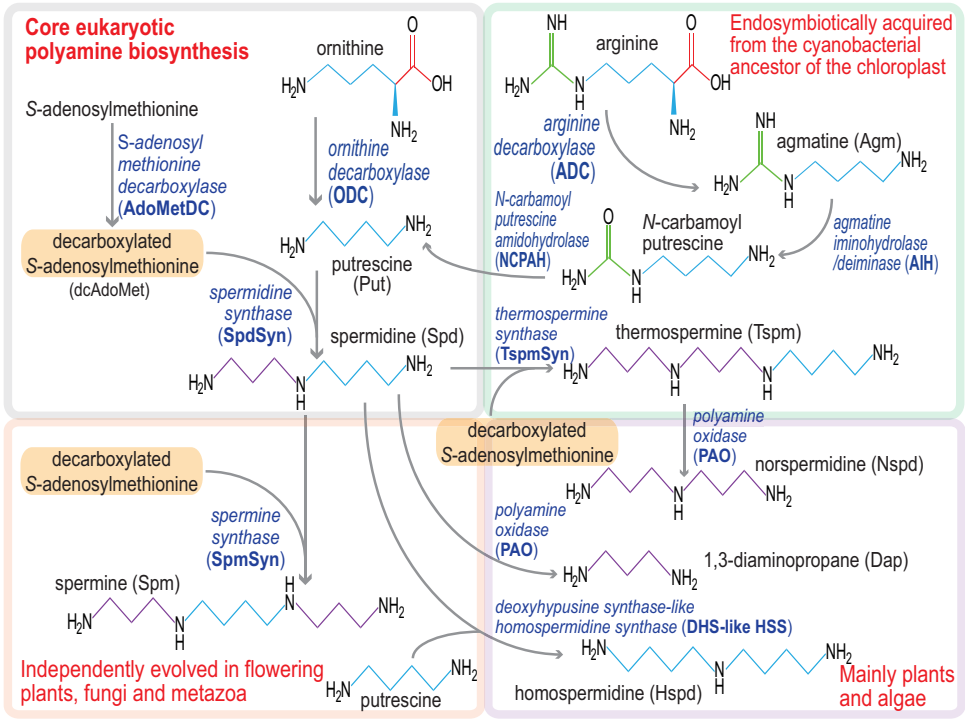

FIGURE 2. **Evolutionary diversification of polyamine biosynthesis in eukaryotes.** The ancestral polyamine biosynthetic pathway in eukaryotes synthesized Spd. Spm biosynthesis evolved independently at least three times, and Tspm biosynthesis was acquired from the cyanobacterial ancestor of the chloroplast. Hspd biosynthesis evolved independently multiple times in flowering plants by gene duplication of deoxyhypusine synthase. Dap and Nspd are products of Spm/Spd and Tspm catabolism, respectively.

which is a completely different enzyme (Fig. 2), the plant enzyme must use Spd as a co-substrate.

In some single-celled heterotrophs, including the ciliate *Paramecium tetraurelia* (SAR supergroup), heterolobosean amoeba *Sawyeria marylandensis* (Excavata), and slime mold *Physarum polycephalum* (Amoebozoa), Hspd is produced using a horizontally acquired bacterial HSS (7, 39, 40). The bacterially derived HSS is from an entirely different fold and evolutionary origin from the DHS-like HSS (39). Many single-celled parasites have lost their polyamine biosynthetic pathway, usually those with an intracellular parasitic lifestyle, and even multicellular schistosome worms have discarded polyamine biosynthesis (7). These Spd-auxotrophic organisms must acquire Spd from their host.

An enigmatic area of polyamine metabolism in eukaryotes is the production of triamine Nspd and tetraamine Nspm (Fig. 1). Both of these unusual polyamines have been detected in lower, single-celled eukaryotes including dinoflagellates, cryptophytes, haptophytes, *Euglena* species, and diatoms (41, 42). Nspd is also present in the green alga phylum Chlorophyta, where it is prevalent in classes Trebouxiophyceae, Chlorophyceae, including *Chlamydomonas* and *Volvox*, and Ulvophyceae but absent in Prasinophyceae (43). Mosses and the flowering plant alfalfa were also found to contain Nspd and Nspm (44, 45). Little is known about the biosynthesis of Nspd and Nspm in eukaryotes, and there is no equivalent of the Nspd biosynthetic pathway found in the γ-proteobacterium *Vibrio cholerae*. It is also noticeable that Dap, the precursor of Nspd in *V. cholerae*, is rarely detected in eukaryotes. Intriguingly, production of Dap from radiolabeled Spd was demonstrated in the leguminous plant alfalfa (46), and it is known that plant polyamine oxidases can produce Dap (Fig. 2) as a co-product of the oxidation of Spd (47). However, the alfalfa aminopropyltransferase did not recognize Dap as a substrate, although it was able to produce Spd, Spm, and Tspm from Put (48). Production of Nspd in eukaryotes therefore was a mystery until very recently, when it was shown that a plant polyamine oxidase produces Nspd as a catabolic product from Tspm (49). It is possible that Nspm could be biosynthetically produced from the catabolic product Nspd by standard aminopropylation; however, there is no published evidence for this route of Nspm biosynthesis. There is a correlation between the presence of homologues of the *A. thaliana acl5*-encoded TspmSyn in genome sequences (25) and the identification of Nspd in the corresponding organisms.

An unusual group of polyamines is present in the biosilica glass-containing diatoms. They contain species-specific long chain polyamines (LCPAs), based on a single Put, Spd, or Dap unit to which is added multiple repeating aminopropyl units, which may or may not be *N*-methylated on each repeating unit (50, 51). It is thought that the LCPAs participate in the condensation of silicic acid to form silica through a phase separation process that also involves proteins that are modified by a separate class of LCPAs linked through a lysine residue (52, 53). From genome analysis, it appears likely that the diatom LCPAs are synthesized by a set of horizontally acquired bacterial AdoMetDC-aminopropyltransferase fusion proteins occasionally containing methyltransferase (SET) domains (54). LCPAs that are similar but lack *N*-methylation are found in glass sponges where they may also be involved in biosilica formation

(55). LCPAs have been detected in the silicifying haptophyte coccolithophore *Prymnesium neolepis*, consisting of multiple *N*-methylated aminopropyl repeat units extending from the ϵ-amino group of lysine (56).

Eukaryotic Synopsis

In conclusion, the core eukaryotic polyamine biosynthetic pathway consists of the production of Spd from ornithine, with the aminobutyl group of Spd used for the essential hypusine modification of translation factor eIF5A. The Last Eukaryotic Common Ancestor very probably encoded the same core pathway, consisting of an alanine racemase fold ODC, AdoMetDC, and the aminopropyltransferase SpdSyn. Through endosymbiotic gene transfer, the cyanobacterial ancestor of the chloroplast contributed the ADC, AIH, and NCPAH pathway from arginine to Put, found now mainly in terrestrial plants, and also TspmSyn, found in the Archaeplastida and species that have undergone secondary and tertiary endosymbiotic acquisition of a red or green alga. In addition to these enzymes acquired by endosymbiotic gene transfer, polyamine biosynthesis has expanded either by duplication of the gene encoding SpdSyn to form SpmSyn in flowering plants and yeasts or by horizontal acquisition of a bacterial fusion gene that evolved to encode the metazoan SpmSyn. In some plants, Cad can be produced by an ODC that has evolved to recognize lysine as well as ornithine, and Hspd is produced by an enzyme that evolved from a gene duplication of gene encoding DHS to form a DHS-like HSS. Some single-celled eukaryotes have horizontally acquired a bacterial HSS. Dap and Nspd are products of catabolism of Spd/Spm and Tspm by polyamine oxidases. The LCPAs of diatoms are very likely synthesized by bacterially derived AdoMetDC-aminopropyltransferase fusion proteins that have evolved through acquisition of methyltransferase and chromatin modification domains.

Polyamines in Bacteria

The bacterial analogue of eIF5A, elongation factor EF-P, is modified by lysine rather than by an aminobutyl group from Spd (57, 58), and there is no known conserved function of any polyamine in bacteria. Reflecting these observations is the presence of a more varied polyamine repertoire in bacteria. Spd is the most commonly found triamine, although many bacteria from diverse phyla produce only Hspd, and a much smaller number of bacteria produce only Nspd (59). There is also a diversity of diamines found in bacteria, and by far the most common is Put, but Cad is also widespread in Proteobacteria, and Dap is found sporadically in diverse phyla.

Diamines are mainly produced biosynthetically, but in a much more phylogenetically limited group of bacteria, they are produced as a response to acid stress, through specific acid-induced decarboxylation of arginine, ornithine, and lysine and subsequent export of Agm, Put, and Cad (60, 61). Dap is produced as a precursor of Nspd in the Vibrionales (62–64) and is also produced in the absence of Nspd production in species such as *Acinetobacter baumannii* (63). Biosynthesis of Dap involves two enzymes: L-2,4-diaminobutyrate:2-ketoglutarate 4-aminotransferase (DABA AT) and L-2,4-diaminobutyrate decarboxylase (DABA DC). There are several pathways for Put production in bacteria: directly through ODC activity or indirectly by ADC to form Agm, and then directly from Agm to Put using agmatinase/agmatine ureohydrolase (AUH), or indirectly from Agm via *N*-carbamoylputrescine to Put using AIH and NCPAH. The most prevalent route, decarboxylation of arginine, is performed by ADC enzymes that have convergently evolved from at least four different protein folds (65). Cad and Dap can be produced by dedicated genes encoding lysine decarboxylase (LDC), and by DABA AT/DABA DC that are incorporated into gene clusters of siderophore biosynthetic enzymes, and in these cases, the diamine is incorporated into the siderophore structure (66). A phylogenetically limited diamine, found almost exclusively in β-proteobacteria, is 2-hydroxyputrescine (59), but the hydroxylating enzyme has not yet been identified.

The most prevalent triamine in bacteria is Spd, and in contrast to eukaryotes, there are two alternative pathways for Spd biosynthesis: the AdoMet-dependent pathway using AdoMetDC and SpdSyn found in all three domains of life (67), and a bacteria-specific aspartate β-semialdehyde-dependent pathway (Fig. 3) that uses carboxyspermidine dehydrogenase (CASDH) and carboxyspermidine decarboxylase (CASDC) (64, 68, 69). A variant AdoMet-dependent pathway is present in some bacteria such as the extreme hyperthermophile *Thermus thermophilus*, where Agm is aminopropylated to form aminopropylagmatine, the substrate for an AUH homologue that then produces Spd (70). There is inherent biosynthetic flexibility in both alternative pathways. When Put supply was made limiting by growing an *Escherichia coli* AUH mutant in arginine-containing medium, aminopropylcadaverine (Fig. 1) was formed (71), and it was later shown that aminopropylcadaverine is as effective as Spd in restoring normal growth to a polyamine auxotroph (72). Production of aminopropylcadaverine by the AdoMetDC/SpdSyn pathway has also been demonstrated with mammalian and fungal cells (73, 74).

The CASDC/CASDH pathway was shown to produce Nspd from Dap and Spd from Put in *V. cholerae* (64); and Spd from Put, and aminopropylcadaverine and bis(aminopropylcadaverine) from Cad in the α-proteobacterium *Agrobacterium tumefaciens* (75). Triamine Hspd can be produced either by HSS, an enzyme related to CASDH, or from the DHS homologue DHS-like HSS (39). The HSS enzyme of *Bradyrhizobium japonicum* is able to aminobutylate Cad to form 4-aminobutylcadaverine (39, 76), and it was later demonstrated to be a common feature of HSS from diverse phyla expressed in *E. coli* (39). It should be pointed out that although the plant DHS-like HSS enzymes have been functionally confirmed, the evidence for the bacterial DHS-like HSS activity is still circumstantial.

It had been accepted dogma that bacteria do not produce Spm (77); however, that supposition was incorrect, and in fact Spm has been detected in diverse bacteria (25). No specific bacterial SpmSyn has been identified, and it is likely that in some species the Spd biosynthetic machinery can recognize Spd as a substrate to synthesize Spm (75). It has also been claimed that homologues of the plant *A. thaliana acl5*-encoded aminopropyltransferase TspmSyn found in bacteria are also specific for Tspm synthesis (77); however, it is more likely that those homologues encode agmatine aminopropyltransferase (70), because there are no reports of Tspm in the bacteria that pos-

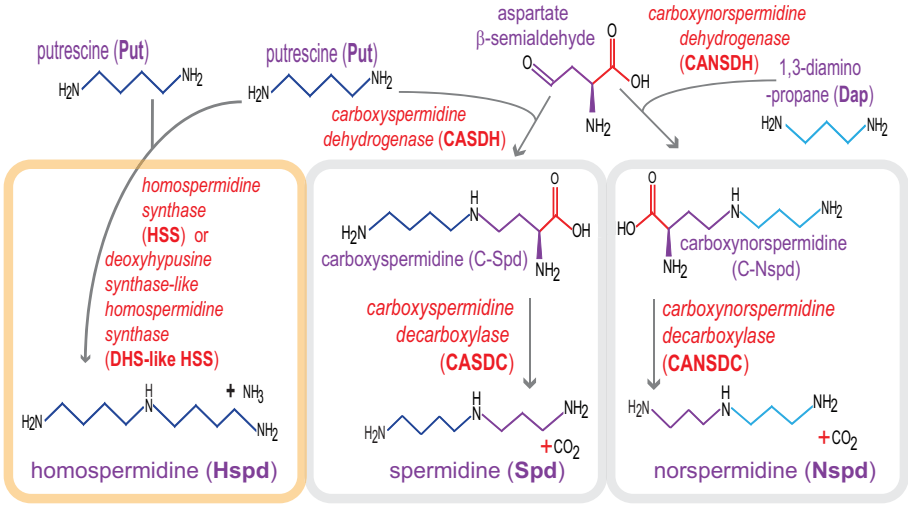

FIGURE 3. **Bacteria-specific polyamine biosynthetic pathways.** Enzyme names are indicated in *red*. Carboxyspermidine (*C-Spd*) and carboxynorspermidine (*C-Nspd*) do not accumulate in wild type bacteria. Two different proteins, HSS or DHS-like HSS, can produce Hspd. The *S*-adenosylmethionine-dependent pathway for Spd biosynthesis is found in all three domains of life and is not shown. Similarly, the aminopropylagmatine variant pathway is also found in archaea and is not shown. The aspartate β-semialdehyde-derived aminopropyl group is shown in *purple*.

sess Acl5 homologues. In some bacteria such as the α-proteobacterium *Rhodothalassium salexigens*, Hspd is aminopropylated to form the tetraamine aminopropylhomospermidine (78). Aminopropylated Nspd, *i.e.* the tetraamine Nspm (Fig. 1), is found in diverse hyperthermophiles (79), but the biosynthetic pathway is uncharacterized. The wide repertoire of tetraamine and longer chain polyamines found in the extreme hyperthermophile *T. thermophilus* is likely to be synthesized by the agmatine aminopropyltransferase, as this enzyme can also recognize Nspd and Spd as substrates (80). It is not known how Nspd is produced in *T. thermophilus*, but it is possible that Nspd may be a product of Tspm oxidation.

Polyamines in Archaea

Archaea possess a version of eIF5A that is also modified by hypusine formation (81), and inhibition of DHS by N^1-guanyl-1,7-diaminoheptane causes cell cycle arrest in the crenarchaeote *Sulfolobus acidocaldarius* (82). Because all archaeal genomes encode a DHS homologue, it can be reasonably assumed that Spd will be required for cell growth in all archaea. It was discovered that Agm is essential for cell growth of *Thermococcus kodakaraensis* (83) and cannot be substituted by Put or Spd. Subsequently, it was shown that Agm is used to modify a cytidine in the anticodon of archaeal tRNA(Ile) and that the agmatine modification (agmatidine) is essential for decoding AUA (84, 85). The hypusine and agmatidine modifications mean that archaea must synthesize Spd or Hspd (Hspd can donate an aminobutyl group for deoxyhypusine formation) and that it must be through the ADC pathway to produce Agm. Although Spd is the most common triamine in archaea, Hspd is prevalent in the Methanobacteria, Methanococci, and Methanomicrobia (86).

There are two forms of ADC, a trimeric pyruvoyl-dependent enzyme (87, 88), and mainly in the Crenarchaeota, a paralogue of AdoMetDC that has acquired the ability to recognize arginine as a substrate (89). Two forms of agmatinase in archaea have been identified: the enzyme from *Pyrococcus horikoshii* is dependent on manganese, cobalt, or calcium (90), whereas that from *Methanocaldococcus jannaschii* is dependent on iron (91). Production of Spd from Put is by the activity of AdoMetDC and aminopropyltransferase SpdSyn (92, 93). The aminopropyltransferase of *Sulfolobus solfataricus* was found to recognize a range of diamines and triamines (92). The variant AdoMet-dependent aminopropylagmatine pathway for Spd biosynthesis, previously identified in the bacterial extreme hyperthermophile *T. thermophilus*, was found in the euryarchaeote *T. kodakaraensis* (94).

Although there is no biochemical characterization of the Hspd biosynthetic enzymes in archaea, homologues of the bacterial HSS are present in *Methanosarcina* species (39), and genomic analysis of DHS homologues in archaea indicates that some genomes encode two homologues, suggesting that one may act as a DHS-like HSS. Many halophilic archaea (Halobacteria) do not appear to accumulate any polyamine except Agm (95), and yet every halobacterial genome encodes DHS. It may be that DHS is able to transfer the aminobutyl group of Agm to the archaeal aIF5A, or that the DHS is involved in a novel modification to aIF5A. Archaeal extremophiles may contain a very diverse polyamine repertoire including Nspd and Nspm, and longer aminopropylated versions (caldopentamine, caldohexamine) (96). Some of these species encode one or two homologues of the plant Acl5 thermospermine synthase, and *in vitro* analysis indicates that these aminopropyltransferases have a relaxed substrate specificity and are able to produce a range of longer chain polyamines (97). What controls the products produced *in vivo* is unknown.

Conclusions and Future Perspectives

Although the search term "polyamine" will retrieve more than 93,000 publications from PubMed, there has been relatively little effort to systematically address the function of polyamines, particularly in bacteria. Most of the major routes for polyamine biosynthesis appear to have been identified, but for the most part, the regulation and function of polyamine biosynthesis in bacteria are an extant mystery. It is clear that poly-

amines are essential for growth in some bacterial species and influence biofilm formation in others. Furthermore, polyamines are prominent in many natural products produced in bacteria, particularly siderophores. A more systematic and comparative approach to reveal conserved and specialized functions of polyamines in bacteria is required, especially at the molecular level. This is pertinent to medically relevant pathogens, where polyamines have been implicated in pathogenesis and virulence.

An important question that requires addressing in eukaryotes is whether there are functions of Spd in addition to modifying eIF5A and serving as a precursor of tetraamine biosynthesis. In addition, the *in vivo* molecular functions of Spm and Tspm are still unknown, although Spm is essential for mouse development (98) and Tspm is essential for normal growth and development of *A. thaliana* (32). Intriguingly, Spm is not required for normal laboratory growth of yeast and *A. thaliana*. With these major gaps in our knowledge, there are still profound questions to be answered in eukaryotic polyamine biology. Finally, the study of polyamines is a multidisciplinary field that affords an opportunity to consider life in its biologically widest and evolutionarily deepest extent, and has immediate biomedical and biotechnological relevance.

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