Chapter 1
Biosynthesis of Polyamines in Eukaryotes, Archaea, and Bacteria

Anthony J. Michael

Abstract As with all metabolic pathways, not only has polyamine biosynthesis been subject to divergent and convergent evolution and horizontal gene transfer, but many pathogenic and commensal organisms have abandoned the task altogether and instead obtain polyamines from the environment. Reflecting primary metabolism in general, polyamine biosynthesis is more diverse in Bacteria than it is in eukaryotes and Archaea. Each of the three physiologically relevant triamines, that is, spermidine, *sym*-homospermidine, and *sym*-norspermidine, can be synthesized by at least two distinct, evolutionarily independent pathways. Synthesis of tetraamines has evolved independently in Bacteria, Archaea, plants, yeasts, and animals. Because of the relative ease of genomic sequencing and the ever-increasing number of complete genome sequences available, it will now be easier to determine which polyamines are likely to be present in an organism by using genomic rather than chemical analysis. The following chapter is a guide to the biosynthetic diversity of polyamine formation and the evolutionary mechanisms generating that diversity.

Keywords Agmatine • Archaea • Bacteria • Carboxyspermidine • Eukaryote • Homospermidine • Norspermidine • Polyamine • Spermidine • Thermospermine

1.1 Introduction

Eukaryotic and archaeal cells must synthesize or take up spermidine because it has an essential role in posttranslational modification of the translation factor IF5A, known as hypusination (Park et al. 2010). In baker's yeast, hypusinated eIF5A has been shown to stimulate the peptidyl transferase activity of the ribosome and to be essential for translation of mRNAs encoding polyproline tracts (Gutierrez et al. 2013). The analogous bacterial translation factor EF-P is also required for rapid translation of mRNAs containing polyproline tracts (Doerfel et al. 2013; Ude et al. 2013). In contrast to the spermidine-dependent hypusine modification of eIF5A, the bacterial EF-P

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protein is modified by the addition of (R)-β-lysine in a posttranslational modification known as lysinylation (Yanagisawa et al. 2010; Roy et al. 2011). Therefore, in eukaryotes and Archaea, in contrast to Bacteria, cell growth and proliferation are absolutely dependent on spermidine biosynthesis or its acquisition through uptake transport.

The evolutionary event that gave rise to the hypusine modification of eIF5A in the common ancestor of Archaea and eukaryotes effectively locked life to spermidine biosynthesis or uptake. Deoxyhypusine synthase, which transfers the aminobutyl group of spermidine to eIF5A, is an essential gene in single-celled eukaryotes such as *Leishmania donovani* (Chawla et al. 2010), *Trypanosoma brucei* (Nguyen et al. 2013), and baker's yeast (Park et al. 1998), and also in the mouse (Nishimura et al. 2012). Bacterial life is not constrained by the need for spermidine in the modification of an essential translation factor, and bacteria may synthesize a diverse range of polyamines, including the triamines *sym*-norspermidine, spermidine, and *sym*-homospermidine, or none at all (Hamana and Matsuzaki 1992). There may be other essential roles of spermidine in eukaryotic life, but it is difficult to separate the role of spermidine in eIF5A modification from its role in other cellular processes, although it has been shown that polyamines may affect translation initiation in a manner different from the effect of eIF5A (Landau et al. 2010). In most animals (metazoa), in *Saccharomycotina* yeasts, and in flowering plants, spermidine is a precursor for spermine biosynthesis and for thermospermine biosynthesis in plants (Pegg and Michael 2010).

In contrast to the essential requirement for spermidine in eukaryotic and archaeal life, the role of polyamines in bacteria is less clear. Spermidine is essential for planktonic growth of the gram-negative γ-proteobacterium *Pseudomonas aeruginosa* PAO1 (Nakada and Itoh 2003) and the ε-proteobacterium *Campylobacter jejuni* (Hanfrey et al. 2011), whereas the gram-positive firmicute *Bacillus subtilis* does not require polyamines for normal planktonic growth (Burrell et al. 2010). In other γ-proteobacteria, polyamine depletion reduces planktonic growth rate by approximately 40 %, for example, *Yersinia pestis* (Patel et al. 2006), *Vibrio cholerae* (Lee et al. 2009), *Salmonella typhimurium* (Green et al. 2011), and *Escherichia coli* (Chattopadhyay et al. 2009). Thus, there may not be a conserved core role of polyamines in bacterial physiology but rather a diverse range of functions dependent on ecological and physiological context.

1.2 Polyamine Biosynthesis

The evolutionary processes shaping the formation of biosynthetic pathways include gene duplication, gene loss, gene fusion, and horizontal and endosymbiotic gene transfer. Complete or partial loss of polyamine biosynthesis is a prominent characteristic of single-celled parasites, which have subsequently become dependent on polyamine uptake. Examples include the loss of ornithine decarboxylase (ODC) in *Trypanosoma brucei*, *T. conglese*, *T. vivax*, and *T. cruzi*, followed by the reacquisition of ODC by horizontal gene transfer from a vertebrate source in the African

trypanosome lineage but not in *T. cruzi* (Steglich and Schaeffer 2006). The related *Leishmania* parasites did not lose the ODC gene. Genomic inspection indicates that spermidine biosynthesis has also been lost in *Giardia*, *Trichomonas*, *Toxoplasma*, *Cryptosporidium*, *Entamoeba*, and *Microsporidia* (unpublished results). Gene duplication and subsequent neo-functionalization of the additional gene copy has given rise to spermine synthase from spermidine synthase in *Saccharomycotina* yeasts and flowering plants (Pegg and Michael 2010), as well as the evolution of antizyme inhibitor from ODC (Murakami et al. 1996). Gene fusion of two bacterial *S*-adenosylmethionine decarboxylase (AdoMetDC) open reading frames gave rise to the eukaryotic AdoMetDC (Toms et al. 2004), and gene fusion of a bacterial AdoMetDC to the N-terminus of bacterial spermidine synthase, followed by loss of catalytic function of the AdoMetDC domain, gave rise to the metazoan spermine synthase (Wu et al. 2008). Plant-specific acquisition of the genes for arginine decarboxylase (ADC), agmatine iminohydrolase (AIH), and *N*-carbamoylputrescine amidohydrolase (NCPAH), which together produce putrescine from arginine, is an example of endosymbiotic gene transfer from the cyanobacterial progenitor of the chloroplast to the host nuclear genome (Illingworth et al. 2003). The following sections briefly describe polyamine biosynthesis in eukaryotes, Archaea, and Bacteria.

1.2.1 Eukaryotes

Production of spermidine from putrescine is the most conserved feature of polyamine biosynthesis in eukaryotic cells. However, there are alternative putrescine biosynthetic routes, and tetraamine biosynthesis has evolved independently several times. Except for plants, all other eukaryotes synthesize putrescine from ornithine using ODC (Fig. 1.1), which is a head-to-tail homodimer with the active site formed across the dimer interface (Pegg 2006). The form of ODC found in eukaryotes was thought to be specific to eukaryotes; however, orthologues from the same structural class are also found in bacteria, especially α-proteobacteria (Lee et al. 2007). This finding may explain the evolutionary provenance of the eukaryotic ODC, because the *Rickettsiales* order of the α-proteobacteria is thought to be the origin of the mitochondrion (Andersson et al. 2003). Paradoxically, extant members of the *Rickettsiales*, which are intracellular pathogens, have lost the genes for polyamine biosynthesis. An α-proteobacterial ODC gene in the mitochondrial progenitor could have been transferred by endosymbiotic gene transfer to the host nucleus. Regulation of ODC activity by the extraordinary antizyme–antizyme inhibitor system will be described elsewhere in this book.

The case for endosymbiotic origin of the genes for putrescine biosynthesis from arginine in plants (ADC, AIH, and NCPAH) via the cyanobacterial progenitor of the chloroplast is very strong (Illingworth et al. 2003). Most plants therefore have two pathways for putrescine biosynthesis (Fig. 1.1): from ornithine, and from arginine (Fuell et al. 2010). Some plants, including *Arabidopsis thaliana* and moss, have lost the ODC pathway to putrescine, whereas some single-celled green algae have lost

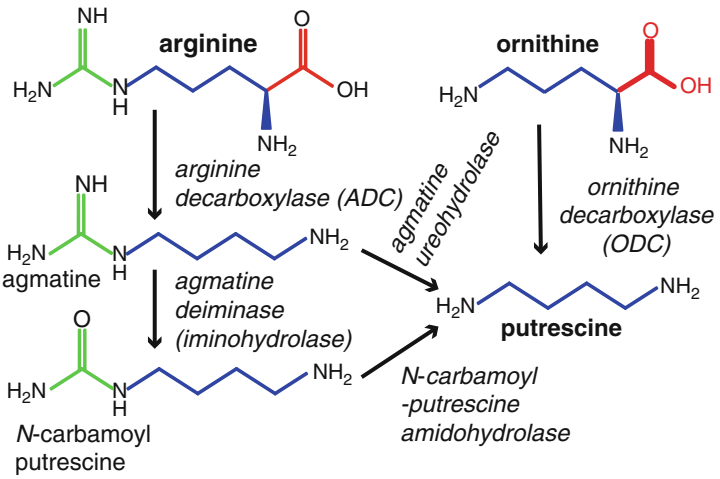

Fig. 1.1 Putrescine biosynthetic pathways

the ADC pathway (Fuell et al. 2010). In some single-celled eukaryotes, ODC is present in the absence of the rest of the spermidine pathway, for example, *Trichomonas vaginalis* (Yarlett et al. 2000).

The pathway for conversion of putrescine to spermidine is highly conserved in eukaryotes (Fig. 1.2). Spermidine synthase (SpdSyn) is an aminopropyl transferase found in all three domains of life and transfers an aminopropyl group from decarboxylated *S*-adenosylmethionine (dcAdoMet) to putrescine to form spermidine (Wu et al. 2007). Decarboxylation of AdoMet is performed by AdoMetDC, a pyruvoyl-dependent enzyme, which was likely present in the last eukaryotic common ancestor. The pyruvoyl group is generated from an internal serine residue exposed by an autocatalytic self-cleavage reaction that is stimulated by putrescine in mammalian cells (Pegg 2009). Translation of AdoMetDC mRNA is regulated by small upstream open reading frames encoding inhibitory peptides in both mammalian and plant cells (Raney et al. 2002; Hanfrey et al. 2005; Ivanov et al. 2010). In *Plasmodium falciparum*, the AdoMetDC open reading frame is fused to the N-terminus of ODC to form a bifunctional enzyme (Muller et al. 2000); a similar fusion of AdoMetDC and ODC is found in single-celled green algal *Micromonas* species (Green et al. 2011).

Synthesis of tetraamines has evolved independently several times in eukaryotes. Spermine is formed by the transfer of an aminopropyl group from dcAdoMet to the aminobutyl side of spermidine to form a symmetrical tetraamine (Fig. 1.2). In humans, the spermine synthase (SpmSyn) X-ray crystal structure revealed that the enzyme is a fusion between a noncatalytic bacterial AdoMetDC-like domain at the N-terminus and a spermidine synthase-like domain (Wu et al. 2008). The N-terminal AdoMetDC-like domain is essential for dimer formation and enzymatic activity although it is not catalytic and no autocatalytic self-processing occurs. Human-type SpmSyn is found in almost all animals (Metazoa) except nematodes and in some choanoflagellates, which are the closest single-celled relatives of metazoa (Pegg and Michael 2010). Fusions of a functional AdoMetDC and a

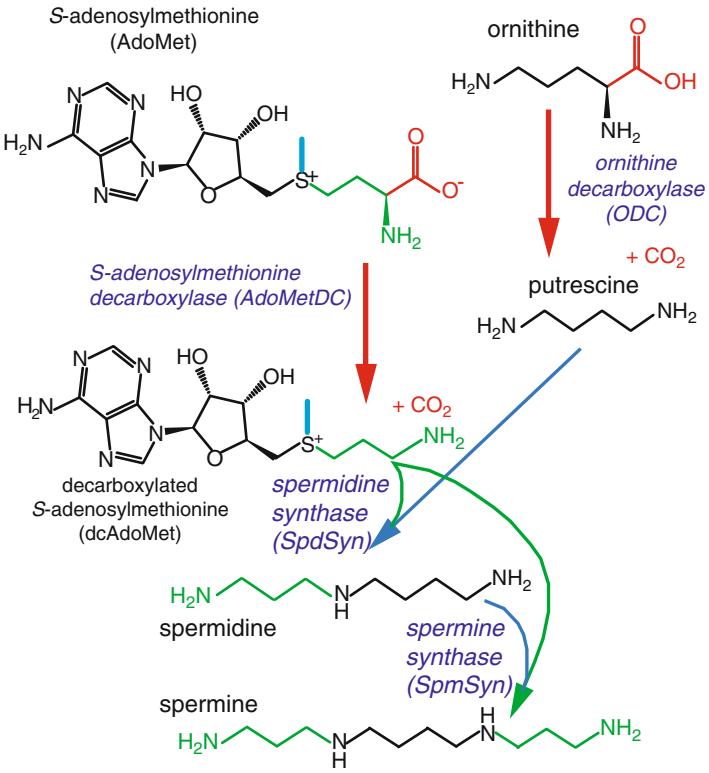

Fig. 1.2 Spermidine and spermine biosynthesis in eukaryotes

functional aminopropyl transferase are found in diverse bacterial phyla (Green et al. 2011), and it is likely that the origin of the human-like SpmSyn was the acquisition of such a bacterial gene fusion by horizontal gene transfer in the single-celled common ancestors of animals. In contrast, the yeast SpmSyn represents a relatively recent gene duplication of the SpdSyn gene and subsequent evolution of an altered substrate specificity so that spermidine rather than putrescine is recognized. The yeast-type SpmSyn is found in only a small group of yeast species, the *Saccharomycotina* yeasts, which includes *Candida albicans*, whereas the rest of the fungi do not possess a SpmSyn gene and do not accumulate spermine (Pegg and Michael 2010). Similarly, the SpmSyn of flowering plants evolved independently by gene duplication of SpdSyn and is not found in nonflowering plants (Pegg and Michael 2010).

In contrast to the relatively recent evolution of spermine biosynthesis in plants, synthesis of the unsymmetrical tetraamine thermospermine is found throughout the plant lineage (Pegg and Michael 2010). Thermospermine is synthesized by an aminopropyl transferase, thermospermine synthase (TspmSyn), that transfers an aminopropyl group from dcAdoMet to the aminopropyl side of Spd to form an unsymmetrical tetraamine. Not only are homologues of TspmSyn found in the plant

lineage, but they are also present in diatoms and related phyla, probably as a result of secondary endosymbiosis events and subsequent transfer of the TspmSyn gene from the red algal endosymbiont to the host nucleus (Pegg and Michael 2010). In the flowering plant *Arabidopsis thaliana*, genetic depletion of thermospermine results in a severe stem growth defect (Hanzawa et al. 2000; Knott et al. 2007), whereas spermine is dispensable for normal growth and development (Imai et al. 2004). However, Spm is required for resistance to drought stress (Yamaguchi et al. 2007).

1.2.2 Archaea

The general configuration of polyamine biosynthesis in Archaea consists of putrescine production by ADC and agmatinase (agmatine ureohydrolase, AUH), and spermidine production by AdoMetDC and SpdSyn. However, differing from plants, which have a pyridoxal 5′-phosphate-dependent ADC, the ADC of Archaea is a small pyruvoyl-dependent enzyme. The euryarchaeote *Methanocaldococcus jannaschii* ADC exhibits nonhydrolytic self-cleavage at a serine–serine peptide bond in the proenzyme to form a 5-kDa β-subunit and a 12-kDa α-subunit (Graham et al. 2002). Similarly to AdoMetDC, the pyruvoyl group formed after autocatalytic cleavage is found at the N-terminus of the α-subunit. In contrast to the euryarchaeotal ADC, the crenarchaeon *Sulfolobus solfataricus* possesses an ADC that is homologous to the archaeal AdoMetDC and has arisen by gene duplication of AdoMetDC early on in crenarchaeal evolution (Giles and Graham 2008). Change of substrate specificity from AdoMet to arginine appears to be determined by the N-terminal domain. The AUH of *Pyrococcus horikoshii* is similar to bacterial orthologues and is dependent on Co^{2+}, Ca^{2+}, or Mn^{2+} (Goda et al. 2005); however, the AUH of *M. jannaschii* is Fe^{2+} dependent (Miller et al. 2012). Although the AdoMetDC of Archaea (Kim et al. 2000) is similar to the typical bacterial AdoMetDC exemplified by the *Thermotoga martima* enzyme (Toms et al. 2004), the aminopropyl transferase of both Crenarchaeota and Euryarchaeota appears to be an agmatine aminopropyl transferase producing aminopropyl agmatine (Cacciapuoti et al. 2007; Morimoto et al. 2010), suggesting that the archaeal AUH enzymes that have been characterized may be aminopropyl agmatine ureohydrolases rather than agmatine ureohydrolases. Production of long-chain and branched polyamines from thermophilic Archaea is covered elsewhere in this book. An important gap in our knowledge of polyamine biosynthesis in Archaea is the formation of *sym*-norspermidine. Although it has been shown that the spermidine biosynthetic pathway aminopropyl transferase of *Sulfolobus solfataricus* can use 1,3-diaminopropane as a substrate to produce norspermidine, we still do not know how 1,3-diaminopropane is produced in Archaea outside the Halobacteria. Within the Halobacteria, 2,4-diaminobutyrate aminotransferase (DABA AT) and 2,4-diaminobutyrate decarboxylase (DABA DC), which together synthesize 1,3-diaminopropane from aspartate β-semialdehyde (Lee et al. 2009), are present in gene clusters, probably expressing schizokinin-like siderophore biosynthetic enzymes (Burrell et al. 2012) that have been acquired from bacteria by horizontal gene transfer. One possible source of 1,3-diaminopropane in

Archaea outside the Halobacteria could be the oxidation of spermidine to give 1,3-diaminopropane and 4-aminobutyraldehyde, although such an activity has not been reported in Archaea.

1.2.3 Bacteria

Bacteria vary in the types of polyamine they produce, and they can use different biosynthetic pathways to produce the same polyamine (Fig. 1.3), and the same pathway to produce different polyamines. More prominently than in eukaryotes and Archaea, polyamine biosynthesis in bacteria is highly modular, with conspicuous horizontal transfer of not only biosynthetic modules via transfer of operons but also transfer of individual genes from within modules. As a consequence, polyamine biosynthetic pathways are configured in multiple different ways in different bacteria. Usually, bacteria produce a diamine and triamine; however, some bacteria produce longer-chain polyamines, some produce only diamines, and others, especially commensals and pathogens, do not produce any polyamines (Hamana and Matsuzaki 1992). Synthesis of spermidine is phylogenetically more widely distributed than the synthesis of *sym*-homospermidine, whereas *sym*-norspermidine synthesis has a much narrower distribution, being confined mainly to the *Vibrionales* in the γ-Proteobacteria and in some hyperthermophilic bacteria. Known bacterial pathways for the production of spermidine and *sym*-homospermidine are shown in Fig. 1.3. Synthesis of *sym*-norspermidine has been described completely only for *Vibrio cholerae*, but individual enzymes for its biosynthesis have been described in other γ-Proteobacteria (Lee et al. 2009). Similar enzymes produce *sym-norspermidine* from 1,3-diaminopropane in species such as *V. cholerae*, and spermidine from putrescine in considerably more species, that is, carboxy(nor)spermidine dehydrogenase (CANSDH/CASDH) and carboxy(nor)spermidine decarboxylase (CANSDC/CASDC). In *V. cholerae*, CANSDH and CANSDC synthesize s*ym*-norspermidine from 1,3-diaminopropane, although the same enzymes can synthesize spermidine from putrescine in the same strain (Lee et al. 2009). Similarly, CASDH and CASDC synthesize spermidine from putrescine in the ε-proteobacterium *Campylobacter jejuni*, but this species does not synthesize 1,3-diaminopropane (Hanfrey et al. 2011). No X-ray crystal structure is available for CANSDH; however, it does exhibit some homology with the homospermidine synthase enzyme (Shaw et al. 2010). The crystal structure of *C. jejuni* CASDC shows that it is closely related to *meso*-diaminopimelate decarboxylase (the last step in lysine biosynthesis), biosynthetic ADC and ODC of the alanine racemase-fold, bifunctional ODC/lysine decarboxylase, and eukaryotic antizyme inhibitor (Deng et al. 2010).

Spermidine is also synthesized from putrescine by the well-known AdoMetDC/SpdSyn route in many bacteria, and this pathway is entirely distinct from the CASDH/CASDC pathway. Three known classes of AdoMetDC are found in bacteria: a Mg^{2+}-dependent, class IA form typified by the *Escherichia coli* AdoMetDC, a Mg^{2+}-independent class IB form typical of *Bacillus subtilis* and *Thermotoga maritima* (Toms et al. 2004), and a class II form, regarded as the eukaryotic form but found

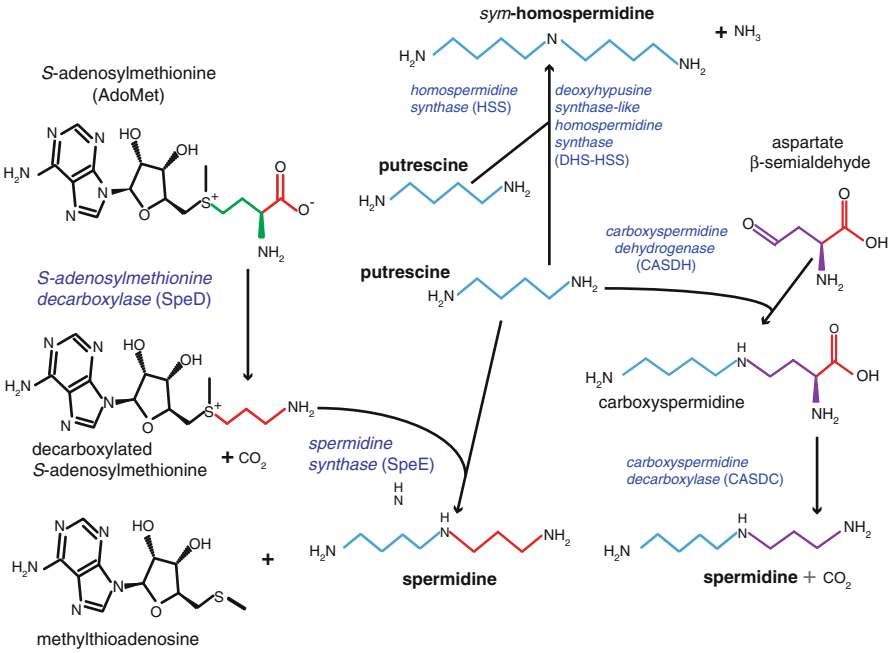

Fig. 1.3 Spermidine and *sym*-homospermidine biosynthetic pathways in bacteria

also in many *Shewanella* species (e.g., YP_563282 from *Shewanella denitrificans* OS217), where it was probably acquired once by horizontal gene transfer from a eukaryotic source followed by vertical inheritance within the *Shewanella* genus (unpublished observations). Although most aminopropyl transferases in bacteria are likely to be spermidine synthases, some species such as *Thermus thermophilus* possess an agmatine aminopropyl transferase (Ohnuma et al. 2011). The long-chain polyamines produced by *T. thermophilus* are discussed in another chapter. Spermine is found in a surprisingly wide group of bacteria, but no specific spermine synthase has been reported (Pegg and Michael 2010). Often the AdoMetDC and SpdSyn genes are found as an operon/gene cluster, which has given rise episodically to functional AdoMetDC–aminopropyl transferase gene fusions in a phylogenetically wide range of bacteria (Green et al. 2011). Synthesis of polyamines by the AdoMetDC/SpdSyn route is expensive because of the consumption of AdoMet. A methionine salvage pathway operates in many Bacteria, Archaea, and eukaryotes to retrieve the methionine component of the SpdSyn co-product 5′-methylthioadenosine (Albers 2009). It is possible that the selection of aspartate β-semialdehyde over AdoMet for spermidine biosynthesis in many bacteria is influenced by the metabolic cost of AdoMet consumption.

An important fact for understanding the role of triamine polyamines in bacterial physiology is that many bacteria from diverse phyla produce only *sym-homospermidine* and not spermidine (Hamana and Matsuzaki 1992; Shaw et al. 2010). Therefore, any conserved role of triamines in bacteria cannot be dependent

on their exact structure, that is, symmetry and length. The corollary of this argument is that there may be no conserved role of polyamines in Bacteria, even in related species. Two pathways are present for *sym*-homospermidine synthesis from putrescine in Bacteria (Fig. 1.3): the enzyme homospermidine synthase (Tholl et al. 1996) is found predominantly in the α-Proteobacteria; and a deoxyhypusine synthase-like homospermidine synthase is found in a more diverse range of phyla (Shaw et al. 2010). Support for the role of the deoxyhypusine synthase-like enzyme in bacterial *sym*-homospermidine biosynthesis remains correlative.

The role of diamines in bacterial physiology is wider than simply to provide the precursor for *sym*-norspermidine, spermidine, and *sym*-homospermidine biosynthesis. Many iron-binding siderophore molecules are based on 1,3-diaminopropane, putrescine, or cadaverine structural backbones, such as schizokinen, acinetoferrin, putrebactin, rhizoferrin, arthrobactin, and desferroxiamines (Burrell et al. 2012). The diamines provide only a structural role in these molecules and do not participate directly in iron binding. Particularly in the case of the 1,3-diaminopropane- and cadaverine-based siderophores, the diamine biosynthetic genes are located within the siderophore biosynthetic gene cluster. Synthesis of 1,3-diaminopropane by DABA AT and DABA DC as a precursor to *sym*-norspermidine formation is limited mainly to the *Vibrionales*, where the two genes are fused to produce a fusion protein. Some species such as the γ-proteobacterium *Acinetobacter baumannii* synthesize 1,3-diaminopropane as their sole polyamine, and in the case of *A. baumannii*, synthesis of 1,3-diaminopropane is essential for surface-associated motility, which is a common trait of clinical isolates (Skiebe et al. 2012). Two molecules of 1,3-diaminopropane are present in the *A. baumannii* siderophore acinetoferrin (Okujo et al. 1994). Cadaverine is not a precursor for triamine synthesis except in a few rare cases, and it is debatable whether *N*-aminopropyl cadaverine is physiologically relevant. The lysine decarboxylase that forms cadaverine from lysine has evolved independently three times from different protein folds: once from the alanine racemase-fold (Lee et al. 2007), and twice from the aspartate aminotransferase-fold (Kanjee et al. 2011; Burrell et al. 2012). Thus, lysine decarboxylation has evolved by both convergent and pseudoconvergent evolution, that is, from different protein folds, and independently within the same protein fold.

Putrescine is the predominant precursor for triamine biosynthesis in bacteria and can be synthesized directly from ornithine or indirectly from arginine (Fig. 1.1). There are two known forms of ODC, one derived from the aspartate aminotransferase fold, exemplified by the biosynthetic ODC (SpeC) of *E. coli*; and another form homologous to the eukaryotic ODC, derived from the alanine racemase fold (Lee et al. 2007), which includes bifunctional ODC/lysine decarboxylase enzymes. In bacteria, ADC proteins can be found from at least three different folds (Burrell et al. 2010), revealing the convergent evolutionary pressure for arginine decarboxylation and polyamine biosynthesis. The product of ADC, agmatine, can be converted directly into putrescine via the activity of AUH (agmatinase), which is homologous to arginase (Ahn et al. 2004). Alternatively, agmatine deiminase and NCPAH produce putrescine from agmatine via *N*-carbamoylputrescine (Nakada and Itoh 2003), as found also in plant putrescine biosynthesis (Fig. 1.1).

1.3 Future Perspectives

Primary polyamine biosynthesis is not well understood in several phyla of Bacteria, most notably the Actinobacteria. An interesting area where the role for polyamine biosynthesis is not understood is in bacteriophages and viruses. In some viruses, such as the chloroviruses, an entire pathway for *sym*-homospermidine is present (Baumann et al. 2007), whereas in some bacteriophages individual genes such as functional homospermidine synthase can be found (Shaw et al. 2010). A nontrivial task for understanding the roles of polyamines in cellular physiology in the three domains of life, and also in viral and phage biology, will be to construct an atlas of polyamine biosynthetic pathways so that any new genome sequence can be easily interrogated to determine how polyamines are made by that organism. This work will be a prelude to the task of determining what polyamines do.

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