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Aminoacyl-tRNA synthetase complexes: molecular multitasking revealed

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Abstract

The accurate synthesis of proteins, dictated by the corresponding nucleotide sequence encoded in mRNA, is essential for cell growth and survival. Central to this process are the aminoacyl-tRNA synthetases (aaRSs), which provide amino acid substrates for the growing polypeptide chain in the form of aminoacyl-tRNAs. The aaRSs are essential for coupling the correct amino acid and tRNA molecules, but are also known to associate in higher order complexes with proteins involved in processes beyond translation. Multiprotein complexes containing aaRSs are found in all three domains of life playing roles in splicing, apoptosis, viral assembly, and regulation of transcription and translation. An overview of the complexes aaRSs form in all domains of life is presented, demonstrating the extensive network of connections between the translational machinery and cellular components involved in a myriad of essential processes beyond protein synthesis.

Keywords

aminoacyl-tRNA synthetase; translation; amino acid

Introduction

The faithful translation of mRNA into protein requires aminoacyl-tRNA synthetases (aaRSs), which provide the elongating polypeptide chain with amino acids in the form of aminoacyl-tRNAs (aa-tRNA). The aaRSs are responsible for accurately attaching the correct amino acid onto the cognate tRNA molecule in a two-step reaction. The amino acid is first activated with ATP, forming an aminoacyladenylate intermediate. Once activated, the amino acid is transferred to the 3' end of its corresponding tRNA molecule to be used for protein synthesis. Although related by this common mechanism of aminoacylation, aaRSs are separated into two classes (I and II) based on the structural topologies of their active sites (Cusack *et al.*, 1990; Eriani *et al.*, 1990).

Class I aaRSs are generally monomeric and composed of a Rossmann-nucleotide-binding fold, containing the highly conserved sequence elements KMSKS and HIGH. Class I enzymes approach tRNA from the minor groove of the tRNA acceptor stem, aminoacylating the terminal adenosine of the tRNA molecule at the 2'-OH position. Class II aaRSs are generally multimeric enzymes that approach the major groove of their respective tRNAs, charging the 3'-OH of the terminal adenosine. Once synthesized, aa-tRNAs are selectively bound by EF-1A in archaea

and eukaryotes (homologous to the bacterial EF-Tu) as a ternary complex with GTP and ushered to the ribosome during protein synthesis. Eukaryotic aaRSs are distinguished by the presence of appended domains at either the N- or C-terminus, which are generally absent from their bacterial/archaeal counterparts (Mirande, 1991). These appendages to the catalytic cores of several aaRSs are non-catalytic and instead function to mediate protein–protein interactions or act as general RNA-binding domains (Cahuzac *et al.*, 2000; Robinson *et al.*, 2000; Guigou *et al.*, 2004).

An elaborate network of protein–protein interactions is required for efficient translation in all domains of life. AaRSs must correctly bind a diverse array of molecules to perform their essential function of aminoacylation, including ATP, amino acids, tRNAs, and in some cases other aaRSs. Also, several aaRSs associate with additional or auxiliary protein factors that are primarily used in cellular tasks beyond translation, expanding the repertoire of functions aaRSs may pursue (Fig. 1). Although many of these associations were first described in eukaryotic cells, numerous multi-enzyme complexes containing aaRSs have recently been identified in both bacteria and archaea (Table 1).

Complexes in bacteria

Bacterial aaRSs are generally thought to function as stand-alone proteins to carry out the fundamental task of aminoacylation. However, a handful of binary complexes comprised of one aaRS and a second protein factor have recently been discovered in bacteria, with one early report suggesting the formation of a higher order multi-aaRS complex (Harris, 1987). These binary complexes are involved in a diverse range of functions, from editing of misacylated tRNAs to metabolite biosynthesis.

Prolyl-tRNA synthetase :YbaK

Accurate translation of the genetic code relies on the correct pairing of amino acids with their cognate tRNAs. In order to preserve the fidelity of protein synthesis, misactivated amino acids and mischarged tRNAs must be efficiently hydrolyzed to avoid infiltration of the genetic code by noncognate amino acids (Baldwin & Berg, 1966; Eldred & Schimmel, 1972; Fersht & Dingwall, 1979; Kim *et al.*, 1993; Schmidt & Schimmel, 1994; Roy *et al.*, 2004; Williams & Martinis, 2006). This may be accomplished by discrete, free-standing editing proteins or by editing domains appended to the catalytic cores of aaRSs (Ahel *et al.*, 2003; Wong *et al.*, 2003; Korencic *et al.*, 2004; Fukunaga & Yokoyama, 2007a, b). Prolyl-tRNA synthetase (ProRS) is known to misactivate tRNA^{Pro} with alanine and cysteine (Ambrogelly *et al.*, 2002; An & Musier-Forsyth, 2005). Although most ProRS enzymes have editing domains that efficiently deacylate Ala-tRNA^{Pro}, ProRS is unable to clear Cys-tRNA^{Pro} (Beuning & Musier-Forsyth, 2001; An & Musier-Forsyth, 2005; Ruan & Söll, 2005). To overcome this deficiency, bacterial ProRS forms stable interactions with YbaK, a free-standing homologue of the ProRS Ala-tRNA^{Pro}-editing domain (An & Musier-Forsyth, 2004, 2005; Ruan & Söll, 2005).

Stable ternary complex formation between bacterial ProRS, tRNA^{Pro}, and YbaK results in hydrolysis of mischarged Cys-tRNA^{Pro} both in vitro and in vivo (An & Musier-Forsyth, 2005; Ruan & Söll, 2005). YbaK, a general tRNA-binding protein, does not specifically recognize tRNA^{Pro}, necessitating protein interactions with ProRS for correct substrate binding. Interestingly, YbaK not only deacylates Cys-tRNA^{Pro}, but may also diminish the formation of mischarged Cys-tRNA^{Pro} by ProRS, further guarding against the incorporation of noncognate amino acids into the growing polypeptide chain (An & Musier-Forsyth, 2005). In competition studies, YbaK was unable to compete with EF-Tu for Cys-tRNA^{Pro}, suggesting that YbaK hydrolyzes mischarged tRNAs before their release from ProRS. The inability of YbaK alone to either specifically recognize tRNA^{Pro} or to compete with EF-Tu for binding of the

mischarged species means that complex formation between YbaK and ProRS is essential for efficient hydrolysis of mischarged Cys-tRNA^{Pro}.

Transamidosome (aspartyl-tRNA synthetase : amidotransferase)

While some mischarged aa-tRNAs are hydrolyzed by appended or discrete editing domains, protein synthesis in many bacterial species rely on the incorrect coupling of certain amino acid and tRNA pairs. Such is the case for the synthesis of Asn-tRNA^{Asn} and Gln-tRNA^{Gln}, which proceeds via the specific mischarging of tRNA^{Asn} and tRNA^{Gln} by aspartyl- and glutamyl-tRNA synthetases (AspRS and GluRS), respectively (Schon *et al.*, 1988; Feng *et al.*, 2005; Bailly *et al.*, 2007). The indirect synthesis of Asn-tRNA^{Asn} requires a two-step reaction in which first a nondiscriminating AspRS mischarges tRNA^{Asn} with aspartic acid (Becker & Kern, 1998; Tumbula-Hansen *et al.*, 2002; Min *et al.*, 2003; Cardoso *et al.*, 2006). The misacylated Asp-tRNA^{Asn} is then bound by the GatCAB amidotransferase, which functions to convert the aspartic acid moiety to asparagine in the presence of an amide donor. Similarly, Gln-tRNA^{Gln} in bacteria and organelles is synthesized via an indirect pathway, which requires misacylation of tRNA^{Gln} by GluRS and subsequent conversion to Gln-tRNA^{Gln} by the GatCAB amidotransferase (Curnow *et al.*, 1998; Racznik *et al.*, 2001; Salazar *et al.*, 2001; Oshikane *et al.*, 2006). The synthesis of Asn-tRNA^{Asn} and Gln-tRNA^{Gln} via indirect pathways is essential for those bacterial species whose genomes do not code for asparaginyl- or glutaminyl-tRNA synthetases (AsnRS or GlnRS, respectively), providing the sole route for biosynthesis of these amino acid : tRNA pairs.

The rate-limiting step in this tRNA-dependent reaction is amide transfer prior to the formation of Asn-tRNA^{Asn} (Bailly *et al.*, 2007). Recently, it was discovered that the bacterial AspRS stably associates with amidotransferase in the presence of tRNA^{Asn}, forming the transamidosome complex. Within the context of the transamidosome, the rate of Asp-tRNA^{Asn} conversion to Asn-tRNA^{Asn} was significantly enhanced, as compared to free amidotransferase. This suggests that the transfer of Asp-tRNA^{Asn} from AspRS to amidotransferase requires stable complex formation between the two proteins for efficient conversion. Although it has not been observed *in vitro*, a similar complex between the nondiscriminating GluRS and amidotransferase has also been suggested to occur in the cell (Oshikane *et al.*, 2006; Bailly *et al.*, 2007). The transamidosome harbors two proteins that execute consecutive functions: AspRS and amidotransferase. Protein-protein interactions between the aaRS and amidotransferase may be necessary not only to enhance the synthesis of Asn-tRNA^{Asn}, but may also be important to facilitate the direct transfer of the vital Asp-tRNA^{Asn} intermediate from AspRS to the amidotransferase, preventing spontaneous hydrolysis in the cytoplasm.

Tryptophanyl-tRNA synthetase : nitric oxide synthase (NOS)

Many bacteria harbor multiple copies of aaRSs encoded in the same genome (Brown *et al.*, 2003; Salazar *et al.*, 2003; Levensgood *et al.*, 2004; Ataide *et al.*, 2005; Ataide & Ibba, 2006). One such example is *Deinococcus radiodurans*, which harbors two genes encoding tryptophanyl-tRNA synthetase (TrpRS I and TrpRS II) (Buddha *et al.*, 2004a, b). Although the two TrpRSs contain the conserved amino acid residues responsible for aminoacylation of tRNA^{Trp} with tryptophan (Trp), TrpRS II is unusual in that it is structurally more similar to human TrpRS and is induced in response to damage caused by radiation (Buddha *et al.*, 2004a). In addition, TrpRS II contains an N-terminal extension similar to other proteins involved in stress responses in bacteria and has been shown to associate with nitric oxide synthase (NOS) (Buddha *et al.*, 2004a, b).

In mammals, nitric oxide is synthesized from the oxidation of arginine (Arg), and functions in nerve signal transmission, vasodilation, and the immune system (Kers *et al.*, 2004). Some

bacterial species harbor truncated homologues of the mammalian NOS, which have been identified to perform novel functions in bacteria. In complex with TrpRS II and tRNA^{Trp}, the bacterial NOS catalyzes the regiospecific nitration of Trp from Arg at the four-position, producing 4-Nitro-Trp (Buddha *et al.*, 2004a). Complex formation between TrpRS II and NOS favored the activities of both associated enzymes. TrpRS II increased NOS solubility and affinity for its arginine substrate, facilitating the specific nitration of Trp from Arg (Buddha *et al.*, 2004a, b). TrpRS II may also supply NOS with adenylated-Trp for subsequent nitration or nitrosylation, as Trp nitration does not occur with free Trp *in vitro*.

Both TrpRS I and TrpRS II are able to aminoacylate tRNA with Trp, although the efficiency of TrpRS II is about fivefold lower than TrpRS I (Buddha *et al.*, 2004a). In addition to the canonical Trp substrate, TrpRS II has been observed to charge tRNA with 4-nitro-Trp in the presence of ATP with nearly the same aminoacylation efficiency as with Trp (Buddha & Crane, 2005). Although the role of TrpRS II catalyzed 4-nitro-Trp aminoacylation is largely unknown, it may function outside of protein synthesis as *D. radiodurans* encodes two TrpRSs, with TrpRS II expression only induced in response to specific stimuli such as radiation damage. 4-nitro-Trp may play a role in the synthesis of other metabolites or may perhaps function in a role similar to that of charged tRNA in peptidoglycan production, where the aa-tRNA functions outside of protein synthesis to provide amino acids required for cell membrane biosynthesis (Ibba & Söll, 2004; Kers *et al.*, 2004; Roy & Ibba, 2008).

Complexes in archaea

Although binary complexes containing one aaRS are generally the norm in bacteria, archaea and eukaryotes have been found to harbor higher order complexes composed of multiple aaRS activities in association with a variety of cellular factors as described below.

Prolyl-tRNA synthetase : Mj1338

In an early report, several if not all aaRSs were observed to associate into a large multi-aminoacyl-tRNA synthetase complex (MSC) in the archaeon *Haloarcula marismortui*, providing precedence for the existence of higher order complexes containing aaRSs in archaea (Goldgur & Safro, 1994). More recently, ProRS has been found to associate in *Methanocaldococcus jannaschii* with a metabolic protein (Mj1338) predicted to be involved in one-carbon metabolism in archaea (Lipman *et al.*, 2003). Although the function of Mj1338 has not been completely resolved, the metabolic protein has been demonstrated to possess a general affinity for tRNA. The archaeal ProRS bound Mj1338 with a K_D of about 1.4 μ M, indicating a stable protein-protein interaction. Although the formation of a higher order complex has not been verified, lysyl-tRNA synthetase (LysRS) and AspRS each interacted independently with Mj1338, suggesting a possible association with the archaeal ProRS : Mj1338 complex.

As is the case for the higher order complex of aaRSs discovered in *H. marismortui*, the biological function of complex formation between archaeal ProRS and Mj1338 remains largely unknown, as complex formation did not stimulate aminoacylation activity. Although further experimentation would be required to investigate the formation of a higher order complex in *M. jannaschii*, these specific aaRSs (ProRS, LysRS, and AspRS) are noteworthy as their eukaryotic counterparts are all known to associate into a larger MSC in mammalian cells composed of nine aaRS activities and three auxiliary proteins (Mirande *et al.*, 1985; Kerjan *et al.*, 1994; Quevillon *et al.*, 1999; Robinson *et al.*, 2000).

Lysyl-tRNA synthetase : leucyl-tRNA synthetase : prolyl-tRNA synthetase

In the archaeal species *Methanothermobacter thermautotrophicus*, a MSC composed of LysRS, LeuRS, and ProRS was identified via yeast two-hybrid screening of an *M. thermautotrophicus* cDNA library with LysRS and ProRS as bait proteins (Praetorius-Ibba *et al.*, 2005, 2007). Formation of a stable complex between LysRS, LeuRS, and ProRS was further confirmed *in vitro* and *in vivo* via copurification experiments using both the corresponding His-tagged proteins and archaeal cell-free extracts (Praetorius-Ibba *et al.*, 2007). Pairwise binding affinities were determined from fluorescence anisotropy studies, indicating that LeuRS bound LysRS and ProRS with comparable K_D s of about 0.3–0.9 μM , lending support to the formation of a stable MSC in archaea.

The functional consequences of complex formation were investigated by determining the steady-state aminoacylation parameters of each aaRS alone or in the MSC. In the presence of LeuRS, the catalytic efficiencies of aminoacylation by LysRS and ProRS were enhanced three- and fivefold, respectively, while no significant changes in the kinetics of aminoacylation by LeuRS were observed. No further changes were identified upon addition of the aaRSs in alternative combinations. This indicates the possible role of an archaeal MSC comprised of three aaRSs in which LeuRS improves the catalytic efficiencies of tRNA aminoacylation by both LysRS and ProRS. Interestingly, these three aaRSs activities are also found in the macromolecular mammalian MSC, suggesting that the biological role of aaRS complexes in translation may be to enhance aminoacylation by the associated aaRSs.

The archaeon *M. thermautotrophicus* also harbors a complex between LeuRS and EF-1A, a translation elongation factor that specifically binds and escorts aa-tRNAs to the ribosome. First identified via yeast two-hybrid screening of an *M. thermautotrophicus* cDNA library, complex formation between EF-1A and LeuRS was confirmed by co-immuno-precipitation and fluorescence anisotropy experiments, from which a K_D of about 0.7 μM was determined (Hausmann *et al.*, 2007). In complex with EF-1A, aminoacylation by LeuRS was enhanced threefold, with an eightfold increase in the k_{cat} of Leu-tRNA^{Leu} synthesis, suggesting that perhaps a conformational change occurs upon complex formation. The activities of EF-1A, however, remained largely unaffected. Unlike the archaeal EF-1A, the bacterial homolog EF-Tu had no effect on aminoacylation by LeuRS, indicating that the enhanced rate of Leu-tRNA^{Leu} synthesis was neither a result of product sequestration by EF-1A (known to protect the labile ester bond of aa-tRNA) nor was it the nonspecific effect of a GTPase. EF-1A has also been suggested to associate *in vivo* with the *M. thermautotrophicus* MSC, composed of LysRS, LeuRS, and ProRS, possibly through interactions with LeuRS (Hausmann *et al.*, 2007). Although EF-1A enhances the k_{cat} of Leu-tRNA^{Leu} synthesis, no change in aminoacylation by LysRS or ProRS was observed in the presence of EF-1A. Taken together, the association of all four proteins involved in translation results in enhanced aminoacylation by LysRS, LeuRS, and ProRS (Praetorius-Ibba *et al.*, 2005, 2007; Hausmann *et al.*, 2007).

It has been suggested that aminoacylation by class I aaRSs may be rate-limited by aa-tRNA release, while class II enzymes are rate-limited by a step before product release (Zhang *et al.*, 2006). These distinctions between class I and class II aaRSs may compel an association of translation elongation factors with class I aaRSs for efficient aa-tRNA release while class II aaRSs may not necessarily require stable interactions with EF-1A for product release. Stable protein–protein interactions between LeuRS, a class I aaRS, and EF-1A lend support to this notion. Further, aaRSs and EF-1A perform consecutive functions in translation, aminoacylation of tRNA and subsequent delivery to the ribosome. Although the molecular mechanism remains largely unknown, complex formation between the elongation factor and an aaRS may favor the direct hand-off of aa-tRNA from the aaRS to the elongation factor without diffusion into the cytoplasm, which was first suggested in the case of the valyl-tRNA synthetase (ValRS) : EF-1A complex in human cells (Negrutskii & Deutscher, 1991;

Stapulionis & Deutscher, 1995; Negrutskii & El'skaya, 1998; Negrutskii *et al.*, 1999; Petrushenko *et al.*, 2002; Yang *et al.*, 2006). In accordance with this proposed model, the association of EF-1A with the archaeal MSC may serve to directly transfer aa-tRNAs synthesized by the associated aaRSs to EF-1A for delivery to the ribosome. Further studies are now necessary to determine if these MSCs are widespread in archaea, which would provide new insights into their possible functions in translation.

Complexes in eukaryotes

A variety of multiprotein complexes containing aaRSs exists throughout all three domains of life. In eukaryotes these complexes tend to be larger than those discovered in bacteria and archaea and also perform a wider range of functions from aminoacylation to noncanonical functions beyond translation. The true identity of complexes that occur *in vivo* may be masked, however, possibly due to the fragility of the complex, loosely associated peripheral proteins, or transient interactions that disassociate during copurification procedures. With this in mind, a comprehensive overview of the complexes currently known to form in eukaryotes is presented.

Glutamyl-tRNA synthetase : Arc1p : methionyltRNA synthetase

In *Saccharomyces cerevisiae*, glutamyl- and methionyl-tRNA synthetases (GluRS and MetRS, respectively) stably interact with aminoacyl-tRNA synthetase cofactor I (Arc1p), a nonsynthetase accessory protein (Simos *et al.*, 1996, 1998; Galani *et al.*, 2001; Karanasios *et al.*, 2007). Protein-protein interactions are mediated through the N-terminal domains of each associated component, as observed from biochemical studies and from modeling of two binary complexes of Arc1p with each aaRS (Deinert *et al.*, 2001; Simader *et al.*, 2006). Discrete residues of Arc1p have been identified as critical for binding GluRS and MetRS, mediating ternary complex formation (Galani *et al.*, 2001; Karanasios *et al.*, 2007). Arc1p harbors an EMAPII-like domain at its C-terminus, containing an oligonucleotide-binding (OB) domain, and a positively charged central domain, which enables Arc1p to act as a general tRNA-binding factor (Simos *et al.*, 1996, 1998). As part of the ternary complex, Arc1p preferentially facilitates the binding of the cognate tRNA substrates (tRNA^{Glu} and tRNA^{Met}) to the associated aaRSs, thus increasing the catalytic efficiencies of both GluRS and MetRS.

Bacterial tRNA-binding protein (Trbp111) and human p43 (an auxiliary protein of the mammalian MSC) both harbor tRNA-binding domains similar to that found in the C-terminus of Arc1p and can in fact functionally replace Arc1p to complement a synthetic lethal *arc1⁻ los1⁻* strain of *S. cerevisiae* (Simos *et al.*, 1996; Quevillon *et al.*, 1997; Swairjo *et al.*, 2000; Deinert *et al.*, 2001; Golinelli-Cohen *et al.*, 2004). Based on models of Trbp111, Arc1p has been suggested to interact with the top corner of the tRNA substrates, which is also in agreement with biochemical studies implicating the tRNA D- and T Ψ C-loops as part of the binding site for Arc1p (Simos *et al.*, 1996; Swairjo *et al.*, 2000). Both GluRS and MetRS are class I aaRSs, known to interact with the inner L portion of the tRNA molecule, which may permit simultaneous associations of Arc1p and aaRSs with the tRNA substrates in complex (Senger *et al.*, 1995; Sekine *et al.*, 2001).

Arc1p in complex with GluRS and MetRS has been observed to preferentially facilitate the binding of tRNA^{Glu} and tRNA^{Met} to each aaRS, possibly by promoting structural rearrangements (Simos *et al.*, 1998; Galani *et al.*, 2001; Simader *et al.*, 2006; Golinelli-Cohen & Mirande, 2007). Although unbound GluRS is able to bind its cognate tRNA^{Glu} with moderate affinity, tRNA binding is greatly influenced by the presence of Arc1p. In complex, the apparent K_D for tRNA^{Glu} is reduced about 120-fold to 30 nM (Graindorge *et al.*, 2005). Steady-state aminoacylation kinetic parameters could not be determined, however, because *in vitro* transcribed tRNA^{Glu} proved a poor substrate for aminoacylation. In the case of MetRS, the

k_{cat} for tRNA aminoacylation increased almost fivefold in the presence of Arc1p as compared to MetRS alone (Simos *et al.*, 1996). Arc1p facilitated the binding of tRNA^{Met} to MetRS by significantly decreasing (about 100-fold) the K_M of tRNA^{Met}, as compared to the aaRS alone ($K_M \sim 10 \mu\text{M}$).

Beyond its role in enhanced binding of cognate tRNAs to MetRS and GluRS, the Arc1p complex also regulates the subcellular localization of each associated component (Galani *et al.*, 2001; Golinelli-Cohen & Mirande, 2007). Arc1p is exclusively found in the cytoplasm due to export by Xpo1p (Galani *et al.*, 2001, 2005). When associated with Arc1p, both GluRS and MetRS localize to the cytoplasm, while disruption of the complex due to N-terminal truncations of each protein allows entrance of the individual aaRSs into the nucleus (Galani *et al.*, 2001, 2005; Karanasios *et al.*, 2007). Arc1p may also interact indirectly with Los1p (a nuclear pore-associated protein involved in tRNA export), as discovered from synthetic lethal screens using a disrupted *los1⁻* strain, indicating the involvement of Arc1p in tRNA export from the nucleus (Simos *et al.*, 1996, 1998). Translation factor EF-1A was also discovered in a suppressor screen of a synthetically lethal *los1⁻* strain, suggesting that EF-1A may usher newly exported tRNA from the nucleus to the corresponding aaRSs (Sarkar *et al.*, 1999; Grosshans *et al.*, 2000a, b; McGuire & Mangroo, 2007). Taken together, these data reveal how Arc1p coordinates events between protein synthesis and tRNA export in *S. cerevisiae*.

Seryl-tRNA synthetase : Pex21p

In addition to the Arc1p : GluRS : MetRS complex, *S. cerevisiae* also harbors a complex between seryl-tRNA synthetase (SerRS) and Pex21p, a protein involved in peroxisome biosynthesis. First identified by yeast two-hybrid analysis, pull-down experiments indicated that Pex21p and SerRS associate in cell-free extracts, suggesting complex formation *in vivo* (Rocak *et al.*, 2002). The C-terminus of SerRS, which is not essential for cellular viability or aminoacylation, mediates protein-protein interactions with Pex21p (Godinic *et al.*, 2007; Mocibob & Weygand-Durasevic, 2008). In complex, Pex21p promoted the binding of tRNA^{Ser} to SerRS, slightly enhancing aminoacylation (Rocak *et al.*, 2002; Godinic *et al.*, 2007). Pex21p may induce conformational changes in SerRS to enhance the binding of cognate tRNA, thereby playing a similar role to that of Arc1p in complex with GluRS and MetRS (Simos *et al.*, 1998; Rocak *et al.*, 2002; Simader *et al.*, 2006; Godinic *et al.*, 2007).

Peroxisomes, which are involved in the metabolism of fatty acids and other metabolites, function as part of the secretory pathway to post-translationally import peroxisomal enzymes across the peroxisome membrane. Although the functional consequences of complex formation on the activity of Pex21p remain to be discovered, the SerRS : Pex21p complex provides a connection between translation and peroxisome biosynthesis. SerRS is also involved in the synthesis of diadenosine oligophosphates, which may act as a signal of oxidative stress (Lopez-Huertas *et al.*, 2000). Peroxisome biosynthesis genes are also known to be induced by hydrogen peroxide and other stressors to the cell, suggesting that complex formation between SerRS and Pex21p may contribute to coordination of stress signaling networks in *S. cerevisiae* (Lee *et al.*, 1983; Belrhali *et al.*, 1995; Godinic *et al.*, 2007).

Tyrosyl-tRNA synthetase (TyrRS) : Knr4

A connection between tyrosyl-tRNA synthetase (TyrRS) and a protein involved in cell wall biosynthesis (Knr4) has been identified in *S. cerevisiae* from DNA microarray, yeast two-hybrid, and pull-down experiments (Dagkessamanskaia *et al.*, 2001; Ivakhno & Kornelyuk, 2005). DNA microarray analyses demonstrated that TyrRS gene expression during sporulation correlated well with the expression of Knr4, as well as other genes that participate in cell-wall assembly (Ivakhno & Kornelyuk, 2005). Further, disruption of the gene encoding Knr4 reduced glucan synthase activity and resulted in decreased spore formation, which was associated with

a concomitant activation of TyrRS during sporulation (Chu *et al.*, 1998). Although the biological function of this cellular association is largely unknown, dityrosine is an essential component of the outermost layer of the spore wall, suggesting a collaborative effect between TyrRS and Knr4 to promote dityrosine formation during sporulation in *S. cerevisiae* (Briza *et al.*, 1986; Coluccio *et al.*, 2004).

Valyl-tRNA synthetase : EF-1H

Translation elongation requires the correct synthesis of aa-tRNA by aaRSs and their subsequent delivery to the ribosome by EF-1A. In human cells, the GTPase EF-1A associates with the guanine nucleotide recycling machinery, EF-1B, to form the larger elongation factor 1H (EF-1H) complex. Upon codon-anticodon recognition on the ribosome, GTP is hydrolyzed, releasing the GDP-bound form of EF-1A. EF-1B then functions to recycle GDP to GTP, permitting EF-1A to pursue another round of tRNA selection. A stable complex between human ValRS and EF-1H provides a link between these essential steps in translation (Motorin *et al.*, 1988; Venema *et al.*, 1991; Bec *et al.*, 1994; Minella *et al.*, 1998; Negrutskii *et al.*, 1999). The N-terminal appended domain of ValRS was identified to mediate protein : protein interactions, as it strongly associates with the EF-1d subunit of EF-1H (Negrutskii *et al.*, 1999). Although the stoichiometry of the EF-1H : ValRS complex is debated, the presence of excess EF-1A and GTP enhanced the catalytic efficiency of ValRS almost twofold, while the K_M for tRNA^{Val} remained unaffected (Negrutskii *et al.*, 1999). This increase in the catalytic efficiency was not observed in the presence of EF-1A : GDP or bacterial EF-Tu : GTP, indicating that the increased levels of ValtRNA^{Val} were due to improved catalysis by ValRS, and not the protective effects of EF-1A.

The EF-1A : ValRS complex correlates well with the ability of the elongation factor to form complexes with and enhance the rate of aminoacylation by class I aaRSs (Kern & Gangloff, 1981; Zhang *et al.*, 2006), as also observed for the EF-1A : LeuRS complex in archaea (Hausmann *et al.*, 2007). EF-1A has been observed to associate with the class II aaRS, human AspRS, and stimulated the rate of AspRNA^{Asp} release (Reed & Yang, 1994; Reed *et al.*, 1994). More recently, EF-1A has been suggested to interact with class II human LysRS, slightly enhancing aminoacylation by LysRS (Guzzo & Yang, 2008). An interaction between human TrpRS and EF-1A has also been proposed, although stable complex formation has not yet been confirmed (Yang *et al.*, 2006); EF-1A has also been shown to enhance aminoacylation by MetRS (Kaminska *et al.*, 2001).

AaRSs and EF-1A perform two consecutive functions in translation: aminoacylation and the subsequent delivery of aa-tRNA to the ribosome. The link between these two translational enzymes lends support to the notion that protein-protein interactions between aaRSs and EF-1A may serve as a vector, directly transferring aa-tRNA from aaRSs to the ribosome. Further extending this role, EF-1A : GDP may then complete the cycle by accepting uncharged tRNA from the ribosomal E site for another round of aminoacylation by the associated aaRS (Petrushenko *et al.*, 1997). This is evidenced by the unusual complex phenylalanyl-tRNA synthetase (PheRS) forms with EF-1A : GDP and uncharged tRNA (Dibbelt & Zachau, 1981; Petrushenko *et al.*, 1997, 2002). Beyond translation, EF-1A has also been implicated in chaperone-like functions, such as protecting from denaturation and promoting renaturation of PheRS and SerRS (Gonen *et al.*, 1994; Kudlicki *et al.*, 1997; Caldas *et al.*, 1998; Hotokezaka *et al.*, 2002; Lukash *et al.*, 2004). Through a concerted effort, EF-1A may associate with aaRSs in eukaryotes and archaea to facilitate the delivery of aa-tRNA to the ribosome and to promote protein stability.

Mammalian MSC

In mammalian cells, a larger 1.4 MDa multi-aaRS complex exists, composed of nine aaRS activities (leucyl-, lysyl-, prolyl-, isoleucyl-, methionyl-, glutamyl-, glutaminyl-, arginyl-, and aspartyl-tRNA synthetases) (Bandyopadhyay & Deutscher, 1971; Kerjan *et al.*, 1994; Quevillon *et al.*, 1999; Robinson *et al.*, 2000). Three non-aaRS factors p38, p43, and p18 complete the complex, playing roles in tRNA binding and complex stability/assembly. The MSC is composed of a mixture of class I and class II aaRSs, indicating that the distinction between the complexed and free forms does not solely reside in the structural architectures of their active sites nor the amino acids that are activated and attached to their corresponding tRNA molecules. It has been observed that the aaRSs responsible for coupling charged amino acids and hydrophobic, nonaromatic amino acids to tRNA molecules are all present within the complex, while those aminoacylating the smallest and largest amino acids are absent (Wolfson & Knight, 2005). It is unknown why certain aaRSs unite into a larger complex while others exist as free-standing proteins. It is possible, however, that several other, or perhaps even all, aaRSs associate with the complex more transiently in the cell and the current model of the MSC may be a reflection of experimental limitations when copurifying macromolecular complexes.

Although the composition of the proteins stably associated in the mammalian MSC was deciphered nearly 30 years ago, the exact structural arrangement and assembly of the complex remain undefined. Through biochemical, genetic, and cryo-electron microscopic analyses, however, a clearer picture of the MSC has been captured (Norcum, 1989, 1999; Quevillon *et al.*, 1999; Kim *et al.*, 2000; Robinson *et al.*, 2000; Han *et al.*, 2003; Wolfson & Knight, 2005). The MSC particle is compact, as visualized by electron and immunoelectron microscopy, and assembles into a V-shaped complex, possibly via the association of three subcomplexes (Norcum, 1989, 1999; Norcum & Warrington, 1998). Localized in one arm are AspRS, MetRS, and GlnRS, while on the other arm are LysRS and ArgRS. The bifunctional GluProRS, IleRS, and LeuRS are found at the base of the V-shaped macromolecule, and the polypeptides connect the three subdomains, forming the complete mammalian MSC (Wolfe *et al.*, 2005).

The assembly of the MSC is thought to be highly structured and interdependent on other binding events within the complex. Lending support to the notion of ordered assembly, NaSCN or high concentrations of NaCl result in the release of LysRS and AspRS from the complex, respectively, suggesting that these aaRSs are located near the periphery (Cirakoglu *et al.*, 1985; Norcum, 1991; Agou & Mirande, 1997). MetRS, GlnRS, and ArgRS are also relatively easy to remove from the MSC and have been found as free forms in the cell (Ko *et al.*, 2001; Han *et al.*, 2006a, b). Extensive pairwise yeast two-hybrid screening of each aaRS associated in the MSC was performed, providing insight into all 64 combinations of protein–protein interactions within the complex (Rho *et al.*, 1999). Protein–protein interactions within the mammalian MSC may be mediated through appended domains found in the associated aaRSs, as has been observed for MetRS, LeuRS, and ArgRS (Mirande *et al.*, 1982, 1992; Vellekamp & Deutscher, 1987; Robinson *et al.*, 2000; Guigou *et al.*, 2004; Ling *et al.*, 2005). Conversely, several aaRSs may associate with the MSC through their catalytic domains (LysRS, AspRS, and GlnRS), because deletion of the appended extensions did not abolish interactions with the MSC (Agou & Mirande, 1997; Kim *et al.*, 2000; Robinson *et al.*, 2000; Francin *et al.*, 2002). The interdependence of binding events was further evidenced by the fact that the binding of GlnRS to p38 was significantly enhanced in the presence of p43 and ArgRS, indicating that perhaps a discreet quaternary complex is required for the ordered formation of the MSC (Robinson *et al.*, 2000).

In addition to the nine aaRS activities associated within the MSC, three auxiliary polypeptides (p38, p43, and p18) complete the complex, lending stability to the complex and promoting the

binding of tRNA. The auxiliary protein p38 has been observed to mediate protein–protein interactions, acting as an essential scaffolding protein of the mammalian MSC (Robinson *et al.*, 2000; Kim *et al.*, 2002; Ahn *et al.*, 2003). p38 interacts with nearly all other proteins associated in the MSC over a range of binding affinities between 0.3 nM–5 μ M, emphasizing its role as an indispensable core protein important for assembly and stability of the complex (Quevillon *et al.*, 1999; Robinson *et al.*, 2000; Kim *et al.*, 2002; Ahn *et al.*, 2003; Wolfe *et al.*, 2005). Although the molecular mechanisms are not well-defined, p38 has also been implicated in roles outside of the MSC. For example, p38 has been observed to associate in the nucleus with FUSE-binding protein (a transcriptional activator of c-myc), resulting in ubiquitination of FUSE-binding protein and subsequent down-regulation of c-myc (Kim *et al.*, 2002, 2003). p38 has also been shown to associate with and act as a substrate of Parkin (a protein involved in ubiquitination), which results in the degradation of p38 (Corti *et al.*, 2003; Ko *et al.*, 2005). Autosomal-recessive juvenile parkinsonism is caused by loss-of-function mutations in the gene encoding Parkin, which lead to degeneration of dopaminergic neurons via accumulation of toxic proteins. It has been observed that loss of Parkin function results in the accumulation of nonubiquitinated p38, which leads to the formation of aggresome-like inclusions. Although the mechanism remains largely unknown, this accumulation of p38 may contribute to dopaminergic neurodegeneration, providing a link between a protein normally associated in the mammalian MSC and the neurodegenerative disorder Parkinson's disease.

The p38 polypeptide associates with a second auxiliary protein, p43, which is also an integral part of the MSC (Wolfe *et al.*, 2003). The C-terminus of p43 harbors an endothelial monocyte-activating polypeptide II (EMAPII)-like domain, which confers a general tRNA-binding property (Simos *et al.*, 1996; Quevillon *et al.*, 1997; Swairjo *et al.*, 2000; Deinert *et al.*, 2001). This domain is homologous to the yeast Arc1p protein that facilitates the binding of cognate tRNA substrates to MetRS and GluRS (Golinelli-Cohen & Mirande, 2007). The EMAPII-like domain, which may be removed from the full-length p43 following apoptotic cleavage, is involved in altering endothelial functions as a proinflammatory cytokine (Behrendorf *et al.*, 2000; Shalak *et al.*, 2001; Faisal *et al.*, 2007). The p43 EMAPII domain has also been shown to upregulate proinflammatory genes and increase chemotactic migration of polymorphonuclear leukocytes upon cleavage and removal from the MSC (Behrendorf *et al.*, 2000; Park *et al.*, 2002). The multifunctionality of these proteins involved in the mammalian MSC emphasizes the interconnection between translation and cellular processes outside of protein synthesis.

Although the role of the third auxiliary factor p18 remains largely unknown, p18 shares homology with the N-terminus of human ValRS, which is responsible for mediating complex formation with EF-1H (Quevillon & Mirande, 1996; Sang *et al.*, 2002; Park *et al.*, 2005a). EF-1A also associates with LysRS, a member of the mammalian MSC, suggesting that EF-1A may transiently associate with the macromolecular complex to provide an efficient means to shuttle aa-tRNA directly from the MSC to the ribosome during translation (Sang *et al.*, 2002; Guzzo & Yang, 2008). AaRSs have also been observed to copurify with polysomes (Popenko *et al.*, 1994). Whether aaRSs form specific complexes with polysomes or rather associate transiently remains to be determined. Similar to the smaller complex discovered in *M. thermotrophicus*, aaRSs may join to form a macromolecular complex in mammalian cells to enhance the aminoacylation activities of the associated aaRSs (Hausmann *et al.*, 2007; Praetorius-Ibba *et al.*, 2007). Taken together, MSCs characterized from archaea and eukaryotes improve the efficiency of early steps of translation, aa-tRNA synthesis and perhaps subsequent delivery to the ribosome.

Further, increased protein stability or restriction of the associated aaRSs to the cytoplasm, as was observed for the yeast Arc1p : GluRS : MetRS complex, may entice aaRSs to associate

into the higher order MSC complex (Galani *et al.*, 2001). The functional association of nine aaRS activities has also been suggested to provide a sequestered pool of aa-tRNAs specifically for utilization in protein synthesis (Negrutskii & Deutscher, 1991, 1992). Radiolabeled aa-tRNA, introduced into permeabilized CHO cells, were unable to be used as substrates for protein synthesis, while radiolabeled amino acids were efficiently incorporated during translation. This suggests that endogenously aminoacylated tRNAs, synthesized within the MSC, are required for efficient protein synthesis and that the pools of aa-tRNAs within the cell do not mix freely. This is supported by studies of ArgRS, which exists as both complexed (full-length) and free (truncated at its N-terminus) forms, translated from alternative start codons (Sivaram & Deutscher, 1990; Zhang *et al.*, 2006). It was observed that the pool of aa-tRNAs synthesized by ArgRS complexed with the MSC was preferentially utilized as substrates for protein synthesis *in vivo* (Kyriacou & Deutscher, 2008). Although the precise molecular mechanism remains to be deciphered, the work by Deutscher and colleagues lends support to the notion that the mammalian MSC is intimately involved in protein synthesis by directly providing the elongating ribosome with substrates synthesized within the MSC (Negrutskii & Deutscher, 1991; Negrutskii *et al.*, 1999). A larger complex of aaRSs was also discovered in the nucleus, possibly functioning in a role similar to the cytoplasmic MSC counterpart via association with nuclear pore-associated EF-1 α or to promote tRNA export (Popenko *et al.*, 1994; Ko *et al.*, 2002). Taken together, the mammalian MSC has been implicated in a variety of functions including protein stability, restriction of aaRSs to the cytoplasm, coordination of events during translation elongation.

Noncanonical activities of aaRS complexes

IFN- γ activated inhibitor of translation (GAIT) : GluProRS complex

Apart from their primary role of coupling cognate amino acid and tRNA pairs, it has recently become increasingly evident that aaRSs are not limited to protein synthesis (Table 2). In fact, the MSC may act as a repository for aaRSs where in response to cellular changes, aaRSs are subsequently liberated from the complex to participate in noncanonical tasks beyond translation (Lee *et al.*, 2004a; Park *et al.*, 2005b; Ray *et al.*, 2007). The bifunctional GluProRS, which harbors two different aaRS catalytic activities separated by three tandem linker domains, lends support to this notion by participating in the translational silencing of ceruloplasmin (a protein linked to the inflammatory response) (Rho *et al.*, 1998; Fox *et al.*, 2000; Sampath *et al.*, 2004; Ray *et al.*, 2007). Although generally associated with the MSC, GluProRS is phosphorylated in response to IFN- γ by an unknown mechanism, departs from the MSC, and is involved in mRNA silencing of ceruloplasmin via the GAIT complex composed of GluProRS, NS1-associated protein (NSAP1), glyceraldehydes-3-phosphate dehydrogenase (GAPDH), and ribosomal protein L13a (Cirakoglu *et al.*, 1985; Norcum, 1991; Agou & Mirande, 1997). Within the context of this heterotetrameric complex, translation is inhibited by the binding of the GluProRS linker region to a regulatory stem-loop GAIT mRNA element located within the 3'-untranslated region (UTR) of ceruloplasmin.

First, a pre-GAIT complex of GluProRS and NSAP1 is formed that is unable to bind the 3'-UTR region of ceruloplasmin and silence translation, possibly due to the inhibitory effects of NSAP1 (Jia *et al.*, 2008). The association of L13a and GAPDH complete the heterotetrameric GAIT complex, inducing a conformational change that abrogates the inhibitory effects of NSAP1. The GAIT complex is then able to bind the GAIT mRNA element of ceruloplasmin, mediated by the GluProRS WHEP domains, resulting in translation inhibition in response to IFN- γ (Mazumder *et al.*, 2003a, b; Sampath *et al.*, 2004; Kapasi *et al.*, 2007). Although the precise molecular mechanism of translational silencing via the GAIT complex is not well-defined, GAIT mRNA elements are found in more than 30 human mRNAs, suggesting a coordinated regulation of the inflammatory response via a complex involving the multifunctional GluProRS (Mazumder *et al.*, 2003a, b; Sampath *et al.*, 2004).

Lysyl-tRNA synthetase (LysRS) : Gag in HIV1

AaRSs have also been implicated in a number of functions separate from translation, including involvement in HIV type 1 (HIV-1) viral assembly (Stark & Hay, 1998; Halwani *et al.*, 2004; Kleiman *et al.*, 2004; Cen *et al.*, 2001, 2004a, b, c). Human HIV-1, an RNA retrovirus, enters the target cell and converts its RNA genome into DNA using a virally encoded reverse transcriptase (Chan *et al.*, 1999; Dobard *et al.*, 2007; McCulley & Morrow, 2007). Initiation of reverse transcription requires the specific packaging of tRNA^{Lys} into the HIV-1 virions, which functions as a primer for reverse transcriptase by binding near the 5' end of the HIV-1 genomic RNA (Barat *et al.*, 1989; Kleiman & Cen, 2004; McCulley & Morrow, 2007). Following minus strand transfer and reverse transcription of the minus strand DNA, the plus strand DNA is synthesized and the double-stranded DNA copy is translocated into the nucleus of the target cell where it is integrated into the host's chromosomal DNA (Liu *et al.*, 2005; Zeng *et al.*, 2007).

Human LysRS is also selectively packaged into the HIV-1 virion, independent of tRNA^{Lys} incorporation, which is evidenced by the fact that LysRS mutants unable to bind tRNA retain the ability to be packaged (Javanbakht *et al.*, 2003). Incorporation of LysRS into the virion is accomplished via specific interactions with HIV-1 Gag (a dimeric protein involved in assembly of viral particles), which interacts stably with a K_D of about 0.3 μ M (Javanbakht *et al.*, 2003; Guo *et al.*, 2005; Kovaleski *et al.*, 2006).

LysRS is believed to contribute positively to the selective incorporation of tRNA^{Lys}. Lending support to this notion was the discovery that inhibition of LysRS synthesis resulted in reduced tRNA^{Lys} packaging and annealing to the HIV-1 viral RNA (Guo *et al.*, 2003).

The interaction interface between LysRS, a dimeric class II aaRS, and Gag has been mapped to the dimerization domains of each protein, although the precise stoichiometry and multimeric form of each enzyme remain largely unknown (Javanbakht *et al.*, 2003; Kovaleski *et al.*, 2006). It has been postulated that newly synthesized LysRS associates with Gag rapidly before joining the MSC (Halwani *et al.*, 2004). This demonstrates that LysRS, which is an essential part of the mammalian MSC required for efficient protein synthesis, has been recruited from its primary role in translation to take part in the auxiliary function of HIV-1 viral assembly and packaging of its cognate tRNA.

Concluding remarks

Accurate translation of mRNA into protein is essential for cellular viability. Central to this process are the aaRSs, providing amino acid substrates to the ribosome in the form of aminoacyl-tRNAs. It has become increasingly evident that these indispensable enzymes have also accepted tasks in other cellular processes, acting outside of their canonical roles. The aaRSs are capable of acquiring new functions by associating into higher order complexes with proteins used in a variety of cellular tasks in all three domains of life. Most evident in archaea and eukaryotes, these macromolecular complexes are believed to share the common feature of promoting the direct hand-off of aa-tRNA from aaRSs to the ribosome during protein synthesis or connecting translation to other processes in the cell. By communicating with additional protein factors, aaRSs gain roles in alternative cellular processes such as translational silencing and viral assembly.

Multiprotein complexes harboring aaRSs vary in size from binary to macromolecular. This diversity may indicate that other cellular proteins associate with these known complexes, but have remained undiscovered due to the experimental limitations of purification. Providing new insight into previously unknown protein factors beyond the easily purified core may be the key to unlock the biological function of complex formation. Insight into subcellular localization

and dynamic assays *in vivo* will provide further evidence to reveal the physiological role of protein–protein interactions. Another avenue of experimentation to be addressed is how protein complexes respond to physiological changes in the cell. Under different conditions of environmental stress or progression through the cell cycle, it will be of interest to investigate the effects on complex formation, the possible association of other protein factors, and the essentiality of the complex. Advances in proteomics and mass spectrometry may also be used to complement existing genetic and biochemical tools and will be essential to deconvolute the functions of known macromolecular complexes and to aid in the discovery of new complexes, perhaps revealing novel functions.

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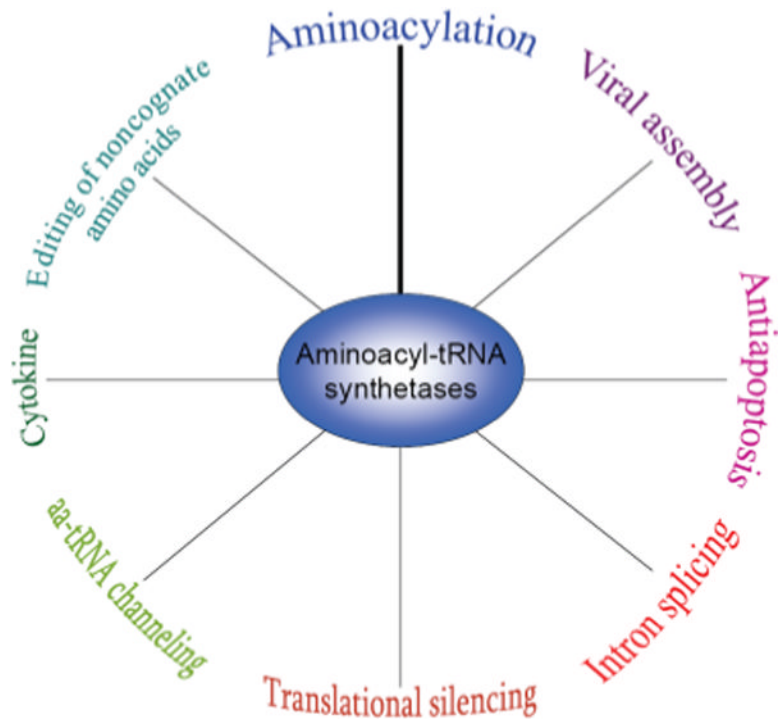


Fig. 1. AARSs impact a diverse range of functions throughout all domains of life.

Table 1
aaRS-containing complexes in all three domains of life

Domain	aaRS component(s) (class)	Accessory protein(s)	Species	Function	References
Bacteria	ProRS (II)	YbaK	<i>H. influenzae</i> ; <i>E. coli</i>	Hydrolysis of Cys-tRNA ^{Pro}	An & Mustier-Forsyth (2004), Ruan & Söll (2005)
	AspRS (II)	GatCAB amidotransferase	<i>T. thermophilus</i>	Conversion of Asp-tRNA ^{Asn} to Asn-tRNA ^{Asn}	Bailly <i>et al.</i> (2007)
	TrpRS (II)	Nitric oxide synthase	<i>D. radiodurans</i>	Nitration of tryptophan, producing 4-nitro-Trp	Buddha <i>et al.</i> (2004a), Buddha <i>et al.</i> (2004b), Buddha & Crane (2005)
Archaea	ProRS (II), (LysRS (I), and AspRS (II))	Mj1338 (metabolic protein)	<i>M. janaschii</i>	Unknown* (enhanced protein stability)	Lipman <i>et al.</i> (2003)
	LysRS (I), LeuRS (I), ProRS (III)	EF-1A	<i>M. thermautotrophicus</i>	Enhanced aminoacylation	Praetorius-Ibba <i>et al.</i> (2005), Praetorius-Ibba <i>et al.</i> (2007), Hausmann <i>et al.</i> (2007)
Eukarya	MetRS (I), GluRS (I)	Arc1p	<i>S. cerevisiae</i>	Enhanced binding affinity of tRNA ^{Met} and tRNA ^{Gln} ; subcellular localization	Simos <i>et al.</i> (1996), Simos <i>et al.</i> (1998), Galani <i>et al.</i> (2001), Karanastios <i>et al.</i> (2007)
	SerRS (II)	Pex21p	<i>S. cerevisiae</i>	Enhanced binding of tRNA ^{Ser} to SerRS	Rocak <i>et al.</i> (2002), Godinic <i>et al.</i> (2007)
	TyrRS (I)	Knr4	<i>S. cerevisiae</i>	Unknown* (dityrosine formation during sporulation)	Dagkessamanskaia <i>et al.</i> (2001), Ivakimo & Komelyuk (2005)
	ValRS (I)	EF-1A	<i>H. sapiens</i>	Enhanced aminoacylation; restriction of associated proteins to the cytoplasm	Motorin <i>et al.</i> (1988), Venema <i>et al.</i> (1991), Bec <i>et al.</i> (1994), Negruński <i>et al.</i> (1999)
	AspRS (II)	EF-1A	<i>H. sapiens</i>	Asp-tRNA ^{Asp} product release	Reed <i>et al.</i> (1994), Reed & Yang (1994)
	LysRS (II) and AspRS (II)	EF-1A and p38	<i>H. sapiens</i>	Enhanced aminoacylation	Guzzo & Yang (2008)
	GluProRS (I, II)	L13a, GAPDH, NSAP1	<i>H. sapiens</i>	Translational silencing	Mazumder <i>et al.</i> (2003b), Sampath <i>et al.</i> (2004), Ray <i>et al.</i> (2007)
	LysRS (II)	HIV-1 Gag	<i>H. sapiens</i>	Viral assembly; packaging of tRNA ^{Lys}	Javanbakht <i>et al.</i> (2003), Guo <i>et al.</i> (2005), Kowaleski <i>et al.</i> (2006)
	LysRS (II), LeuRS (I), IleRS (I), GluProRS (I,II), MetRS (I), GlnRS (I), ArgRS (I), AspRS (II)	p18, p38, p43	Chordates	Unknown* (exclusion of aaRSs from the nucleus, enhanced protein stability; control of noncanonical aaRS functions)	Bandyopadhyay & Deutscher (1971), Mirande <i>et al.</i> (1985), Kerjan <i>et al.</i> (1994), Quevillon <i>et al.</i> (1999), Robinson <i>et al.</i> (2000)

* Proposed.

Table 2

Examples of noncanonical functions of aaRSs

Domain	aaRS component (Class)	Location	Species	Function	References
Bacteria	ThrRS (II)	Cytoplasm	<i>E. coli</i>	Translational control	Brunel <i>et al.</i> (1993), Rombly <i>et al.</i> (1996), Torres-Larios <i>et al.</i> (2002)
Eukarya	AlaRS (II)	Cytoplasm	<i>E. coli</i>	Transcriptional control	Putney & Schimmel (1981)
	LeuRS (I)	Mitochondria	<i>S. cerevisiae</i>	Group I intron splicing	Herbert <i>et al.</i> (1988), Labouesse (1990), Rho <i>et al.</i> (2002)
	TyrRS (I)	Mitochondria	<i>N. crassa</i>	Group I intron splicing	Akins & Lambowitz (1987), Chermiack <i>et al.</i> (1990), Paukstelis <i>et al.</i> (2005)
	MetRS (I)	Nucleus	<i>H. sapiens</i>	Transcription of rRNA	Ko <i>et al.</i> (2000)
	GlnRS (I)	Cytoplasm	<i>H. sapiens</i>	Antiapoptosis	Ko <i>et al.</i> (2001)
	TrpRS (I)	Extracellular	<i>H. sapiens</i>	Angiostatic cytokine (targets endothelial cells)	Otani <i>et al.</i> (2002), Wakasugi <i>et al.</i> (2002b), Kise <i>et al.</i> (2004)
	TyrRS (I)	Extracellular	<i>H. sapiens</i>	Angiogenic cytokine (targets endothelial cells)	Wakasugi <i>et al.</i> (2002a), Greenberg <i>et al.</i> (2008)
	LysRS (II)	Extracellular	<i>H. sapiens</i>	Inflammatory cytokine	Park <i>et al.</i> (2005c)
	LysRS (II)	Plasma membrane	<i>H. sapiens</i>	Viral assembly; packaging of tRNA ^{Lys}	Javanbakht <i>et al.</i> (2003), Guo <i>et al.</i> (2005), Kovaleski <i>et al.</i> (2006)
	LysRS (II)	Nucleus	<i>H. sapiens</i>	Transcriptional control	Lee <i>et al.</i> (2004b)
	HisRS (II)	Cytoplasm	<i>H. sapiens</i>	Chemotactic for leukocytes	Howard <i>et al.</i> (2002)
	GluProRS (I, II)	Cytoplasm	<i>H. sapiens</i>	Translational silencing	Sampath <i>et al.</i> (2004), Ray <i>et al.</i> (2007)