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Review

The fidelity of the translation of the genetic code★✪

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Aminoacyl-tRNA synthetases play a central role in maintaining accuracy during the translation of the genetic code. To achieve this challenging task they have to discriminate against amino acids that are very closely related not only in structure but also in chemical nature. A 'double-sieve' editing model was proposed in the late seventies to explain how two closely related amino acids may be discriminated. However, a clear understanding of this mechanism required structural information on synthetases that are faced with such a problem of amino acid discrimination. The first structural basis for the editing model came recently from the crystal structure of isoleucyl-tRNA synthetase, a class I synthetase, which has to discriminate against valine. The structure showed the presence of two catalytic sites in the same enzyme, one for activation, a coarse sieve which binds both isoleucine and valine, and another for editing, a fine sieve which binds only valine and rejects isoleucine. Another structure of the enzyme in complex with tRNA showed that the tRNA is responsible for the translocation of the misactivated amino-acid substrate from the catalytic site to the editing site. These studies were mainly focused on class I synthetases and the situation was not clear about how class II enzymes discriminate against similar amino acids. The recent structural and enzymatic studies on threonyl-tRNA synthetase, a class II enzyme, reveal how this challenging task is achieved by using a unique zinc ion in the active site as well as by employing a separate domain for specific editing activity. These studies

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Abbreviation: aaRS, aminoacyl-tRNA synthetase.

led us to propose a model which emphasizes the mirror symmetrical approach of the two classes of enzymes and highlights that tRNA is the key player in the evolution of these class of enzymes.

A high fidelity is required in reaction mechanisms that are involved in the information transfer from the genetic code. During translation of the genetic message, aminoacyl-tRNA synthetases (aaRSs) play a very crucial role in maintaining such a high accuracy (Carter, 1993; Schimmel & Söll, 1979). To achieve this challenging task they have to specifically recognize one amino acid out of a pool of twenty protein amino acids and a few non protein amino acids, as well as one cognate tRNA family out of twenty tRNA families (Jakubowski & Goldman, 1992). Specific recognition of tRNA molecules is not a major problem since they are large enough to provide a wide range of specific interactions with the corresponding synthetase (Giege *et al*., 1998). It was shown that the error rate in tRNA selection is of the order of 10^{-6} or lower. However, the situation with the amino-acid substrates is very different in that they are much smaller and there are a few amino acids which have very similar, either structurally or chemically, side chains. In fact, such a problem of amino acid discrimination was first posed by Linus Pauling in 1957 (Pauling, 1957). According to him, if there is only a difference of a single methyl group between two substrates, the difference in their binding energies would not allow the error rate to be better than 1 in 5. However, the observed error rates in the selection of amino acids by their cognate synthetases are much lower, in the range of 10^{-4} to 10^{-5} (Loftfield & Vanderjagt, 1972). Numerous studies were made over the years to understand how synthetases overcome the problem of amino acid discrimination. A clear structural basis on how these enzymes achieve such a high accuracy in selecting their cognate amino-acid substrates is just beginning to emerge. This involves a process called editing or proof-reading by synthetases that are faced with such a problem (Fersht, 1985). This review focuses on the dramatic leap in our understanding of how synthetases discriminate against very closely related amino-acid substrates, made possible by the recent discovery of several key crystal structures.

THE SYNTHETASE FAMILY

AaRSs perform the task of attaching an amino acid to the terminal ribose of their cognate tRNA molecules through a two-step reaction called aminoacylation reaction. In the first step, the amino acid is combined with an ATP molecule to form an aminoacyl adenylate intermediate. In the second step, the amino acid moiety is transferred to the tRNA molecule. These enzymes were broadly partitioned into two classes of 10 enzymes each, as a result of the surprising discovery of the existence of two fundamentally different active sites (Table 1) (Eriani *et al*., 1990). The class I enzymes have a Rossmann-fold (Rossmann *et al*., 1974) catalytic domain whereas in class II enzymes it is based on an antiparallel β-fold flanked by α-helices (Cusack *et al*., 1990; Rould *et al*., 1989; Ruff *et al*., 1991). With a few exceptions, the partitioning is highly correlated with structural and functional characteristics (Arnez & Moras, 1997; Cusack, 1995; Moras, 1992). Class I enzymes are generally monomers whereas the class II enzymes exist as dimers. The class I enzymes approach their tRNA substrates from the minor groove of the acceptor stem and attach the amino acids to the 2′OH group of the terminal ribose. They possess two signature motifs 'HIGH' and 'KMSKS' which are responsible for substrate recognition. In the class II family, the tRNA is approached from the major groove side of the acceptor stem and aminoacylated at the 3′OH group, with the exception of PheRS. Class II enzymes possess three highly conserved motifs. Motif 1 is mainly responsible for the

dimerization of the subunits, whereas the other two motifs possess some key conserved residues which are involved in positioning of the substrates and in the reaction mechanism. Apart from these class-specific features, the enzymes within one class could be grouped depending on similarities exhibited among them. This grouping could depend either upon the possession of similar modules, since aaRSs are modular proteins (Delarue & Moras, 1993; Sankaranarayanan & Moras, 1999), or upon higher conservation in their sequence. Based on these considerations, the two classes are divided into three subgroups each. Moreover, idiosyncratic features that could correspond to specific functions are also seen in aaRSs pertaining to each of the twenty amino acids or even in the same system but from diverse species.

THE PROBLEM OF AMINO ACID DISCRIMINATION

The accuracy of the aminoacylation reaction depends on the ability of aaRSs to specifically recognize the correct amino acid and to attach it to the cognate-tRNA. The tRNA molecules are large enough to present the aaRSs with a large surface area for interaction. This facilitates the selection process and thus the error in tRNA selection is in the range of 10^{-6} or lower. As seen from several crystal structures of aaRS–tRNA complexes, the synthetases have evolved different domains that specifically recognize the anticodon arm (Arnez *et al*., 1995; Cavarelli *et al*., 1993; Cusack *et al*., 1998; Logan *et al*., 1995; Rould *et al*., 1991; Ruff *et al*., 1991; Sankaranarayanan *et al*., 1999), the acceptor arm (Sankaranarayanan

Table 1. Classification of aminoacyl-tRNA synthetases on the basis of structural and functional organization.

The enzymes for which the structure in the apo form or in complex with the tRNA is known are underlined or given in bold, respectively. The enzymes which are shown to possess an editing activity are indicated by an asterisk.

	Class I		Class II	
		Quaternary structure		Quaternary structure
Group a				
	CysRS	α	*GlyRS*	α_2
	ValRS*	α	AlaRS*	α, α_4
	*LeuRS**	α, α_2	**SerRS**	α_2
	IleRS*	α	**ProRS***	α_2
	*MetRS**	α_2	**ThrRS***	α_2
	ArgRS	α	*HisRS*	α_2
Group b				
	GlnRS	α	**AspRS**	α_2
	GluRS	α, $\alpha\beta$	*AsnRS*	α_2
	LysRS	α	**LysRS**	α_2
Group c				
	TyrRS	α_2	**PheRS***	$\alpha_2\beta_2$
	TrpRS	α_2	GlyRS	$\alpha_2\beta_2$

et al., 1999) and in some specific cases the variable loop (Biou *et al*., 1994) of the tRNA molecule, to achieve a high specificity in tRNA recognition. In contrast, the amino acids are much smaller molecules and therefore their recognition poses a more difficult problem. For most of the amino acids, the side chains exhibit strong and unique chemical characteristics so that their selection does not present a major problem. However, side chains of some amino acids are structurally or chemically quite similar, and therefore their specific recognition could be a major problem, for example in the case of valine, isoleucine, threonine, serine, alanine and glycine. This is typically the problem pointed out by Pauling (1957). However, his estimation of the error rate of 1 in 5 between two substrates that differ by a single methylene group is based on a difference in binding energy of 1 kcal/mol. This energy difference corresponds to a methylene group transferred from a hydrophilic to a hydrophobic solvent. Later, this value was estimated to be much higher, 3.4 kcal/mol per methylene group, as the binding is more specific in proteins than in hydrophobic solvents (Fersht *et al*., 1980). Therefore, the error rate corresponding to such a difference in binding is 1 in 200. Even this rate is much higher than what is observed experimentally in the case of synthetases where the error is in the range of 10^{-4} to 10^{-5} (Loftfield & Vanderjagt, 1972). Therefore, the question remained as to 'how do aaRSs achieve such a high specificity in discriminating against similar substrates?'.

EDITING OR PROOFREADING ACTIVITY

The solution to the problem of amino acid discrimination came mainly from the studies on the enzymes IleRS and ValRS. An editing activity was first discovered in IleRS, which specifically hydrolyzed the incorrectly formed products, either valyl adenyalte (Baldwin & Berg, 1966) or val-tRNA^{Ile} (Eldred & Schimmel, 1972). Since it is not possible for a pocket designed for binding isoleucine to discriminate completely against valine, which is smaller by only a methylene group, valine is activated and charged on the tRNA with a frequency of approximately 1 in 300. However, the overall error rate in protein biosynthesis, i.e. the misincorporation of valine instead of isoleucine in a growing polypeptide chain, is only 1 in 3000. This higher rate is achieved through the editing reaction, which enhances the discrimination ratio by a factor of 10. The editing reaction in this enzyme can occur through a 'pre-transfer' or a 'post-transfer' pathway. The pre-transfer mechanism involves the hydrolysis of the incorrectly formed valyl adenylate (Baldwin & Berg, 1966) whereas in the post-transfer mechanism the enzyme deacylates the incorrectly charged val-tRNA^{Ile} (Eldred & Schimmel, 1972). A similar recognition problem is also faced by ValRS which has to discriminate against the isosteric threonine. This enzyme also was shown to possesses an editing activity to eliminate the incorrectly formed threonyl adenylate or thr-tRNA^{Val} (Fersht & Kaethner, 1976). Based on these results a double-sieve editing model for the selection of similar substrates was proposed by Alan Fersht (Fersht, 1985; Fersht & Dingwall, 1979). According to this model, the enzyme first binds amino acids that are similar or smaller than the correct substrate and rejects the ones that are bigger, using a first site named the coarse-sieve. Then, in a second step, the smaller substrates are selectively bound and hydrolyzed using a fine-sieve. Even though the elegant double-sieve editing model could well explain the editing mechanism in IleRS and ValRS, it could not completely explain the editing activity found in a few other synthetases, for example MetRS, PheRS and AlaRS. Different pathways were proposed to account for these cases, which will be discussed briefly later.

AMINO ACID RECOGNITION BY THE CLASS I IleRS

Most of our current understanding on the editing activity comes from the biochemical and structural studies on IleRS. Particularly in the last few years, there has been a surge of information on the editingactivity of this enzyme resulting from the discoveries of the crystal structures of the enzyme in complexes with different substrates (Nureki *et al*., 1998) as well as with the tRNA (Silvian *et al*., 1999). IleRS is a class I enzyme and belongs to the subgroup *Ia* along with enzymes specific for valine, cysteine, leucine, arginine and methionine. Its active site is based on a Rossmann-fold domain consisting of alternating β-strands and α-helices forming a $\beta_6\alpha_4$ structure. A special characteristic of IleRSs from different organisms is that they all possess an insertion in the Rossmann-fold catalytic domain of approximately 200 residues which is called the connective polypeptide 1 (CP1) (Starzyk *et al*., 1987). Mutational studies in a segment of the CP1 fragment have shown that it alters the hydrolysis of val-tRNA^{Ile}, demonstrating that it contains a catalytic center for the editing reaction. Furthermore, the CP1 fragment alone expressed as an independent protein could also specifically hydrolyze the incorrect product (Lin *et al*., 1996). However, the first structural evidence of the double-sieve model came from the crystal structure of IleRS (Fig. 1A) from *Thermus thermophilus* solved in complex with the amino-acid substrates isoleucine or valine (Nureki *et al*., 1998). The structure of the enzyme with isoleucine showed its presence only in the Rossmann-fold catalytic domain. However, in the crystals soaked with valine, the amino acid bound to both the catalytic domain and to a site in the CP1 fragment. The structure showed clearly that the activation site (coarse-sieve) could bind both isoleucine and

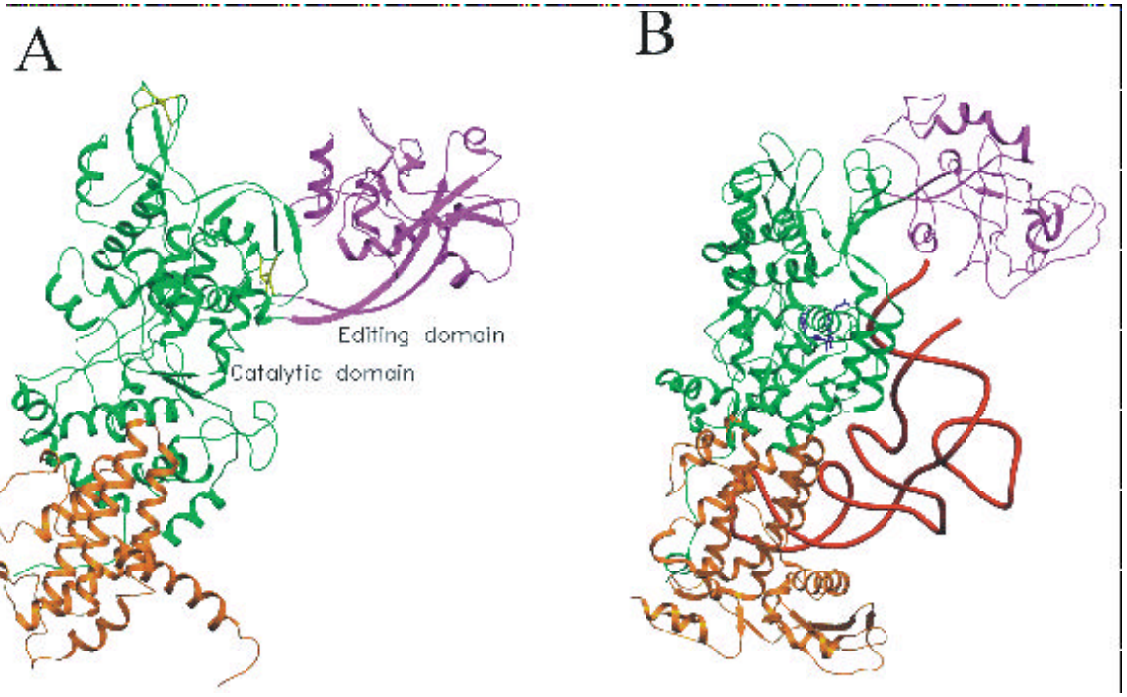

Figure 1. The structure of IleRS complexes.

A) Modular structure of IleRS from *Thermus thermophilus* (Nureki *et al*., 1998). The catalytic domain is indicated in green, the editing domain in pink, the anticodon binding module in orange and the coordination of zinc ion in yellow. B) The structure of IleRS from *Staphylococcusaureus* complexed with tRNA^{Ile} (Silvian *et al*., 1999). The protein modules are indicated as in Fig. 1A and the tRNA and the inhibitor molecule mupirocin are indicated in red and blue, respectively. All the figures except Figs. 3B and 4 were drawn using SETOR (Evans, 1993).

valine, whereas larger amino acids, including leucine, are rejected by the enzyme due to steric hindrance. In the CP1 module, only valine can bind and isoleucine can not fit in the editing pocket (fine-sieve) because of steric hindrance with residues lining the pocket. This study, therefore, is a clear demonstration of the double-sieve mechanism of editing. However, it was not clear as to how the substrate (either val-AMP or val-tRNA^{Ile}) translocation occurs from the catalytic site to the editing site which is more than 25 Å away.

The structure of IleRS from *Staphylococcus aureus* complexed with tRNA^{Ile} and mupirocin (Fig. 1B) suggested a partial answer to the translocation problem (Silvian *et al*., 1999). In this structure, the class I conserved Rossmann-fold active site module contained the mupirocin molecule. In an earlier study, it has been shown that three nucleotides in the D loop of the tRNA are essential for tRNA dependent editing activity (Hale *et al*., 1997). In the structure, the enzyme does not interact with the D loop and therefore it is not clear how the D loop can influence the editing activity. Interestingly, the tRNA^{Ile} acceptor stem, even though only visible till Cytosine 74, is in a helical form which is typical of free tRNA (Robertus *et al*., 1974; Suddath *et al*., 1974) or tRNAs bound to the active site of class II enzymes (Biou *et al*., 1994; Ruff *et al*., 1991). If the helical conformation of the acceptor end is modeled beyond cytosine 74, the 3′ end of the tRNA cannot reach the active site in the Rossmann-fold domain. However, the terminal adenosine is pointing towards the CP1 fragment, interacting particularly with residues His 392 and Tyr 394 which have been shown to be directly involved in the editing activity (Schmidt & Schimmel, 1995). Thus, the structure probably represents an 'editing complex'. The study showed that the tRNA molecule is directly involved in the translocation event, wherein the CCA-end shuttles from the active site to the editing site by shifting from a hairpin conformation to helical conformation. Therefore, the model for post-transfer editing is very similar to that observed in the case of DNA polymerase I where the nascent strand shuttles between the active site and the editing site (Brutlag & Kornberg, 1972; Freemont *et al*., 1988; Joyce & Steitz, 1994). A similar shuttling of the noncognate valyl adenylate has also been shown to be responsible for pre-transfer editing by a kinetic study with a fluorescent probe (Nomanbhoy *et al*., 1999). The mechanism of editing could also be very similar in a related class I enzyme, ValRS, which has to discriminate against threonine. Indeed it activates threonine at an error rate of 1 in 350 to 1 in 400 (Lin & Schimmel, 1996). The enzyme also possesses the CP1 fragment responsible for hydrolyzing the incorrect thr-tRNA^{Val} (Lin *et al*., 1996).

AMINO ACID RECOGNITION BY THE CLASS II ThrRS

Even though a large amount of biochemical and structural data were available on the editing activity of synthetases, most of them were dedicated to class I enzymes. Very little is known about how class II enzymes discriminate against closely related amino acids. In fact, the candidates for editing in class II are not many. The two enzymes that typically fit into the category that require editing are AlaRS and ThrRS. AlaRS has to mainly discriminate against glycine, which is shorter than alanine by one methylene group. ThrRS faces a complex discrimination problem against two closely related amino acids. It has to discriminate against valine, which is isosteric with threonine, and serine, which is shorter by one methyl group. ThrRS is a class II enzyme which is based on an antiparallel β-fold for the catalytic module (Arnez & Moras, 1997). The structure of ThrRS from *Escherichia coli* in complex with its tRNA showed that the enzyme is a modular protein made of four domains (Fig. 2A) (Sankaranarayanan *et al*., 1999). The N-terminal mod-

ules char ac ter is tic of the threonyl sys tem fold into two sep a rate do mains and are con nected to the cat a lytic mod ule through a linker he lix. Surprisingly, the structure showed for the first time the pres ence of a zinc ion in the ac- tive site mod ule of an aaRS, at a po si tion close to the amino acid binding pocket. Structural zinc ions have been found in other synthetas- es, for ex am ple in MetRS (Brunie *et al*., 1990) and IleRS (Nureki *et al*., 1998), but not in the active site. The zinc ion is coordinated by three pro tein lig ands and by a wa ter mol e cule. The strict con ser va tion of the zinc bind ing res idues throughout evolution and mutational stud ies *in vivo* showed that the zinc ion has a cru cial role to play in amino acid rec og ni tion. Also, the co or di na tion of the zinc ion by a wa- ter mol e cule sug gested that it may have a cat a lytic role (Christianson, 1991). A purely struc- tural role for the zinc ion could be ruled out since it is found within the active site and is coordinated to a water molecule. Moreover, the class II catalytic do main has a sta ble ter- tiary fold as found in the structures of other class II synthetases, thus obviating the need for a structural metal cation to stabilize the fold (Arnez & Moras, 1997).

Two crys tal struc tures of a trun cated ver sion of the en zyme (con sist ing of the cat a lytic and anticodon binding domains) complexed with threonine or a threonyl-adenylate analog clearly showed a di rect role for the zinc ion in amino acid rec og ni tion (Sankaranarayanan *et al*., 2000). Upon threonine bind ing, the wa ter molecule is replaced by the threonine sub- strate and the zinc ion in ter acts with both the amino group and the side-chain hydroxyl of the sub strate (Fig. 2B). The zinc ion changes its coordination from tetrahedral, in the ab- sence of the sub strate, to square-based py ram- i dal in the pres ence of the sub strate. Thus, the zinc ion ful fils a new func tion which is nei ther cat a lytic nor struc tural, but acts as a co fac tor in the amino acid recognition process. This mode of in ter ac tion of threonine with the zinc ion clearly showed that the isosteric valine would be re jected by the en zyme, since one of the side chain methyl groups would be in an

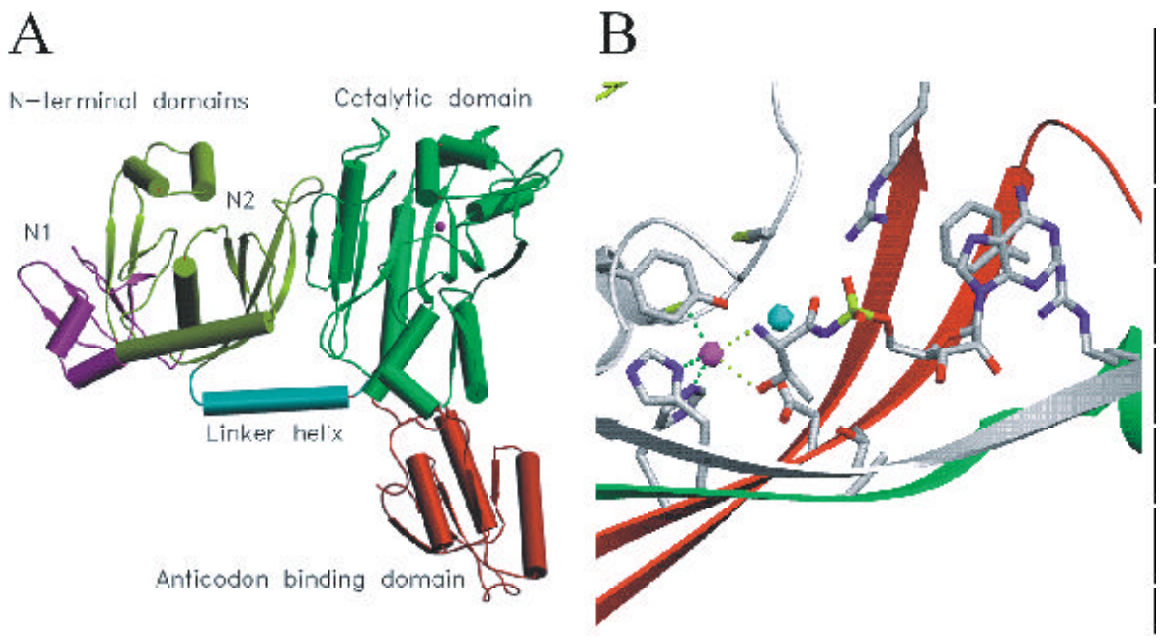

Fig ure 2. The struc ture of ThrRS from *Esche richia coli*.

A) Do main ar chi tec ture of a mono mer ThrRS. Dif fer ent col ors are used to in di cated the dif fer ent mod ules of the en- zyme. B) The ac tive site of the trun cated form of ThrRS show ing the in ter ac tion of the zinc ion with the amino-acid sub strate. The con served mo tifs 2 and 3 are in di cated in red and green, re spec tively. The zinc ion (pink) and a wa ter mol e cule (cyan) are rep re sented as spheres.

unfavorable contact with the zinc ion. Amino acid activation experiments showed that valine is indeed completely rejected by the enzyme. However, the studies showed that serine is activated by the enzyme with a 1000-fold reduced efficiency. Even though this error rate is slightly lower than that observed for the rejection of valine by IleRS and threonine by ValRS at the activation step (Jakubowski & Goldman, 1992), it is higher than that observed *in vivo*. Therefore, an editing mechanism it is necessary to correct the error.

A typical characterization of the existence of a pre-transfer editing mechanism involves the measure of ATP hydrolysis in the presence of noncognate substrates, as observed in the case of some class I synthetases and in AlaRS. In the case of ThrRS, no ATP consumption could be detected, indicating that no error correction takes place at the level of the adenylate. The crystal structure of the enzyme in the presence of a seryl adenylate analog showed that serine interacts with the zinc ion in a way that is very similar to threonine (Dock-Bregeon *et al*., 2000). This further rules out the possibility that the zinc ion could have a catalytic role or that the metal ion could be responsible for hydrolyzing the incorrect adenylate, since such a mechanism would require a different mode of binding of serine compared to threonine. Enzymatic measurements carried out to find out whether a post-transfer editing mechanism exists in ThrRS showed clearly that the enzyme uses its N-terminal module for selective hydrolysis of the incorrectly formed Ser-tRNA^{Thr} (Dock-Bregeon *et al*., 2000). A structural superposition (Fig. 3A) of the acceptor arm of tRNA^{Gln}, from the class I GlnRS–tRNA^{Gln} complex (Rould *et al*., 1989), on top of ThrRS (Sankaranarayanan *et al*., 1999) showed the CCA-end of tRNA^{Gln} pointing towards a pocket in the N2 module of ThrRS (Fig. 3B).

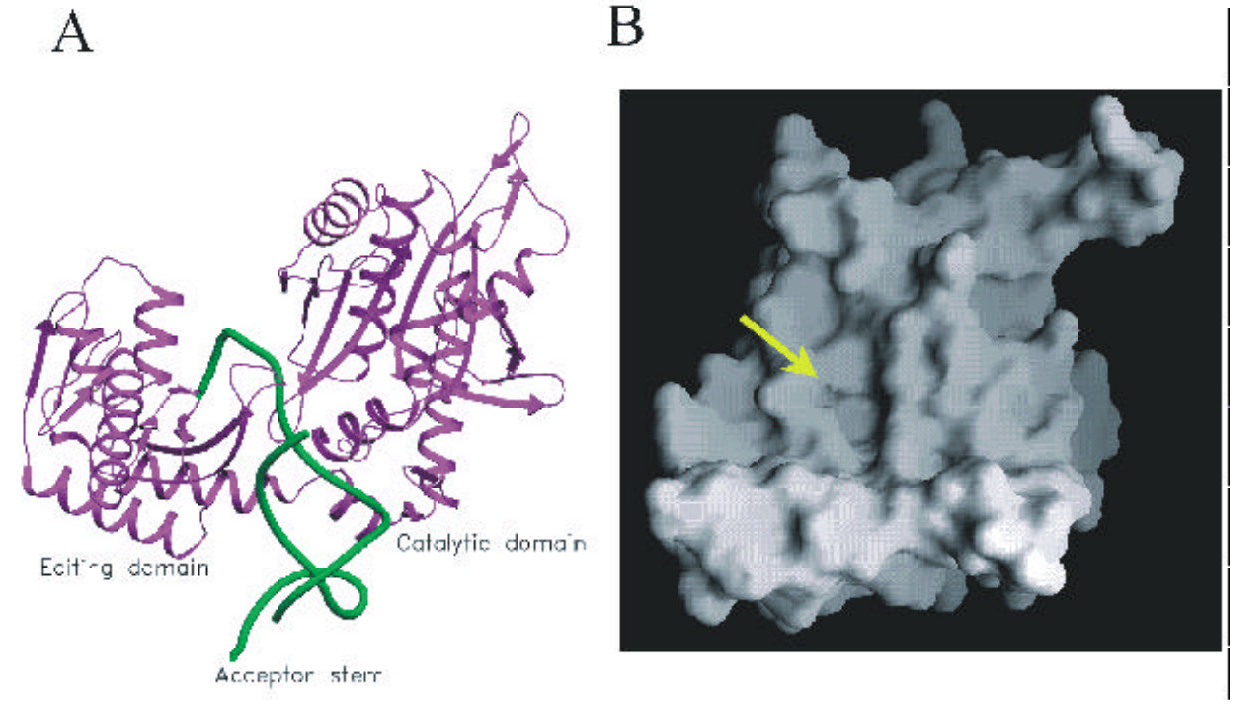

Figure 3. The editing site of ThrRS.

A) Structural superposition of the acceptor arm of tRNA^{Gln} on the ThrRS–tRNA^{Thr} complex structure, showing the acceptor end of tRNA^{Gln} pointing towards a site in the N2 domain of ThrRS. B) Surface representation of the N2 domain, where the editing site is indicated by an arrow. Figure drawn using GRASP (Nicholls &Honig, 1991). Adapted from Dock-Bregeon *et al.* (2000).

This pocket has been implicated earlier as responsible for the editing activity of ThrRS (Sankaranarayanan *et al*., 1999). Mutational studies of the residues surrounding this pocket have shown that it is indeed responsible for the editing activity (Dock-Bregeon *et al*., 2000). Thus, the conformation of the CCA-end of the tRNA changes from helical, assumed in order to reach the active site, to bent which is necessary to reach the editing site. The incorrectly aminoacylated serine moiety is translocated to the editing site by the tRNA and gets hydrolyzed. This mechanism of editing together with the activation mechanism of a class II synthetase can be considered a mirror image of the events in a class I synthetase (Fig. 4).

In ThrRS, the overall mechanism follows the general 'double-sieve' model for editing. However, in contrast to what has been proposed so far, the first is a chemical sieve and not a steric one. This was illustrated by the amino acid activation experiments with an unnatural amino acid β-hydroxynorvaline which is bigger than threonine by one methylene group. This amino acid could be activated by ThrRS (Sankaranarayanan *et al*., 2000), showing that the enzyme uses the zinc ion to select amino acids that possess a hydroxyl group attached to the β-position. Therefore, size is not a strict criterion at the coarse-sieve. Through a tRNA mediated post-transfer editing activity, the smaller amino acid is then selectively hydrolyzed using the second fine-sieve.

EDITING IN OTHER SYSTEMS

In addition to the pre- and post-transfer editing reactions described before, a third pathway is used by MetRS to maintain the accuracy of the aminoacylation reaction (Jakubowski & Fersht, 1981). In this case, the enzyme misactivates homocysteine, which has been shown to cyclize to form homocysteine thiolactone. LeuRS from *E. coli* possesses post-transfer editing activity towards two analogous non-protein amino acids gamma-hydroxyleucine and homocysteine (Englisch *et al*., 1986). The class II PheRS has also been shown to specifically deacylate the mischarged Ile-tRNA^{Phe} (Yarus, 1972). AlaRS has been shown to possess an editing activity for both glycine and serine (Tsui & Fersht, 1981). In this case, glycine fits in the model of a double-sieve editing and it remains to be seen how

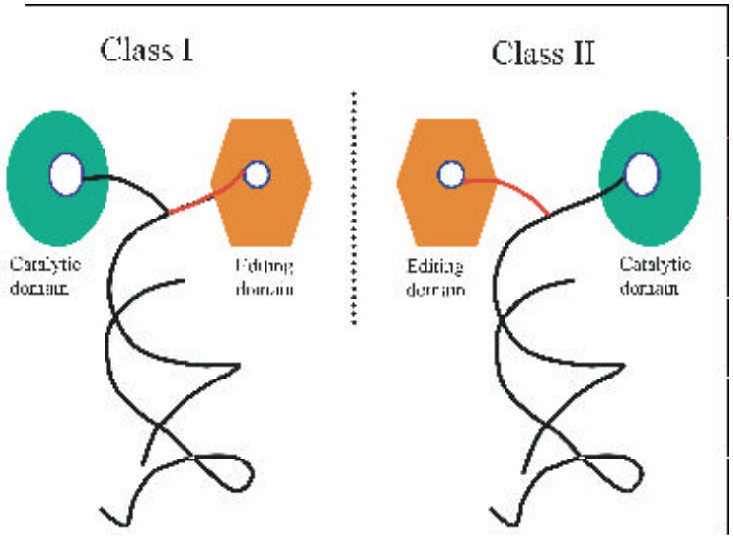

Figure 4. A model of the editing process in both classes of synthetases emphasizing the symmetrical nature of the activation and editing mechanism.

Adapted from Dock-Bregeon *et al.* (2000).

the active site of AlaRS can activate serine. It is also interesting to note that the N2 domain responsible for the editing of ser-tRNA^{Thr} in ThrRS is also present in AlaRS (Sankaranarayanan *et al*., 1999). Both biochemical and structural studies are required to find out whether this domain is involved in the editing activity of AlaRS and to elucidate the editing mechanism. Very recently, it has been shown that ProRS also possesses an editing activity to hydrolyze the micharged ala-tRNA^{Pro} (Beuning & Musier-Forsyth, 2000). The enzyme activates alanine 23000 times less efficiently than the cognate substrate proline. It is argued that since the *in vivo* concentration of alanine (148 μM) in *E. coli* cells is much higher than that of proline (9 μM) (Raunio & Rosenqvist, 1970), the enzyme needs to possess an editing activity to maintain the accuracy in the translation of the genetic code. However, it remains to be seen how these enzymes edit the noncognate amino acids.

CONCLUSIONS

AaRSs are thought to be an ancient family of enzymes which provide a crucial link between the RNA world and proteins. It is believed that the early synthetases were made of only the catalytic module charging mini RNA helices based on an operational RNA code, more ancient than the present anticodon-based genetic code (Schimmel *et al*., 1993). Also, the evolution of the anticodon arm of tRNA led to the evolution of anticodon binding domains in synthetases. Thus, the RNA molecule is a key player in the evolution of the present day synthetases. As the evolutionary pressure on synthetases increased to provide a much higher accuracy, they acquired additional modules responsible for the editing activity. However, the evolutionary process is very much dictated by the ability of the CCA-end of the tRNA molecule to switch between two different conformations (i.e. between helical and bent). It is intriguing that even though both classes of synthetases diverged very early in evolution, they have arrived at similar mechanistic solutions to the problem of maintaining fidelity in the translation of the genetic code.

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