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Review

Histidyl-tRNA Synthetase

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Histidyl-tRNA synthetase (HisRS) is responsible for the synthesis of histidyl-transfer RNA, which is essential for the incorporation of histidine into proteins. This amino acid has uniquely moderate basic properties and is an important group in many catalytic functions of enzymes.

A compilation of currently known primary structures of HisRS shows that the subunits of these homodimeric enzymes consist of 420 – 550 amino acid residues. This represents a relatively short chain length among aminoacyl-tRNA synthetases (aaRS), whose peptide chain sizes range from about 300 to 1100 amino acid residues.

The crystal structures of HisRS from two organisms and their complexes with histidine, histidyl-adenylate and histidinol with ATP have been solved. HisRS from *Escherichia coli* and *Thermus thermophilus* are very similar dimeric enzymes consisting of three domains: the N-terminal catalytic domain containing the six-stranded antiparallel β-sheet and the three motifs characteristic of class II aaRS, a HisRS-specific helical domain inserted between motifs 2 and 3 that may contact the acceptor stem of the tRNA, and a C-terminal α/β domain that may be involved in the recognition of the anticodon stem and loop of $tRNA^{His}$.

The aminoacylation reaction follows the standard two-step mechanism. HisRS also belongs to the group of aaRS that can rapidly synthesize diadenosine tetraphosphate, a compound that is suspected to be involved in several regulatory mechanisms of cell metabolism. Many analogs of histidine have been tested for their properties as substrates or inhibitors of HisRS, leading to the elucidation of structure-activity relationships concerning configuration, importance of the carboxy and amino group, and the nature of the side chain.

HisRS has been found to act as a particularly important antigen in autoimmune diseases such as rheumatic arthritis or myositis. Successful attempts have been made to identify epitopes responsible for the complexation with such auto-antibodies.

Key words: Aminoacylation / ATP / Histidine / Histidyladenylate / Transfer RNA / Translation.

Introduction

Histidine is one of the two standard, i.e. genetically coded, amino acids with a heterocyclic aromatic side chain (Figure 1). The imidazole ring not only plays a role in stabilizing the structure of a protein by its aromatic properties but often has an important function in the catalytic centers of enzymes, e.g. in acid-base catalysis, due to its unique pK value of 6.00. Enzymatic decarboxylation of histidine generates the biologically important compound histamine (compare MacDonald, 1996; Hill *et al*., 1997)

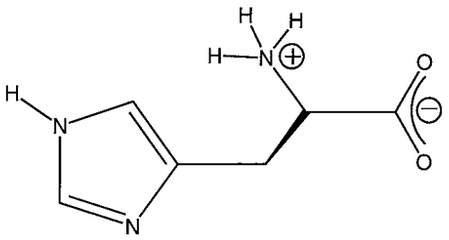


Fig. 1 Chemical Structure of L-Histidine.

Before being incorporated into proteins histidine is attached to the 3′-terminal hydroxy group of a histidine-specific transfer RNA ($tRNA^{His}$) in a two-step process (Loftfield, 1972; Kisselev and Favorova, 1974; Söll and Schimmel, 1974; Eriani *et al*., 1990; Schimmel, 1991a; Burbaum and Schimmel, 1991; Mirande, 1991; Carter, 1993; Giegé *et al*., 1993; Moras, 1993; Delarue and Moras, 1993; Söll and RajBhandary, 1995; Söll and Doolittle, 1995):

$$HisRS + ATP + His \rightarrow HisRS \cdot His\text{-}AMP + PP_i$$

$$HisR \cdot His\text{-}AMP + tRNA^{His} \rightarrow HisRS + His\text{-}tRNA^{His} + AMP$$

These two reactions are catalyzed by histidyl-tRNA synthetase (E.C. 6.1.1.21, CA RN 9068-78-4), also named his-

tidine:tRNA ligase, and abbreviated as HisRS or HRS. Sequence comparisons have shown that HisRS is a class II aminoacyl-tRNA synthetase (aaRS) and may belong to the subgroup IIa together with the enzymes specific for proline, serine, and threonine (Eriani *et al.*, 1990; Cusack *et al.*, 1991).

Approximately 260 papers on HisRS have been published in the past thirty years and are reviewed in this article.

Purification of Histidyl-tRNA Synthetases

Histidyl-tRNA synthetase has been purified from several organisms or tissues (Table 1). The preparation procedures follow nearly all of the classical approaches to enzyme isolation, such as precipitation with ammonium sulfate, polyethyleneimine, polyethyleneglycol, or protamine sulfate; chromatography on DEAE-cellulose, DEAE-Sephadex, Sephadex G-100, phosphocellulose, hydroxylapatite, calcium phosphate gel, and Bio-Rex (Table 1). Chromatography on Affi-Gel blue and DNA-agarose (Chen and Somberg, 1980), Blue Sepharose and Poly-U Sepharose (Biswas *et al.*, 1987a) or high pressure liquid chromatography (Biswas *et al.*, 1987a) and preparative gel chromatography (Kalousek and Konigsberg, 1974) have also been used. These and similar methods have also been applied in the purification of several mutant HisRS proteins (Rühlmann *et al.*, 1997; Yan *et al.*, 1996). A stabilization protocol for isolated human HisRS by hemoglobin or hematin has been described by Biswas *et al.* (1988).

The isolated and purified enzymes always showed dimeric quaternary structures of identical subunits, for which molecular masses were determined between 78 and 122 kDa per dimer (Table 1). The intracellular concentration of HisRS was estimated at 2.3 μM in *Salmonella*

Table 1 Purification of HisRS from Natural Sources.

Source	Grade of purification	Molecular mass [kDa]	References
E. coli			Muench and Berg, 1966
	820-fold	85 (42.5)	Kalousek and Konigsberg, 1974
	351-fold, partial purification		Kern and Lapointe, 1979 Fromant *et al.*, 1981 del Rio *et al.*, 1982
	crystals (HisRS mutants)		Francklyn *et al.*, 1994 Yan *et al.*, 1996; Rühlmann *et al.*, 1997; Augustine and Francklyn, 1997
B. stearothermophilus		102	Grosjean *et al.*, 1976
S. typhimurium	800-fold, 95%	100	De Lorenzo and Ames, 1970
		78 (40)	De Lorenzo *et al.*, 1972; 1974 Boguslawski *et al.*, 1974
T. thermophilus	95%, crystals		Yaremchuk *et al.*, 1995
Streptococcus equisimilis	99%	(47.9)	Menguito *et al.*, 1993a
Baker's yeast	590-fold		Tigerstrom and Tener, 1967
S. cerevisiae		100	Boguslawski *et al.*, 1974
N. crassa			Takeda, 1969
	921-fold	125 (62.5)	Chen and Somberg, 1980
Rat liver		100 – 150	Yang *et al.*, 1984
	11700-fold	96 (50)	Fahoum and Yang, 1987
	multi-enzyme complexes		Badyopadhyay and Deutscher, 1971 Vellekamp *et al.*, 1985 Salomon *et al.*, 1976
		multi-enzyme complex	Ogata *et al.*, 1994 Ogata and Terea, 1994
Rabbit reticulocytes	83780-fold partial purification	122 (64)	Kane *et al.*, 1978 Alzhanova *et al.*, 1982 Smith *et al.*, 1979
Beef liver	partial purification		Walker *et al.*, 1983
Bovine liver	> 2650-fold	160 (80)	Walker and Jeffrey, 1987
HeLa cells	5110-fold	120 (55)	Biswas *et al.*, 1987a, b, 1988
CHO cells	partial purification, multi-enzyme complex		Ritter *et al.*, 1979 Pahuski *et al.*, 1983
Several eukaryotes	partial purification, multi-enzyme complex		Ussery *et al.*, 1977

Source, grade of purification as far as given, molecular masses of the dimeric enzymes (α_2) and in brackets of the single subunits (α), as estimated by the authors in the cited references.

typhimurium (De Lorenzo and Ames, 1970). Whereas HisRS from several bacteria or mammalian organisms have been successfully purified, isolation of HisRS enzymes from plants has never been published. Only very few multienzyme complexes containing HisRS activities have been found; this is consistent with the observation that HisRS belongs to a type of aaRS which is usually found nonassociated *in vivo* (Dang and Dang 1986, compare also Freist and Gauss, 1995a). Large amounts of HisRS can be prepared by using overexpression vectors for HisRS genes, which is discussed below.

Histidyl-tRNA Synthetase Genes

The first structural gene for histidyl-tRNA synthetase was identified in *Escherichia coli* and localized at 53.8 min on the *E. coli* genome (Parker and Fishman, 1979). This gene, called *hisS*, turned out to be one of the smallest aaRS genes (Freedman *et al*., 1985). The corresponding polypeptide consists of 423 amino acid residues with a molecular mass of 46.9 kDa per subunit. The 5′-noncoding sequence of the *hisS* gene harbors three potential promoter regions (Fishman *et al*., 1979; Eisenbeis and Parker, 1982). One of them is at the region around position –10, which may be the major promoter (Freedman *et al*., 1985). The *hisS* mRNA transcript contains an interesting feature: nucleotides 132–137 are homologous to the 5′-portion of the anticodon stem and loop of $tRNA^{His}$ and nucleotides 136–142 are homologous to the 3′-side of the dihydrouridine stem and loop (Freedman *et al*., 1985). Expression of the *hisS* message is negatively autoregulated, similarly to that of threonyl-tRNA synthetase from *E. coli* (compare review by Freist and Gauss, 1995b). At a high cellular concentration HisRS binds the tRNA-like structure of the mRNA, thereby arresting its own synthesis by preventing the mRNA from further binding to the ribosome.

Several vectors for overexpression of the *E. coli* HisRS gene have been constructed (Eisenbeis and Parker, 1981; Glade and Englisch, 1988; Markmeyer *et al*., 1990; Englisch *et al*., 1990; Francklyn *et al*., 1994; Yan *et al*., 1996; Rühlmann *et al*., 1997), some of which have been used to prepare large amounts of purified HisRS (Francklyn *et al*., 1994; Yan *et al*., 1996; Rühlmann *et al*., 1997). Additional constructs can be found in the references listed in Table 2.

The second HisRS gene to be sequenced was that of the yeast *Saccharomyces cerevisiae* (Natsoulis *et al*., 1986). Surprisingly, this gene, called *HTS1*, encodes both cytoplasmic and mitochondrial HisRS. It contains two ATG start codons, one at position –60 and the other at +1. The shorter mRNA encodes the cytoplasmic enzyme, which consists of 526 amino acid residues with a molecular mass of 57.8 kDa per subunit. The larger mRNA encodes 20 additional N-terminal amino acid residues for the mitochondrial enzyme. This N-terminal extension is highly basic (two lysines and two arginines, no other charged amino acids) and may be responsible for the translocation of the enzyme into the mitochondrion. Mutations in the up-

Table 2 HisRS Genes and Proteins.

Source	Length of protein sequence (aa) and remarks	Data base entry number	References
Aquifex aeolicus	403 aa	AE000674	Deckert *et al*., 1998
Archaeoglobus fulgidus	409 aa	AF1642, AE000989	Klenk *et al*., 1997
Bacillus subtilis	424 aa	G69641 Z99118 BACSUCG. HISS	Kunst *et al*., 1997
Borrelia burgdorferi	457 aa	AE001125 AE00783 BB 135	Fraser *et al*., 1997
Caenorhabditis elegans	525 aa	S41763 P34183	Amaar and Baillie, 1993 Wilson *et al*., 1994
Cricetulus griseus (Chinese hamster)	508 aa	A27516	Tsui and Siminovitch, 1987a
Escherichia coli	424 aa	A23890 A65028	Freedman *et al*., 1985
	423 aa (46.9 kDa)	P04804	
	423 aa (Crystal structure)	1KMM 1KMN	Arnez *et al*., 1997 Arnez *et al*., 1995
Escherichia coli K 12		AE000337 U00096	Blattner *et al*., 1997
Fugu rubripes	519 aa	Z54243 P70076	Brenner and Corrochano, 1996
Haemophilus influenzae	423 aa	I64063 P43823	Fleischmann *et al*., 1995
Helicobacter pylori	442 aa	F64668 AE000625 AE000511	Tomb *et al*., 1997
Homo sapiens	506 aa	P49590 U18937	O'Hanlon *et al*., 1995b (HO3)
	509 aa (57.4 kDa)	P12081 I37559 B27516 I53670 S18965	Raben *et al*., 1992b
Mesocricetus auratus (golden hamster)	508 aa	P07178	Tsui and Siminovitch, 1987a
Methanobacterium thermoautotrophicum	411 aa	AE000811	Smith *et al*., 1997

Table 2 Continued.

Source	Length of protein sequence (aa) and remarks	Data base entry number	References
Methanococcus jannaschii	416 aa (48.3 kDa)	G64424 Q58406 U67542	Bult *et al*., 1996
Mus musculus (house mouse)	509 aa (57.4 kDa)	JC5223 Q61035 U39473	Blechynden *et al*., 1996
Mycobacterium leprae	427 aa (48.8 kDa)	S72739 P46696	
Mycobacterium tuberculosis	423 aa (41.1 kDa)	Q50641	
Mycoplasma genitalium	414 aa (48.3 kDa)	H64203 P47281 U39682 L43967	Fraser *et al*., 1995
Mycoplasma pneumoniae	414 aa (47.3 kDa)	S73435 P75069	Himmelreich *et al*., 1996
Oryza sativa (rice)	494 aa (55.3 kDa)	P93422 Z85984	Akashi and Small, 1998
Porphyra purpurea chloroplast (red alga)	430 aa (49.8 kDa)	S73269 P51348	Reith and Munholland, 1995
Rickettsia prowazekii	416 aa	RPX002	Andersson *et al*., 1998
Saccharomyces cerevisiae	546 aa (60.0 kDa)	P07263 Q12095 S54507 B23946 A23946 Z49274 U00094	Natsoulis *et al*., 1986
Salmonella typhimurium	424 aa	AF047040	
Schizosaccharomyces pombe	538 aa	AL022103	
Staphylococcus aureus	420 aa	D76414	Fujimura and Murakami, 1997
Streptococcus equisimilis	425 aa (47.8 kDa)	P30053 Z17214	Menguito *et al*., 1993b
Synechococcus sp.	420 aa (46.6 kDa)	L35476 Q55267	Tsinoremas *et al*., 1994
Synechocystis sp.	447 aa (49.2 kDa) [401 aa (44.3 kDa)]	S76321 Q55653 P74592	Kaneko *et al*., 1995, 1996
Thermus thermophilus	421 aa (47.1 kDa)	1ADJ 1ADY P56194	Åberg *et al*., 1997
Treponema pallidum	442 aa	AE001239 AE000520	Fraser *et al*., 1998

Data bases used besides GenBank, PIR, and SwissProt are Structure Database PDB, and data bases TIGR, NRSub, and BBDB (Borrelia) accessible via Internet. Sources (in alphabetical order), protein length (aa) and molecular masses of proteins as far as given (in brackets), data base entries and references are indicated. When no references are given, data are listed in data bases without literature citation. Due to different stages of research protein chain lengths can differ in different entries (e.g. for *E. coli*). From several organisms also fragments of gene or protein sequences or tagged partial genes are listed in data bases: *Arabidopsis thaliana*: H36569, (Newman *et al*., 1994); *Caenorhabditis briggsae*: RO3701; *Caenorhabditis elegans*: L13152, Z69384, S68230, S41762, Q26342; *Cricetulus* sp.: M19147, (Tsui and Siminovitch, 1987b); *Homo sapiens*: X05345, Z11518, M96946, AA100106, AA100107, AA306702, AA316106, AA323719, AA334715, AA341345, AA353235, AA366480, AA374007, AA374215, AA375856, AA493301, AA494265, AA551428, AA568468, AA576097, AA586865, AA588096, AA588466, H61209, H61301, H62114, U18936, R58011, R60149, R60150, R73621, T28829, T29350, T40241, T47266, T47267, T71354, T71516, W73095; *Lactococcus lactis* supsp. *lactis*: P328 (Delorme *et al*., 1992); *Mus musculus*: AA016683, AA042064, AA117083, AA124255, AA146434, AA172676, AA259866, AA260645, AA387037, AA432605, AA529528, AA624234, AA636154, AA667688, W41575; *Mycoplasma capricolum*: Z33137 (Bork *et al*., 1995); *Pyrococcus furiosus*: AA113561; *Rattus norwegicus*: C07003; *Rattus* sp.: H34149 (Lee *et al*., 1995); *Streptococcus equisimilis*: S30232, S30233; *Sulfolobus shibatae*: L36863, P46220; *Sus scrofa*: F14533, Q29207 (Winteroe *et al*., 1996); *Trypanosoma brucei rhodesiense*: B07332 (el-Sayed and Donelson, 1997).

stream ATG (–60) affected the synthesis of only the mitochondrial enzyme, mutations in the downstream ATG (+1) that of the cytosolic enzyme alone (Chiu *et al*., 1992). Deletions of the first 20 amino acid residues produce a functional cytoplasmic enzyme, which does not provide mitochondrial function. However, if this truncated cytoplasmic enzyme is overexpressed mitochondrial function is restored. These results suggest that the 'long' enzyme contains two additional domains at the amino-terminus that together allow efficient localization in the mitochondrion, whereas neither is sufficient by itself for this function. The first domain is likely to be cleaved upon delivery to the mitochondrion, while the second (residues 21–53) is present in both forms.

The HisRS gene of *Streptococcus equisimilis* has an overall identity of 58% and 20% with the *E. coli* and yeast HisRS genes, respectively. It encodes a polypeptide of 426 amino acid residues with a molecular mass of 47.9

kDa. The protein contains all three motifs characteristic of class II aaRS (Menguito *et al*., 1993a, b).

The nucleotide sequence of the human HisRS gene has been published together with that of Chinese hamster ovary (CHO) cells by Tsui and Siminovitch (1987a). Both enzymes were reported to consist of 508 amino acid residues with a molecular mass of about 57 kDa per subunit and approximate 50% homology with the yeast enzyme. Multiple translation start sites were postulated for the hamster gene RNA transcript (Tsui and Siminovitch, 1987b). Two types of transcripts of the human gene were detected: a longer transcript that is initiated from a single transcription start point (TSP) located approximately 455 bp upstream of the 5′ end of the open reading frame, and a shorter transcript initiated from multiple TSP located approximately 32 to 82 bp upstream from the ATG start codon (Tsui *et al*., 1993). It is not clear at this point whether the longer transcript codes for the mitochondrial HisRS and the shorter for the cytoplasmic version.

The human HisRS gene, which is situated on chromosome 5 (Wasmuth and Carlock, 1986), has been resequenced by Raben *et al*. (1991a, b, 1992a, b). The newly determined sequence differed in 48 positions, including insertions and deletions, from that published by Tsui and Siminovitch (1987a). It codes for a polypeptide consisting of 509 amino acids with a calculated molecular mass of 57.4 kDa per subunit. It is partly homologous with the yeast and *E. coli* enzymes and contains the characteristic sequence motifs of class II aaRS. A bidirectional promoter element may coordinate both transcription of the human HisRS gene and synthesis of an opposite-strand mRNA that encodes a protein homologous to HisRS (O'Hanlon *et al*., 1995a, b); this latter protein may be the mitochondrial counterpart of the cytosolic enzyme.

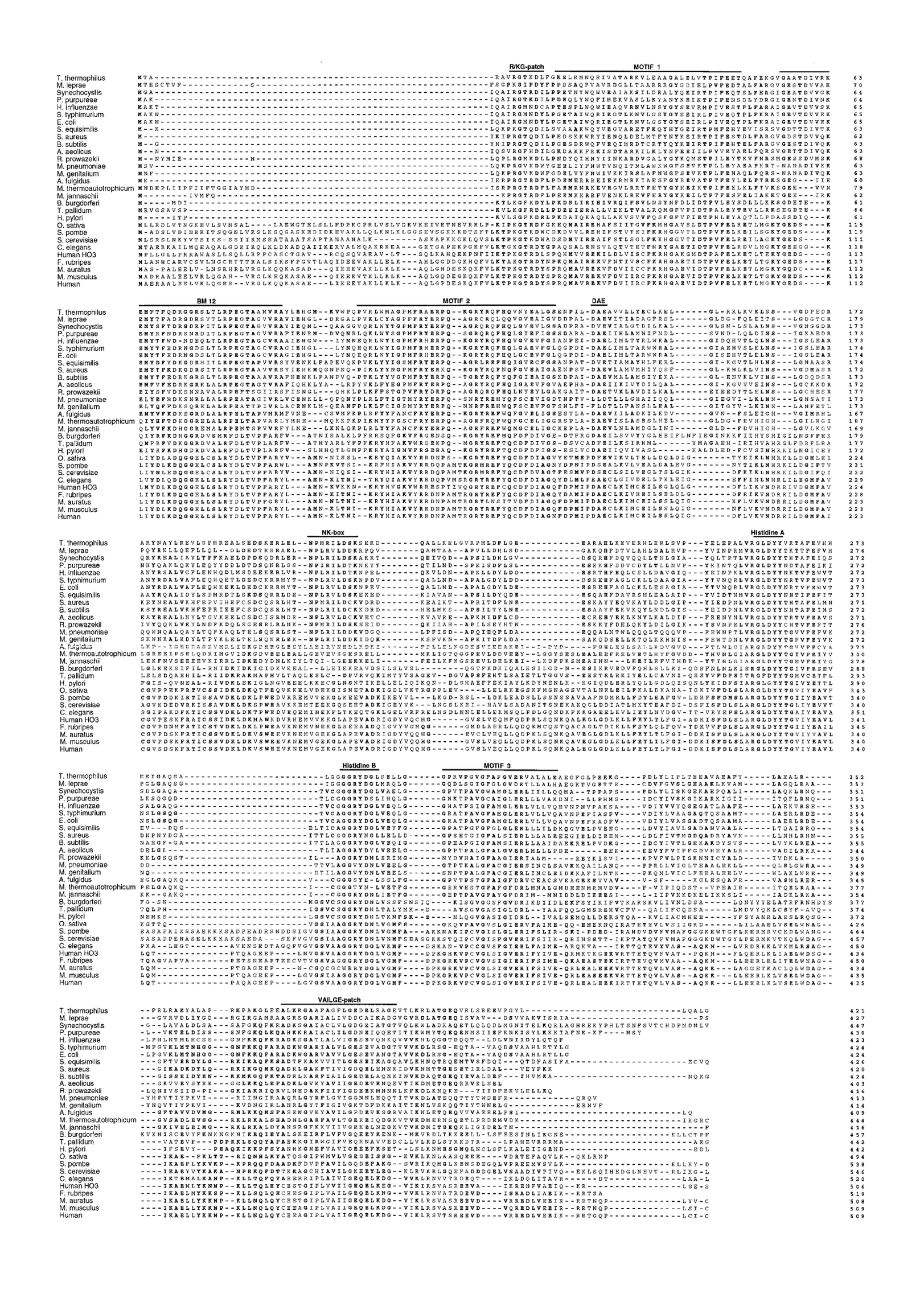
HisRS genes from many additional organisms have been sequenced in part or completely (compare also Szymanski and Barciszewski, 1999). Murine HisRS (Blechynden *et al*., 1996) is 90% homologous with the human enzyme and consists of 509 amino acid residues, giving a molecular mass of 57.4 kDa. The *hisS* gene of the fish *Fugu rubripes*, which codes for a HisRS of 519 amino acid residues, is 72% identical to its human counterpart (Brenner and Corrochano, 1996). The genes are recorded in six data bases and listed in Table 2. Their number is increasing rapidly, and many more may already have been cloned and sequenced, e.g. the gene from *Staphylococcus aureus* (Hodgson and Lawlor, 1997). A comparison of the 29 currently known HisRS sequences (Figure 2) shows a clear distinction between enzymes with or without an N-terminal leader of up to 60 amino acid residues. The longer proteins are found in eukaryotic organisms whereas enzymes lacking this N-terminal leader peptide occur in prokaryotic or archaebacterial organisms.

All HisRS have the three motifs that characterize class II aaRS, motifs 1, 2 and 3. In addition, there are conserved regions shared by all HisRS enzymes. The first such motif in the sequence is the so-called R/KG-patch (Rühlmann *et al*., 1997); mutant *E. coli* proteins lacking amino acids 2–17 show a hundred-fold reduction in enzymatic activity and are inactive when lacking 18 or more amino acids (Rühlmann *et al*., 1997). The segment between motifs 1 and 2, named BM12, contains many conserved residues and forms part of the dimer interface. The regions Histidine A (Lv/aRGLDYY) and Histidine B (AGGRYDGL), located between motifs 2 and 3, are highly conserved and form part of the histidine-binding pocket (Arnez *et al*., 1995; Åberg *et al*., 1997). Histidine B can vary at the R and the third G position, which may be indicative of a specific class of organisms. While bacterial and mammalian HisRS have invariant Histidine B core sequences, the enzymes from yeast, rice and the chloroplast of the alga *Phorphyra purpurea* have a change at the third G position. Archaebacterial and mycoplasmal sequences differ at both variable core positions. In addition, the length of the protein chain between Histidine A and Histidine B may also reflect the phylogenetic category of a species. In the C-terminal domain the most highly conserved sequence is the GExExxxG motif (Arnez *et al*., 1995) preceded by a stretch of hydrophobic residues, mostly VAIL, in various permutations. The two motifs together are termed the VAILGE patch.

A phylogenetic tree of 29 HisRS sequences is shown in Figure 3. As expected eubacterial organisms are followed by archaebacteria and eukaryotes including higher organisms. Interestingly the enzymes from *Helicobacter pylori* and *Borrelia burgdorferi* are very similar. This is consistent with the high similarity among other genes of these invasive spirochetes (Fraser *et al*., 1998) and may confirm the validity of this phylogenetic tree. As HisRS sequences from more organisms are determined, the phylogenetic tree and species classification based on HisRS signature motifs will be refined.

Several mutant HisRS proteins have been isolated from *E. coli, S. typhimurium,* and CHO cells using *in vivo* genetic approaches; these strains are temperature sensitive or require exogeneous histidine due to altered HisRS activities (Nass, 1967; Straus and Ames, 1973; Thompson *et al*., 1977, 1978; Adair *et al*., 1978; Ashman, 1978; Hirst and Piper, 1992). In addition, mutant HisRS proteins have been obtained by site-directed mutagenesis of the *hisS* gene subcloned into plasmid vectors (Arnez *et al*., 1997; Rühlmann *et al*., 1997) and illustrate specific points regarding enzyme structure and function. By contrast, few of the genetically obtained mutants have yielded such information. For example, a hamster temperature-sensitive mutant called tsBN250, which is defective in the G1 phase of the

Fig. 2 Multiple Alignments of HisRS Sequences Using the CLUSTAL Algorithm.
Data bank accession numbers of the HisRS sequences are included in those of Table 2. Identical amino acids are printed in bold types, regions of similar sequence parts as motifs 1, 2 and 3, the Histidine A, Histidine B, and the BM 12 parts, which ared discussed in the text, and additionally four other regions (R/KG, DAE, NK and VAILGE) which are common to all HisRS, are marked by overlining.


R/KG-patch
MOTIF 1
BM 12
MOTIF 2
DAE
NK-box
Histidine A
Histidine B
MOTIF 3
VAILGE-patch
T. thermophilus
M. leprae
Synechocystis
P. purpureae
H. influenzae
S. typhimurium
E. coli
S. equisimilis
S. aureus
B. subtilis
A. aeolicus
R. prowazekii
M. pneumoniae
M. genitalium
A. fulgidus
M. thermoautotrophicum
M. jannaschii
B. burgdorferi
T. pallidum
H. pylori
O. sativa
S. pombe
S. cerevisiae
C. elegans
Human HO3
F. rubripes
M. auratus
M. musculus
Human

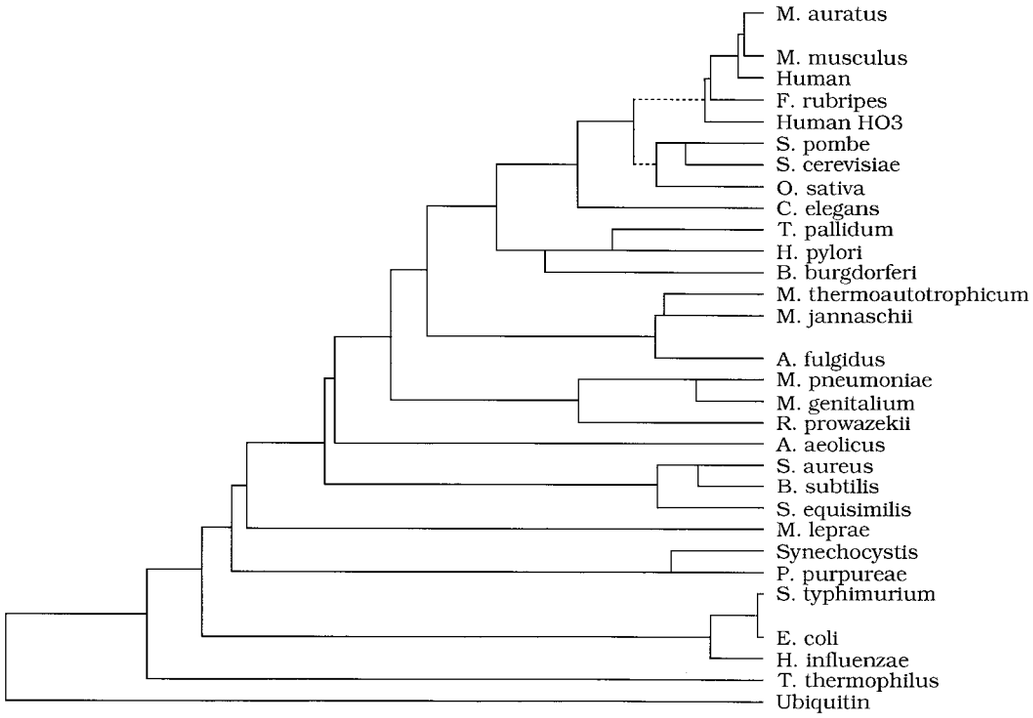


Fig. 3 Phylogenetic Tree of HisRS Sequences Rooted by the Unrelated Small Protein Ubiquitin.

cell cycle, has been localized to the 362nd codon, where a point mutation converted an arginine to a histidine (Motomura *et al*., 1996). The resulting loss/drop of HisRS activity may reduce the cellular concentration of cyclin D1, resulting in a G1 arrest. In addition, some of the mutant HisRS linked to decreased control of histidine biosynthesis isolated from *S. typhimurium* by Roth, Ames and coworkers (Roth *et al*., 1966; Roth and Ames, 1966) have recently been biochemically characterized in light of the three-dimensional structural information, linking some critical interactions in the active center of HisRS and regulation of histidine biosynthesis (Francklyn *et al*., 1998).

Investigations of expression of aaRS genes, such as that of ThrRS, have revealed very complex regulatory mechanisms in *E. coli* and *B. subtilis* (for compilations see Putzer *et al*., 1995 and Condon *et al*., 1996). These are different for any particular aaRS. It is reasonable to expect that the intracellular concentration of the respective amino acid is the ultimate governing parameter. However, this has not been shown unambiguously. Very little is known about the regulation of expression of the HisRS genes. There are structural similarities to $tRNA^{His}$ in the promoter sequences of the HisRS gene transcript from *E. coli* (Freedman *et al.*, 1985) and in the leader region of that from *S. typhimurium* (Ames *et al*., 1983). The cellular levels of $tRNA^{His}$, His-$tRNA^{His}$ (McGinnis and Williams, 1972a, b; Roth and Ames, 1966; Roth *et al*., 1966; Lewis and Ames, 1972; Francklyn *et al*., 1998) and HisRS (De Lorenzo *et al*., 1972; Brenner *et al*., 1972; Wyche *et al*., 1974; Coleman and Williams, 1974) have been identified as important regulatory parameters in *S. typhimurium*. The GCN2 protein, which contains sequences homologous to histidyl-tRNA synthetases and protein kinases, stimulates the expression of amino acid biosynthetic genes under conditions of amino acid starvation in *S. cerevisiae* (Wek *et al*., 1989, 1990, 1995; Zhu *et al*., 1996). It has been suggested that the regions of GCN2 homologous to HisRS respond to uncharged $tRNA^{His}$ by activating their own kinase function. GCN2 cannot function as HisRS because it lacks the key residues of motif 3 and the histidine-binding region (positions 257 – 264 in the *E. coli* HisRS sequence) (Arnez *et al*., 1995). A protein encoded by a putative histidine operon of *Lactococcus lactis,* whose sequence has been partially determined, has been found to be homologous to HisRS; however, it lacks motif 3 and may thus have a function similar to that of GCN2 (Delorme *et al*., 1992).

Crystal Structure of Histidyl-tRNA Synthetase

The three-dimensional structures of HisRS from two prokaryotic organisms, *E. coli* (Arnez *et al*., 1995) and *T. thermophilus* (Åberg *et al*., 1997), have been determined. In this section we describe the overall structures. More detailed discussions about the structure-function relationships in the active site and histidine or $tRNA^{His}$ recognition follow in the subsequent sections.

Histidyl-tRNA synthetase from *E. coli* (HRSec) was purified from overproducing cells to a high degree of homogeneity that permitted the crystallization of the enzyme in the presence of ATP and histidine (Francklyn *et al*., 1994). Two crystal forms were obtained, one monoclinic and the other triclinic. The monoclinic form belonged to the space

group $P2_1$, with unit cell dimensions a = 61.4 Å, b = 110.7 Å, c = 196.8 Å, β = 98°. The triclinic form belonged to the space group P1, with unit cell dimensions a = 61.4 Å, b = 110.7 Å, c = 108.7 Å, α = 115.0°, β = 97.4°, γ = 90.0° (Arnez *et al*., 1995). X-ray diffraction analyses revealed four monomers per asymmetric unit in both crystal forms, i.e. two homodimers.

Histidyl-tRNA synthetase from *T. thermophilus* (HRStt) was purified from HB-8 and HB-27 cells and crystallized in the presence of histidine (Yaremchuk *et al*., 1995). The crystals belong to the space group $P2_12_12_1$ with unit cell dimensions a = 171.3 Å, b = 214.7 Å, c = 49.3 Å, α = β = γ = 90° (Åberg *et al*., 1997). X-ray diffraction analyses showed two homodimers in the asymmetric unit.

The two structures are very similar. Each monomer consists of two domains. The catalytic core is situated in the N-terminal domain (Figure 4), which includes residues 1–320. The structure is based on a seven-stranded β-sheet, comprising one parallel and six antiparallel β-strands flanked by three α-helices, and contains the structural elements corresponding to the three motifs that are characteristic for class II aaRS. The C-terminal domain, which includes residues 330–424, is a mixed α/β domain of four parallel and one antiparallel β-strands and three α-helices. The two modules are connected by a 10-residue linker peptide. In addition, there is an insertion module between motifs 2 and 3 in the N-terminal domain (residues 170–229), which consists of four α-helices. It is well defined in the HRStt structure but mostly disordered in the HRSec structure. This module may interact with the acceptor stem of $tRNA^{His}$.

HisRS, like many other class II aaRS, is a homodimeric enzyme (Figure 4B). Three main regions of the N-terminal domain contribute to the dimer interface, the α-helix and β-strand of motif 1, the β-hairpin between motifs 1 and 2, and the extreme N-terminal tail and β-strand. The motif 1 strand, the back of motif 2 strands, the β-hairpin and the extreme N-terminal β-strand contribute residues to the hydrophobic pocket, e.g. Ile45, Val46, Phe70, and Phe-112. The β-hairpin, part of the conserved BM12 region, interacts with its symmetry-related counterpart to form a β-sheet that caps the pocket. The motif 1 helix of one monomer interacts with that of the other monomer in the dimer; in this case, the key interaction is a salt bridge. The 'R/KG-patch' is part of the extreme N-terminal tail; the side chain of the basic residue, however, does not participate in the dimer interface.

Both enzymes were cocrystallized with substrates that take part in the first step of aminoacylation, i.e. the activation of histidine. These are histidine and ATP. The enzyme

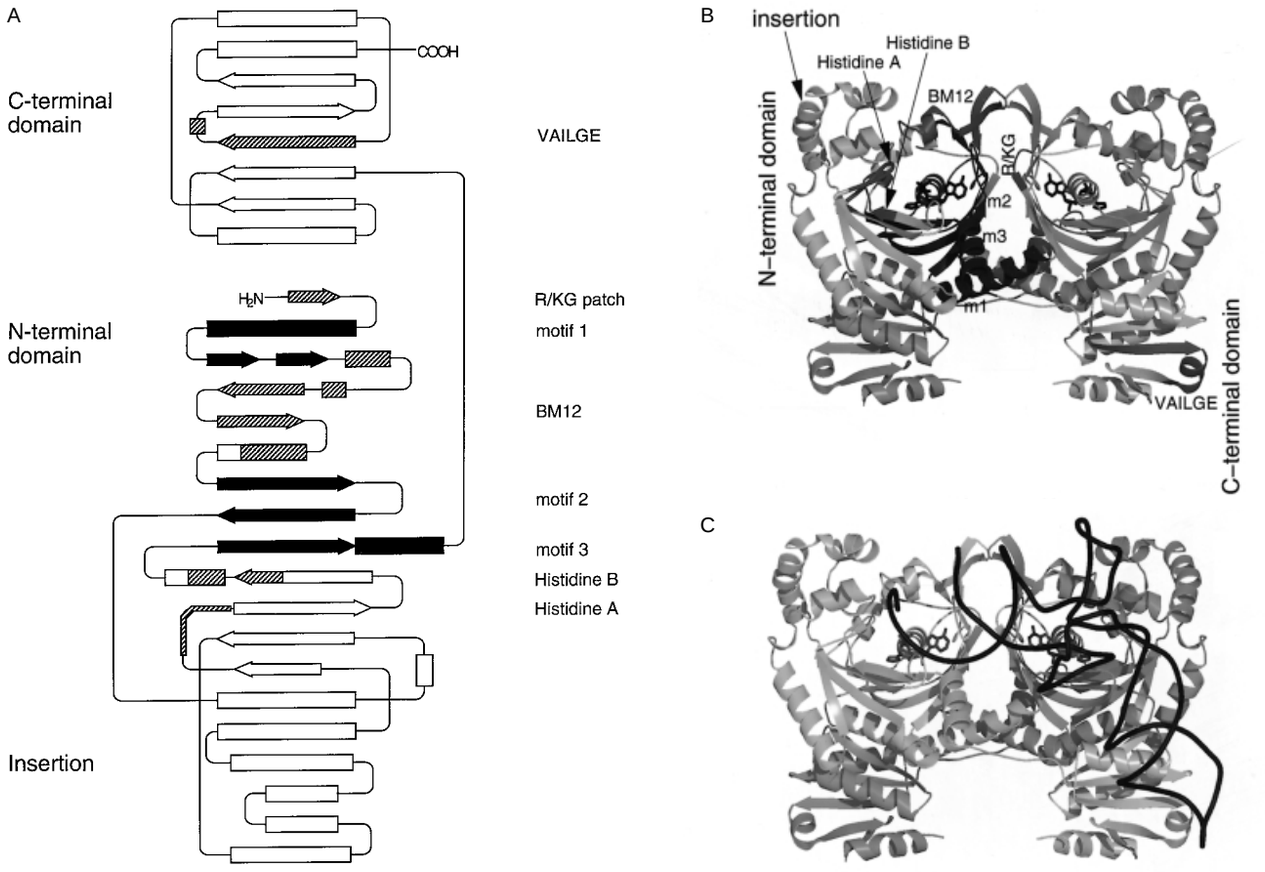


Fig. 4 The Three-Dimensional Structure of HisRS from *E. coli*.
(A) Topology diagram. Motifs 1, 2, and 3 are marked in black, the Histidine A, Histidine B, R/KG-patch, BM12 and VAILGE-patch regions are indicated by hatching. (B) Ribbon drawing of the dimeric enzyme. The class II structural motifs are rendered in black and the additional conserved elements in dark gray. (C) A docking model of tRNA on HisRS.

catalyzes the reaction before or during crystal growth, which results in the formation of histidyl adenylate in the active site (Arnez *et al*., 1995; Åberg *et al*., 1997). This is the enzyme-product complex for the first reaction. In addition, two enzyme-substrate complexes have been analyzed, the HisRStt:histidine complex (Åberg *et al*., 1997) and the HRSec:histidinol:ATP (Arnez *et al*., 1997). Histidinol is a non-reactive analog of histidine and a potent inhibitor of the reaction (Lepore *et al*., 1975).

The active site cleft is formed primarily by the motif 2 β-strands and loop, the motif 3 β-strand and the N-terminal portion of the motif 3 helix, and the two β-strands immediately adjacent to motif 3. These elements form the 'floor' of the cleft. Additional important elements form the 'walls'. The α-helix-loop-3_{10}-helix between motif 1 and 2 that precedes the β-hairpin of the dimer interface (described above; both are part of the conserved BM12 region) is in a position analogous to that of the 'flipping loop' of aspartyl-tRNA synthetase (Schmitt *et al*., 1998). The helix immediately preceding motif 2 and a long loop (between motif 2 and 3) form part of the amino acid binding pocket.

Histidine binds to a pocket bounded by the end of the second β-strand of motif 2, the beginning of the motif 3 β-strand, the end of the strand adjacent to the motif 3 strand which continues into an α-helix, and the long loop. These structural elements contain residues that are strictly conserved among all HisRS. The long loop contains the Histidine A sequence motif LVRGLDYY (residues 257 – 264 in both HRSec and HRStt). The element adjacent to the motif 3 strand harbors the Histidine B sequence motif GGRYDG (residues 285 – 290 in both enzymes). The end of the motif 2 strand contributes a highly conserved glutamate (Glu131 in HRSec and Glu130 in HRStt), which accepts a hydrogen bond from the protonated ε-nitrogen of the histidine side chain. It is held in a restrained position by Tyr107, Thr85 of the α-helix preceding motif 2 and by Tyr288 of the Histidine B motif. The latter Tyr also forms the back of the binding pocket. Tyr264 of the Histidine A motif donates a hydrogen bond to the δ-nitrogen of the histidine ring and accepts a hydrogen bond from Arg259 of the same motif. Tyr263 interacts with the π electron system of the imidazole ring of histidine. The ring lies flat against the floor, which is composed mostly of Gly; any side chains are pointing away from the pocket.

The two functions that constitute the common portion of the amino acid, i.e. the ammonium and carboxylate groups, are recognized by residues largely conserved among class II aaRS. The motif 2 carboxylate that interacts with the ammonium group of the amino acid is replaced by a Gly in prokaryotic HisRS. However, the helix preceding motif 2 contributes a carboxylate, Glu83, which interacts with the ammonium and which is conserved among all HisRS. The side chain also interacts with Tyr263 of the Histidine A motif. The amide oxygen of the conserved Gln127 accepts hydrogen bonds from the ammonium and a bound water molecule; the latter donates a hydrogen bond to Tyr107 and accepts one from the ammonium. The amide nitrogen of Gln127 donates a hydrogen bond to the carboxylate of the bound histidine. This orients the carboxylate to react with ATP.

The ATP molecule is bound in a classical class II aaRS fashion. The adenine ring stacks upon the class II conserved Phe125. Glu115, also conserved among class II aaRS, contacts the exocyclic 6-amino group, which also interacts with the backbone oxygen of Tyr122 of the motif 2 loop. The peptide nitrogen of Tyr122 interacts with the N1 of the ring. These interactions select adenine over other purines. The 3′-OH of the ribose forms a hydrogen bond with the backbone carbonyl of Thr281. The triphosphate bends over the adenosine moiety, a conformation observed in the yeast AspRS (Cavarelli *et al*., 1994) and SerRS from *T. thermophilus* (Belrhali *et al*., 1995) and may be unique to class II aaRS (Arnez and Moras, 1997). It is similar to the structures proposed by Sundaralingam in 1969 for the complex formed by ATP and one Mg^{2+}. Two divalent metal ions (Mn^{2+}) bridge the β- and γ-phosphates (Arnez *et al*., 1997), which has also been observed with other class II aaRS such as SerRS and AspRS (Schmitt *et al*., 1998). Two Arg residues, one contributed by the motif 2 loop and the other by the motif 3 helix, interact with the γ-phosphate. The former Arg is nearly invariable and the latter highly conserved among class II aaRS. The α-phosphate is clamped by two Arg. One is the strictly conserved class II aaRS motif 2 Arg113, and the other is the Histidine A Arg259. The latter Arg replaces the metal ion seen coordinating the α-phosphate in the SerRS:ATP complex. Arg259 is important for catalysis because it may play a critical role in stabilizing the transition state in adenylate formation (Arnez *et al*., 1997). This arginine appears to be a unique feature of HisRS. To test the possibility of replacing Arg259 with a Mg^{2+}, mutations were introduced in the HisRS active center to engineer a divalent metal site and were tested in a series of computer simulations (Arnez *et al*., 1998); some of them are expected to be catalytically active.

The histidyl-adenylate product interacts with the enzyme in the same fashion as histidine and the adenosine monophosphate moiety of ATP in the enzyme-substrate complex. The only changes are the loss of the pyrophosphate with the two divalent metal ions. The motif 3 Arg311 stays in place while the motif 2 loop Arg121 may swing away or stack on the adenine ring. The adenylate assumes the extended conformation also seen in other class II aaRS. Binding and processing of the common portion of the amino acid and of ATP is within the usual framework of class II aaRS.

The C-terminal mixed α/β domain is shared by other class IIa aaRS. It is most probably involved in the recognition of the anticodon stem of $tRNA^{His}$. The most highly conserved sequence segment in this module is the VAILGE-patch, which consists of a hydrophobic stretch on a β-strand followed by GExExxxE on a short α-helix (Figure 4A). In a docking model of the dimeric HisRS and $tRNA^{His}$, which was obtained by inserting the acceptor stem of $tRNA^{His}$ into the catalytic cleft [based on a superposition of the yeast AspRS:$tRNA^{Asp}$ complex (Cavarelli *et*

al., 1994) on the active site domain of HisRS] and packing the anticodon arm against the C-terminal domain (Arnez *et al*., 1995) (Figure 4C), the anticodon is in the proximity of the GExExxxE motif. Further understanding of the structural parameters of the second step of the aminoacylation reaction will depend on the determination of the three-dimensional structure of the HisRS · $tRNA^{His}$ complex. To this effect, crystals of such a complex from *T. thermophilus* have already been obtained (Yaremchuk *et al*., 1995).

Mechanism of Enzyme Action

The chemical reaction mechanism of HisRS does not differ fundamentally from those of other aaRS. Activation of histidine and histidylation of $tRNA^{His}$ were first analyzed with HisRS from *S. typhimurium* (Di Natale *et al*., 1974; De Lorenzo and Ames, 1970). The ATP/PP_i exchange reaction, whose kinetics reflect those of the adenylate formation, showed a broad pH optimum in the range of 6.9 – 7.5, with the highest activity at pH 7.2. The reaction attained its maximal rate at a Mg^{2+}:ATP ratio of 3:1 (Di Natale *et al*., 1974). The aminoacylation reaction has its pH optimum between 7.2 and 8.5, with the highest activity at pH 7.75 and the best Mg^{2+}: ATP ratio of 2 : 1 (De Lorenzo and Ames, 1970) (for K_m values see Table 3). The ATP/PP_i exchange reaction is inhibited by $tRNA^{His}$ or periodate oxidized $tRNA^{His}$oxi. This inhibition by $tRNA^{His}$ was found to be non-competitive with respect to histidine and uncompetitive with respect to ATP, indicating distinct binding sites for both small molecule substrates and for $tRNA^{His}$ (Di Natale *et al*., 1974).

Recent kinetic studies of class I and class II aaRS from *E. coli* are consistent with these results (Airas, 1996). Generally, class II aaRS require three Mg^{2+} ions for the activation reaction and class I enzymes only one Mg^{2+}. These observations were ultimately confirmed by X-ray analyses of HisRS crystals (Arnez and Moras, 1997; Arnez *et al*., 1997). Three Mg^{2+} ions stabilize the conformation of ATP bound by class II enzymes, with the only notable exception of HisRS so far; this enzyme requires only two Mg^{2+} ions since an Arg (Arg259 in HisRSec) substitutes for the third ion, as described above. Arg259, part of the highly conserved Histidine A motif (Figures 2, 4), is critical for HisRS activity; mutating it to glutamine, lysine (Rühlmann *et al*., 1997) or histidine (Arnez *et al*., 1997) reduces the activity by several orders of magnitude without affecting histidine or ATP binding.

The enzyme binds histidine more tightly at pH 6 than at pH 7, with K_d values of 0.0061 mM and 0.025 mM, respectively. By contrast, the binding of ATP is less dependent on pH, with K_d values of 0.027 mM and 0.017 mM (Di Natale *et al*., 1976). Equilibrium dialysis experiments have shown that the dimeric enzyme binds 1 mol of ATP per mol of enzyme and between 1 and 1.7 mol of histidine per mol of enzyme (Di Natale *et al*., 1976). Remarkably, in the crystal structure of the *E. coli* HisRS the active sites of all four monomers are occupied by histidyl-adenylate (Arnez *et al*., 1995).

The K_m values determined for HisRS from different sources are listed in Table 3. The K_m values of the overall aminoacylation reaction range between 0.08 and 0.59 mM for ATP, between 0.0007 and 0.029 mM for histidine, and between 0.000004 and 0.11 mM for $tRNA^{His}$. The latter two ranges for the Michaelis constants are remarkably large for unknown reasons; a possible explanation would be that the values were obtained over a wide pH range. The K_m values of the ATP/PP_i exchange reaction are between

Table 3 K_m Values of Histidyl-tRNA Synthetases in the Aminoacylation and ATP/PP_i Exchange Reaction, and References.

Source	Aminoacylation			ATP/PP_i exchange			References
	ATP	His	$tRNA^{His}$ [mM]	ATP	His	PP_i [mM]	
E. coli		0.006		0.15 – 0.10 0.32			Kalousek and Konigsberg, 1974
		0.008		0.56			Rühlmann *et al*., 1997
	0.89	0.030	0.0014				Arnez *et al*., 1997
			0.049				Yan *et al*., 1996
			0.0014	0.89	0.03		Augustine and Francklyn, 1997
S. typhimurium				0.15			Roth and Ames, 1966
	0.14	0.025	0.11				De Lorenzo *et al*., 1972 De Lorenzo and Ames, 1970
				0.83	0.125	0.33	Di Natale *et al*., 1974, 1976
		0.029					Lepore *et al*., 1976
S. cerevisiae cyto	0.14	0.0018	0.00067				Boguslawski *et al*., 1974
mito	0.08	0.0009	0.00065				
			0.0008				Rudinger *et al*., 1997
N. crassa	0.59	0.0058	0.00012				Chen and Somberg, 1980
Rabbit reticulocytes	0.08	0.0005	0.000004 – 0.000006				Kane *et al*., 1978

0.15 and 0.83 for ATP, and between 0.10 and 0.15 mM for histidine.

The *E. coli* HisRS has a turnover of 1.7–7 s^{-1} for the aminoacylation reaction and a turnover of 34–142 s^{-1} for the ATP/PP_i exchange reaction (Yan *et al*., 1996; Arnez *et al*., 1997; Augustine and Francklyn, 1997; Rühlmann *et al*., 1997; Francklyn *et al*., 1998). The enzyme from rabbit reticulocytes shows a turnover of 84 min^{-1} (= 1.4 s^{-1}) and has an isoelectric point of 5.1 (Kane *et al*., 1978).

HisRS can form diadenosine polyphosphates in a side reaction under physiological conditions. The enzyme from *E. coli* synthesizes diadenosine tetraphosphate (Ap_4A) in a fast reaction of the histidyl-adenylate with ATP (Goerlich *et al*., 1982). The enzyme from *Bacillus stearothermophilus* is also able to synthesize the hybrid polyphosphates Ap_4G, Ap_4U, Ap_3U (Traut, 1987). Ap_4A is suspected to play a regulatory role in DNA replication and cell proliferation, but these hypotheses have not been confirmed as yet (compare Plateau and Blanquet, 1994). The histidyl-adenylate bound in the active site of HisRS from *B. stearothermophilus* can also react with amines (Kitahata *et al*., 1985a), hydrazides (Kitahata, 1985b), amino acids or amino acid amides (Nakajima *et al*., 1984, 1986; Tsuratani *et al*., 1986), yielding the corresponding amino acid derivatives or dipeptides.

Titration of HisRS from *S. typhimurium* with the SH group blocking reagent 5,5′-dithiobis(2-nitrobenzoic acid) blocks two free cysteine residues under normal conditions and four SH groups under denaturing conditions using 8 M urea or *p*-hydroxymercuribenzoate (De Lorenzo *et al*., 1974; Lepore *et al*., 1976). Interestingly, the enzyme activity changes only slowly, reaching a new stable level of activity at a different K_m of aminoacylation, with the K_m for His increased three-fold, for example. This strongly indicates that in contrast to many other aaRS, these SH groups are neither involved in substrate binding nor in the catalytic process. This is confirmed by the crystal structure of HisRS from *E. coli* (Arnez *et al*., 1995), a close relative of *S. typhimurium*, where three Cys are part of the elements forming the active site, but they all point away and do not participate in any enzymologically important interactions. Two Cys residues are in the insertion domain or the helix linking the insertion to the core module and are thus distant from the active site. A transition to an alternate enzyme structure has been suggested (Lepore *et al*., 1976). An observation made with aaRS isolated from brains of rats treated with CH_3-HgCl (Hasegawa *et al*., 1988) might be consistent with this finding; HisRS from this source showed an increased activity, whereas the activities of most other aaRS decreased.

HisRS from *E. coli* has been affinity labeled with pyridoxal-5′-phosphate (PLP) and with other ATP analogs containing a pyridoxal moiety (Kalogerakos *et al*., 1994; Gillet *et al.*, 1996). About three molecules of PLP were incorporated into one molecule of the enzyme. Trypsin digestion of the PLP-labeled enzyme, subsequent RPLC purification of the oligopeptides and Edman degradation showed that four Lys residues (residues 2, 118, 369, and 370) had reacted with the reagent. At low concentrations of PLP (< 1 mM) residues Lys2, Lys369, and Lys370 were labeled and shown to be critical for catalytic activity. All of these residues are positioned to interact with $tRNA^{His}$, as suggested by the docking model of the HisRS:$tRNA^{His}$ complex (Arnez *et al*., 1995); labeling them with PLP would interfere with tRNA binding.

An issue that merits more detailed investigations is the influence of phosphorylation of eukaryotic aaRS on their catalytic properties. Chromatofocussing experiments with aaRS from mouse liver showed that 15 of them, including HisRS, were present in two forms, one of which corresponded to the phosphorylated and the other to the unphosphorylated species (Berg, 1990). This is consistent with an earlier finding that HisRS from CHO cells grown in a medium containing [^{32}P]-orthophosphate had a detectable phosphate moiety attached to a serine residue (Gerken *et al*., 1986), and also agrees with a recent compilation of possible *E. coli* phosphoproteins (Sweeny *et al*., 1995). Furthermore, in mouse uterus and liver, one group of aaRS (specific for Ala, Arg, Glu, Gly, His, Ile, Leu, Lys, Met, Phe, Tyr, and Val) showed decreased activities upon phosphorylation (group I), whereas another group (specific for Asn, Asp, Pro, Ser, and Thr) showed increased activities (group II) (Berg, 1977). The effect of phosphorylation could be reversed by alkaline phosphatase or an endogenous phosphoprotein phosphatase. This latter enzyme is activated by a 3′–5′-cAMP dependent kinase (Berg, 1978).

Specificity for Histidine vs. Histidine Analogs

In the crystal structures of HisRS two hydrogen bonds between the enzyme and the five-membered ring of the histidine side chain were observed. The Nϵ of the imidazole ring is in contact with Glu131 and the Nδ with Tyr263 (Arnez *et al*., 1995; Åberg *et al*., 1997) (Figure 5). The binding energies generated by charged hydrogen bonds are in the range of 3–6 kcal/mol, those of uncharged bonds in the range of 0.5–1.5 kcal/mol (Fersht *et al*., 1985). If noncognate amino acids cannot form one of these hydrogen bonds, the amino acid recognition will decrease by a factor of $e^{(3–6/RT)} \sim 130–1700$ or $e^{(0.5–1.5/RT)} \sim 2–11$, respectively (compare Freist *et al*., 1998); the latter factor cannot be sufficient for specific amino acid binding. One of the two hydrogen bonds to the imidazole side chain involves negatively charged Glu131. The specificity of Tyr263 for the ring nitrogen is enhanced by its other contact with positively charged Arg259. Unfortunately, there are few detailed studies of histidine recognition by HisRS. This is all the more regrettable because 39 amino acid analogs were proven for their qualitites as possible substrates or inhibitors. They are ordered systematically in Figure 6. However, the enzymes were from different sources, so the generalized results have to be treated with caution.

Fifteen histidine analogs (formula 3, 8–19, 21, 39; Figure 6) were tested as inhibitors of the ATP/PP_i exchange

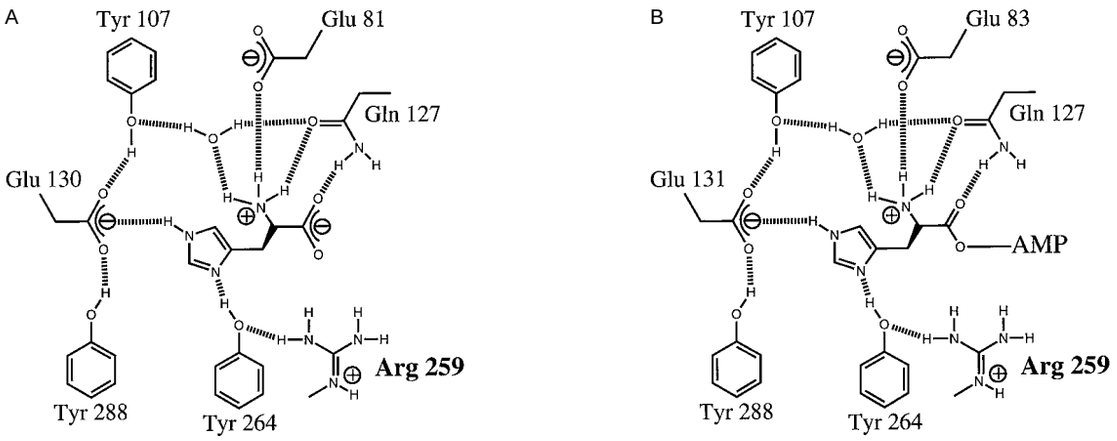


Fig. 5 Schematic View of Hydrogen Bond Interactions of HisRS Residues with Histidine in the Active Site of (A) *T. thermophilus* (Åberg *et al*., 1997) and (B) *E. coli* HisRS (Arnez *et al*., 1995).

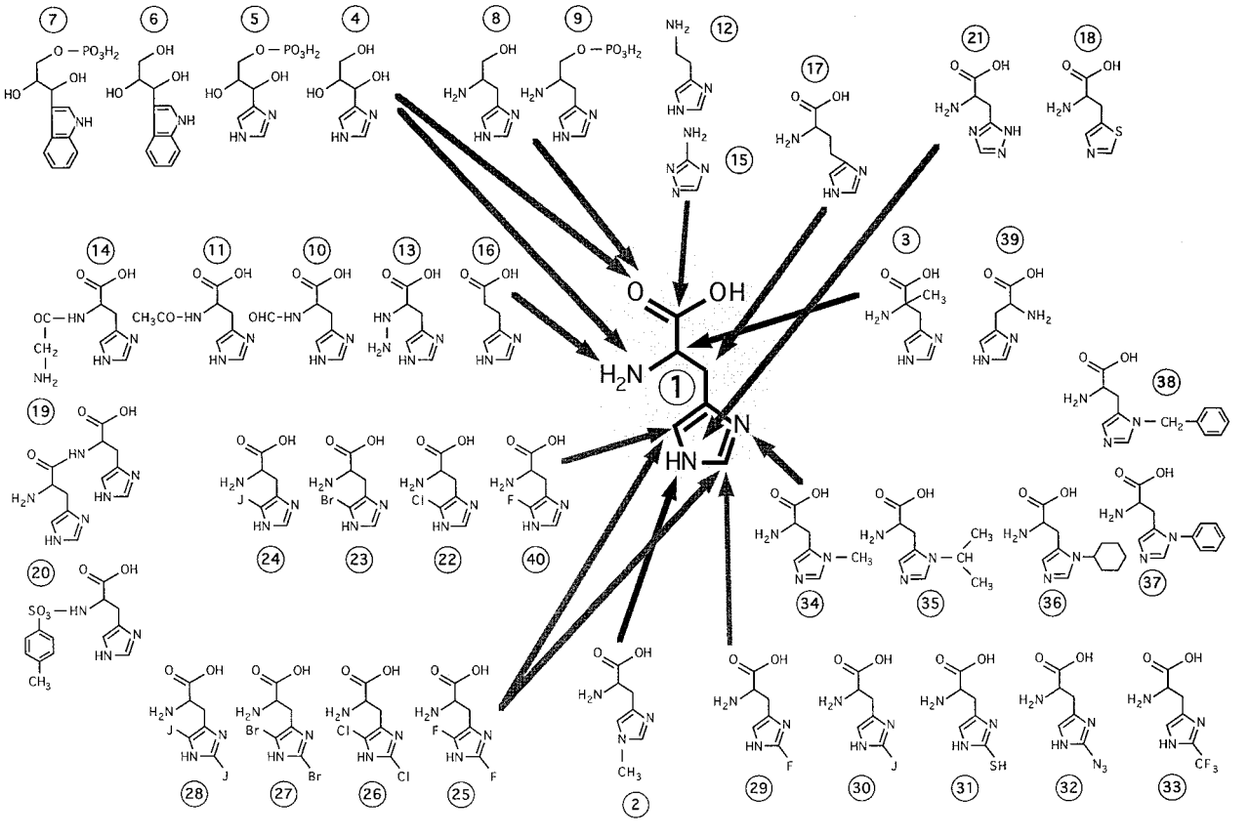


Fig. 6 Analogs of L-Histidine (1) Tested with Histidyl-tRNA Synthetases from Rat Skeletal Muscle (Aminoacylation Reaction, Compound 2; Young *et al*., 1970), *N. crassa* (Aminoacylation Reaction, Compounds 2–5; Spurgeon and Matchett, 1977), *S. typhimurium* (Aminoacylation and ATP/PP_i Exchange Reaction, Compounds 3, 8–19, 39; Lepore *et al*., 1975), and *P. falciparum* (Growth of Parasites, Compounds 2, 3, 11, 20–40; Howard *et al*., 1986):
(2) 1-methyl-L-histidine, (3) α-methylhistidine, (4) imidazoleglycerole, (5) imidazoleglycerole phosphate, (6) indoleglycerole, (7) indoleglycerole phosphate, (8) L-histidinol, (9) L-histidinol phosphate, (10) N-formyl-L-histidine, (11) N-acetyl-L-histidine, (12) histamine, (13) L-hydrazinoimidazoyl-propionic acid, (14) glycyl-L-histidine, (15) 3-amino-1,2,4-triazole, (16) 4-imidazolepropionic acid, (17) D,L-homohistidine, (18) 2-thiazole-DL-alanine, (19) L-histidyl-L-histidine, (20) N-*p*-toluenesulfonyl-L-histidine, (21) 1,2,4-triazole-alanine, (22) 5-chloro-L-histidine, (23) 5-bromo-L-histidine, (24) 5-iodo-L-histidine, (25) 2,5-difluoro-L-histidine, (26) 2,5-dichloro-L-histidine, (27) 2,5-dibromo-L-histidine, (28) 2,5-diiodo-L-histidine, (29) 2-fluoro-L-histidine, (30) 2-iodo-L-histidine, (31) 2-thio-L-histidine, (32) 2-azido-L-histidine, (33) 2-(trifluoromethyl)-L-histidine, (34) 3-methyl-L-histidine, (35) 3-isopropyl-L-histidine, (36) 3-cyclohexyl-L-histidine, (37) 3-phenyl-L-histidine, (38) 3-benzyl-L-histidine, (39) D-histidine, (40) 5-fluoro-L-histidine.

and aminoacylation reactions catalyzed by HisRS from *S. typhimurium* (Lepore *et al*., 1975). L-histidinol (formula 8, Figure 6) is the most potent inhibitor of the ATP/PP_i exchange, with a K_i value of 0.033 mM, while other histidine

analogs show K_i values above 1 mM. Histidinol also inhibits protein biosynthesis in CHO cells (Lofgren and Thompson, 1979). Histidinol-resistant cells amplify their HisRS genes (Tsui and Siminovitch, 1993). L-histidinol and α-methyl-D,L-histidine (formula 3, Figure 6) were the best inhibitors of the aminoacylation reaction, with K_i values of 0.085 mM and 0.059 mM, respectively, while the other analogs exhibited K_i values above 0.1 mM (Lepore *et al*., 1975). HisRS from *Neurospora crassa* is inhibited by imidazoleglycerol (formula 4), imidazoleglycerol phosphate (formula 5), indoleglycerol (formula 6), indoleglycerol phosphate (formula 7) and α-methylhistidine (formula 3, Figure 6) (Spurgeon and Matchett, 1977). These studies led to the following conclusions regarding histidine recognition. First, the enzyme is stereospecific. D-histidine (formula 39, Figure 6) has no influence on enzyme activity. Second, the carboxyl group of histidine is not required for binding. Third, bulky ester groups of histidine prevent the molecules from binding to the enzyme. Fourth, the amino group contributes to binding affinity. Fifth, the size of the side chain ring is important. Sixth, the elemental nature of the hetero atoms in the ring influences its inhibitory properties. These conclusions are consistent with the structure of the *E. coli* HisRS·histidyl-adenylate complex (Arnez *et al*., 1995).

Since the human malaria parasite *Plasmodium falciparum* synthesizes several proteins that are unusually rich in histidine, 25 analogs of histidine (Figure 6) were screened for their capacity to inhibit parasite growth *in vitro* (Howard *et al*., 1986). Remarkable inhibition of parasite protein synthesis was observed with 2-fluoro-L-histidine (formula 29) and 2-iodo-L-histidine (formula 30), whereas the other analogs (formula 2, 3, 11, 20, 22–40, Figure 6) showed little or no effects. Most probably the reduction of growth was due to an inhibition of HisRS.

The potent HisRS inhibitor L-histidinol has been used to mimic histidine starvation, e.g. in studies of protein degradation (Scornik *et al*., 1980; Scornik, 1983, 1984, 1988; Hartman and Mulligan, 1988). Furthermore, L-histidinol was tested as an anticancer drug (Warrington, 1992). L-histidinol resistant CHO cells showed an increased HisRS activity due to gene amplification (Tsui *et al*., 1985).

A partially purified aaRS fraction from rat skeletal muscle was used to test 3-methylhistidine (2) as a substrate for the enzyme (see Figure 6) (Young *et al*., 1970). Since no charging of $tRNA^{His}$ with this analog was observed, 3-methylhistidine occurring in myosin and actin must be formed by posttranslational modification.

These investigations of histidine analogs have not yet led to any pharmaceutical or biochemical applications, for the following possible reasons. Histidine may not have been modified in suitable ways. Analogs with six-membered rings or with a phosphorus atom substituted for a nitrogen atom have not yet been tested. Furthermore, the available analogs may not have been tested in a sufficient number of biological systems.

Specificity for ATP vs. ATP Analogs

Histidyl-tRNA synthetase from *S. typhimurium* is highly selective for ATP. It does not bind other nucleoside-triphosphates occurring in the cell, such as GTP, CTP, TTP and UTP (Di Natale *et al*., 1976). Deoxy-ATP is a poor substrate, with a 40-fold higher K_m than that of ATP. Adenosine, ADP and adenosine 5′-(β,γ-methylene)triphosphate are competitive inhibitors, while AMP is a noncompetitive inhibitor. This has led to the conclusion that binding of ATP requires interactions of the amino group of the adenine base. In the sugar moiety the 2′ and 5′ positions were determined as essential, whereas the phosphate groups enhance the binding.

Eight ATP analogs have been tested as substrates or inhibitors of HisRS from *E. coli* and yeast (Freist *et al*., 1981). 2-Chloro-ATP was a substrate of both enzymes. Six additional analogs inhibited the yeast enzyme, while another inhibitor was found for the *E. coli* enzyme. The requirements of ATP recognition include the same parts of the molecule as stated for the enzyme from *S. typhimurium* but must also include the 3′ position of the sugar moiety.

These results are in agreement with the crystal structures of the *E. coli* HisRS:histidyl-adenylate and HisRS:histidinol:ATP complexes (Arnez *et al.,* 1995; 1997) as well as the *T. thermophilus* HisRS:histidyl-adenylate complex (Åberg *et al*., 1997). In all these cases, the enzyme forms hydrogen bonds with the exocyclic amino group of the adenine, the hydroxyl groups and the ring oxygen of the ribose, and the α-phosphate group.

Identity of $tRNA^{His}$

About 120 sequences of histidine-specific tRNAs ($tRNA^{His}$) are known and have been compiled (Sprinzl *et al*., 1998). Compared to other tRNAs, a remarkable feature sets $tRNA^{His}$ apart, an additional base pair in the acceptor stem. The tRNA does not possess any extra arms or loops and contains modified bases in all parts of the molecule. The function of at least one base modification in $tRNA^{His}$ was elucidated by NMR spectroscopy: pseudouridine may stabilize the conformation of its adjacent nucleotides (Davis *et al*., 1998). $tRNA^{His}$ from the plant *Arabidopsis thaliana* possesses an exceptional C_{54} in the highly conserved $GT_{54}\Psi C$ sequence (Akama *et al*., 1998); this sequence is normally conserved throughout prokaryotes, archaebacteria, and eukaryotes. The function of this alteration is unknown. The anticodon sequence of nearly all $tRNA^{His}$ is GUG, with the only known exception of $tRNA^{His}$ from a *Leptomonas* species, which possesses an AUG anticodon (Sprinzl *et al.*, 1998).

The most striking feature of $tRNA^{His}$ is an additional nucleotide at the 5′ end, G-1 (Figure 7), giving rise to the unique G-1·C73 base pair that plays an important role in the recognition and aminoacylation of $tRNA^{His}$ by HisRS. Base replacements at position 73 of the *E. coli* $tRNA^{His}$ led

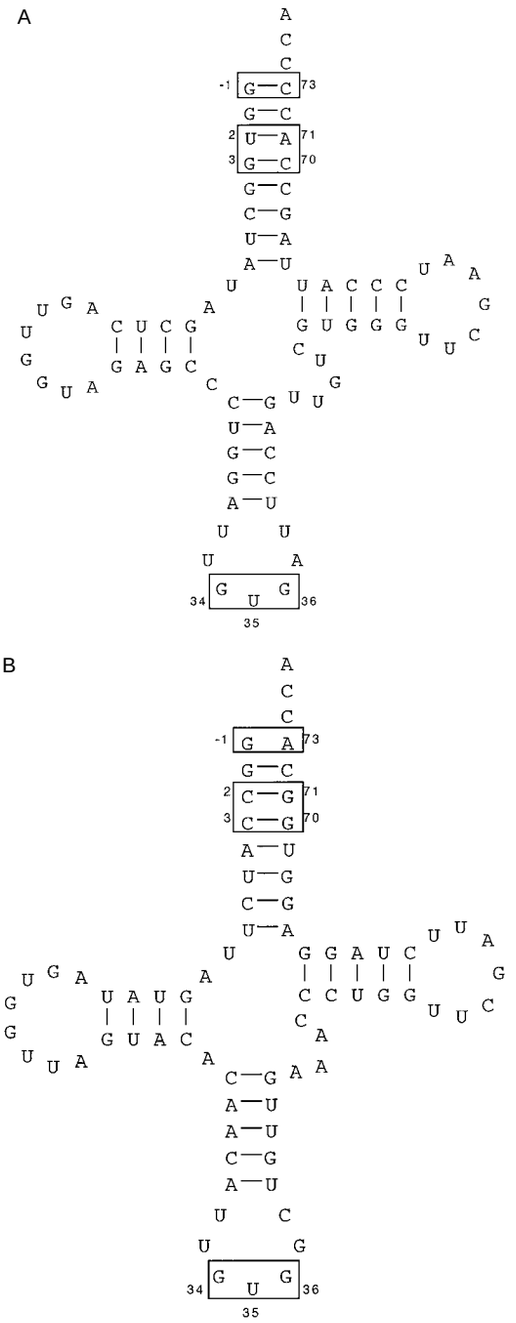


Fig. 7 Cloverleaf Diagram of $tRNA^{His}$ from (A) *E. coli* and (B) Yeast.
Shown are key recognition elements.

to a decrease in V_{max}. Deletion and substitution of G-1 also had significant effects on the aminoacylation reaction (Himeno *et al.*, 1989). However, *in vivo* experiments showed that C73, the 'discriminator base', may be more important than G-1 (Yan and Francklyn, 1994, 1995; Yan *et al.*, 1996; compilation of the *E. coli* tRNA recognition sites in: McClain, 1993). Similarly, the additional base pair in the acceptor stem of the yeast cytoplasmic $tRNA^{His}$, G-1·A73, was found to be crucial, although the identity of the bases was more relaxed (Rudinger *et al.*, 1994; Nameki *et al.*, 1995).

Conflicting results have been obtained with regard to the importance of the anticodon. Changes at the third position of the anticodon of *in vitro* transcripts of the yeast $tRNA^{His}$ had minor effects on histidylation (Rudinger *et al.*, 1994); another study showed that the anticodon was necessary for tRNA recognition (Nameki *et al.*, 1995). A second identity element was found in the anticodon region of $tRNA^{His}$ from *E. coli* (Dräger *et al.*, 1991; Shimizu *et al.*, 1992); it was later reported to be irrelevant (Shimizu *et al.*, 1994). The anticodon was found to play a significant role in tRNA selection by HisRS *in vivo*, with the C-terminal domain largely responsible for recognizing it (Yan and Francklyn, 1995; Yan *et al.*, 1996). A small level of anticooperativity ($\Delta\Delta G = -1.24$ kcal/mol) between recognition of the discriminator base and the anticodon suggested that the two ends of the tRNA are not recognized independently. The docking model of $tRNA^{His}$ on the crystal structure of the *E. coli* HisRS:histidyl-adenylate complex (Arnez *et al.*, 1995) illustrates these interactions, with the acceptor stem of $tRNA^{His}$ in the catalytic cleft and the anticodon arm contacting the C-terminal domain (Figure 4).

The correlation between recognition of the anticodon and the acceptor stem of $tRNA^{His}$ by HisRS, demonstrated above by low anticooperativity, was further confirmed when the N-terminal and C-terminal domains of the *E. coli* HisRS were separately expressed and purified (Augustine and Francklyn, 1997). The N-terminal fragment, which consisted of residues 1–320 (truncated immediately following motif 3), catalyzed the specific aminoacylation of tRNA as well as the ATP/PP_i exchange, but exhibited a reduced selectivity for the C73 discriminator base. The C-terminal fragment was inactive in both reactions. However, it must be essential for the dimeric structure of the enzyme because the N-terminal fragment was monomeric.

Aminoacylation experiments with RNA mini- or microhelices containing four, eight, or thirteen base pairs of $tRNA^{His}$ confirmed the importance of the additional base pair of the acceptor stem for tRNA recognition by both *E. coli* and yeast HisRS (Francklyn and Schimmel, 1990; Schimmel,1991b; Francklyn *et al.*, 1992; Shi *et al.*, 1992; Rudinger *et al.*, 1994; for compilations see also: Buechter and Schimmel, 1993; Schimmel and de Pouplana, 1995). In addition, base pairs 2·71 and 3·70 were seen as minor identity elements in both *E. coli* and yeast $tRNA^{His}$ (Figure 7).

In summary, the 'classical' regions of tRNA recognition, the anticodon loop and acceptor stem, have been identified as essential components of HisRS-$tRNA^{His}$ interaction (Figure 7). The importance of the additional G-1·C73 or G-1·A73 base pairs in the acceptor stem have been established for the *E. coli* and yeast systems. It remains uncertain whether this observation can be extended to a larger number of organisms. In compilations of $tRNA^{His}$ sequences U-1·A73 base pairs can also be found, for instance in phage T5; its importance for tRNA recognition has yet to be shown (compare Sprinzl *et al.*, 1998).

The observation that the RNAs of the tobacco mosaic virus and satellite tobacco mosaic virus could be aminoa-

cylated with histidine by crude aaRS preparations from yeast, rat liver and other mammalian cells (Öberg and Philipson, 1972; Salomon *et al*., 1975, 1976; Litvak *et al*., 1973) was astonishing at first. The RNAs are acylated at their 3′-termini, which contain the tRNA-like sequence C-C-C-A (Carriquiry and Litvak, 1974; Guilley *et al*., 1975). While the 3′-terminal sequence of 71 nucleotides of the TMV RNA does not fold into a cloverleaf secondary structure characteristic of tRNAs (Guilley *et al*., 1975), it has become evident that the RNA sequences of other TMV

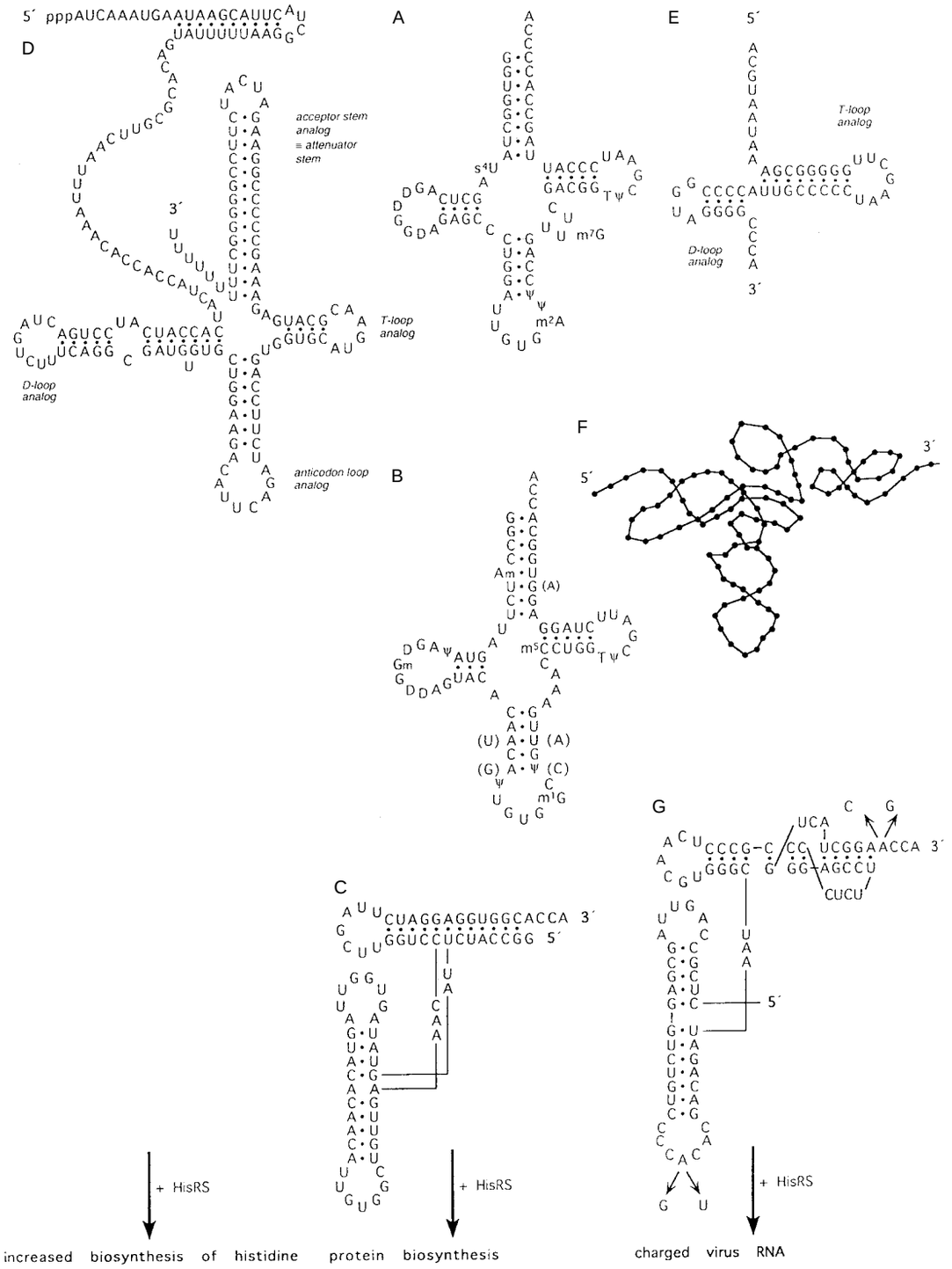


Fig. 8 Structural Homologies of $tRNA^{His}$ with mRNA and Viral RNA.
Middle: cloverleaf diagram of $tRNA^{His}$ from (A) *Salmonella typhimurium* (Singer and Smith, 1972) and (B) yeast (Keith *et al*., 1983), and (C) diagram of a yeast $tRNA^{His}$ transcript arranged to show tertiary folding. Left: (D) mRNA from *S. typhimurium* arranged in a cloverleaf-like structure (Ames *et al*., 1983). Right: tRNA-like folds of (E) the 3′-end of a tobacco mosaic virus RNA (Lamy *et al*., 1975); (F) the 3′-end of a tobacco mosaic virus RNA (Garcia-Arenal, 1988), and (G) the 3′-end of a turnip yellow mosaic virus RNA (Rudinger *et al*., 1997).

strains (GTAMV, U2, and BL) can be folded into tRNA-like, L-shaped structures which are recognized by certain aaRS as substrates (Lamy *et al*., 1975; Joshi *et al*., 1985; Garcia-Arenal, 1988) (Figure 8). Sequence similarities occur in the acceptor stem and the D loop region. The RNA of the turnip yellow mosaic virus (TYMV) is aminoacylated with valine by ValRS from yeast as well as with histidine by HisRS, albeit with lower efficiency (Rudinger *et al*., 1992). This indicates that the TYMV RNA contains essential identity elements recognized by both aaRS enzymes (for compilations see also Mans *et al.*, 1991; Giegé, 1996). Furthermore, the Brome mosaic virus RNA possesses a tRNA-like domain that is aminoacylated with tyrosine, valine, and histidine by the corresponding aaRS from yeast (Felden *et al.*, 1994, 1998). The tRNA-like domain contains major identity elements of the three tRNAs, including a G-1·A73 base pair of $tRNA^{His}$, which is in a pseudoknotted amino acid-accepting branch of the viral RNA (Felden and Giegé, 1998; Schimmel and Alexander, 1998). The biological relevance of aminoacylation of these RNAs still needs to be established. A general correlation between aminoacylation and replication of viral genomes has been discussed by Felden *et al*. (1998).

Histidyl-tRNA Synthetase in Autoimmune Diseases

Autoimmune disorders such as rheumatic arthritis are connected with the appearance of autoantibodies against a variety of macromolecules. Antibodies against an antigen called Jo-1 were found in 20–30% of the sera of myositis patients (Mathews and Bernstein, 1983; Dang *et al*., 1985, 1986; Targoff *et al*., 1988; Targoff and Arnett, 1990; Marguerie *et al*., 1990; Goldstein *et al*., 1990; Tsui and Siminovitch, 1991; Shi *et al*., 1991; Lopez *et al*., 1991; Targoff, 1991, 1993; Hirakata *et al*., 1992; Genth *et al*., 1993; Genth and Mierau, 1993; Treher *et al*., 1993; Garlepp, 1993; O'Neill and Maddison, 1993; Mitra *et al*., 1994; O'Hanlon *et al*., 1994; Chmiel *et al*., 1995; Fischer *et al*., 1995; Gelpi *et al*., 1996; Vazquez-Abad and Rothfield, 1996a; Friedman *et al*., 1996; Rutjes *et al*., 1997; Kalenian and Zweiman, 1997; Miller *et al*., 1998). Immunoblot assays (Williams *et al*., 1986; Fonong *et al*., 1990) and ELISA tests were developed (Biswas *et al*., 1987b; Targoff and Reichlin, 1987) for detection of anti-Jo-1, which does not seem to correlate with cellular muscle damage (Suzuki *et al*., 1993). The Jo-1 antigens have been found to be cytoplasmic and not associated with the cytoskeletal framework (Dang *et al*., 1986; Thiry *et al*., 1988; Vasquez-Abad *et al*., 1996b). Immunoprecipitation experiments with anti-Jo-1 antibodies in the presence of $tRNA^{His}$ identified the Jo-1 antigen as histidyl-tRNA synthetase (Mathews and Bernstein, 1983; Rosa *et al*., 1983). Purified HisRS is recognized by the myositis-specific anti-Jo-1 antibodies (Yang *et al*., 1984; Raben *et al*., 1991a, b). Availability of purified HisRS increased the detection rate of anti-Jo-1 antibodies in the sera of myositis patients to 48.5% (Walker *et al*., 1987).

Purified HisRS from rat liver is recognized by anti-Jo-1 antibodies only in its native form. The antibodies are competitive inhibitors (with respect to both ATP and histidine) of the aminoacylation reaction catalyzed by this enzyme (Fahoum and Yang, 1987). This observation suggests that the antibodies bind close to the ATP- and histidine-binding sites of HisRS. Noncompetitive inhibition was observed with respect to $tRNA^{His}$, indicating that the antibodies bind to free and $tRNA^{His}$-bound HisRS. Autoantibodies from patients with polymyositis and dermatomyositis react with ribonucleoproteins (Hirakata *et al*., 1992). Anti-Jo-1 antibodies exhibit a stronger inhibition of HisRS if the enzyme has been preincubated with $tRNA^{His}$. This may indicate that the antibodies bind to the HisRS:$tRNA^{His}$ complex with a higher affinity than that for the free enzyme. This may have been confirmed in part by the observation that human HisRS alone did not generate myositis in mice (Blechynden *et al*., 1997).

The epitopes that are responsible for recognition of HisRS by anti-Jo-1 antibodies fall into two classes, conformation-independent and conformation-dependent. These epitopes may also vary among myositis patients (Tsui *et al*., 1989; Ramsden *et al*., 1989). Most of the autoantibodies are restricted to the IgG_1 heavy chain isotype (Miller *et al*., 1990a,b). One major epitope has been located in the N-terminal region of the enzyme (Raben *et al*., 1994). A truncated human HisRS lacking the first 60 amino acids is inactive both as antigen and as enzyme. The missing region is predicted to have a coiled-coil structure that resembles the coiled-coil arm at the N-terminus of SerRS, which has not been found in HisRS from *E. coli* and yeast. Peptides consisting of amino acid residues 1–60 and 1–47 of human HisRS have a high helical content and compete with HisRS for the autoantibody sites; comparison with other antibodies has suggested that a long α-helical region which contains two potential coiled-coil domains and a leucine zipper motif may be the main epitope (Rutjes *et al*., 1997). In a more detailed study, amino acid residues 2–44 and 286–509 of the human HisRS were identified as epitopes (Martin *et al*., 1995). However, antibodies raised against peptides containing these two epitopes did not inhibit HisRS activity. It was concluded from this work that the autoantibody which inhibits HisRS must recognize at least three distinct epitopes. Another explanation is that these isolated peptides do not assume the structures they have in HisRS which the antibodies would recognize.

Molecular mimicry may best explain the etiology of myositis and the origin of the human serum antibodies, as HisRS has significant sequence homologies with the polyprotein of the encephalomyocarditis virus (EMCV) (Walker and Jeffrey, 1986, 1988; Blaszczyk *et al*., 1998). This virus is able to produce polymyositis symptoms in mice. Alternatively, the native autoantigen itself may play a direct role in selecting and sustaining the autoantibody response (Miller *et al*., 1990a, b). It has been suggested that anti-Jo-1 antibodies bind only nonlinear epitopes of the

human HisRS that remain exposed when the enzyme is complexed with $tRNA^{His}$.

In addition to HisRS, several other aaRS have been identified as autoantigens. However, HisRS plays a key role in the research of autoimmune diseases because there are numerous investigations and clear experimental effects. The exact structures of the epitopes are still unknown, but such information may be obtained from future X-ray diffraction analyses of the crystallized proteins. Causal therapies of these autoimmune diseases are not yet available; however, changes of the critical epitope structures by chemical methods or genetic engineering may be attainable.

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