Solution Structure of the Orphan PABC Domain from *Saccharomyces cerevisiae* Poly(A)-binding Protein*  

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We have determined the solution structure of the PABC domain from *Saccharomyces cerevisiae* Pab1p and mapped its peptide-binding site. PABC domains are peptide binding domains found in poly(A)-binding proteins (PABP) and are a subset of HECT-family E3 ubiquitin ligases (also known as hyperplastic discs proteins (HYDs)). In mammals, the PABC domain of PABP functions to recruit several different translation factors to the mRNA poly(A) tail. PABC domains are highly conserved, with high specificity for peptide sequences of roughly 12 residues with conserved alanine, phenylalanine, and proline residues at positions 7, 10, and 12. Compared with human PABP, the yeast PABC domain is missing the first α helix, contains two extra amino acids between helices 2 and 3, and has a strongly bent C-terminal helix. These give rise to unique peptide binding specificity wherein yeast PABC binds peptides from Paip2 and RF3 but not Paip1. Mapping of the peptide-binding site reveals that the bend in the C-terminal helix disrupts binding interactions with the N-terminal peptide ligands and leads to greatly reduced binding affinity for the peptides tested. No high affinity or natural binding partners from *S. cerevisiae* could be identified by sequence analysis of known PABC ligands. Comparison of the three known PABC structures shows that the features responsible for peptide binding are highly conserved and responsible for the distinct but overlapping binding specificities.

The yeast poly(A)-binding protein (Pab1p or yPABP) is an essential protein that functions as a scaffold to organize the mRNA ribonucleic acid protein complex around the mRNA poly(A) tail. Pab1p contains 570 amino acids arranged as four N-terminal RNA recognition motifs and a C-terminal PABC domain of ~70 amino acids. The two parts are separated by a largely unstructured region of ~100 amino acids. The N-terminal RNA recognition motifs bind the mRNA poly(A) tail and interact with the eIF4F complex at the mRNA 5′ cap. This Pab1p-eIF4F interaction is important for the circularization of the mRNA in actively translating complexes (1). At the C terminus, the PABC domain acts as a peptide/protein binding domain, recruiting various translation or mRNA processing factors to the mRNA ribonucleic acid protein complex. In yeast, Pab1 is an essential gene whose deletion leads to inhibition of translation initiation, poly(A) shortening, and delay in the onset of mRNA decay (2–4), but those effects can be suppressed by mutations that alter the 60 S subunit of the ribosome as well as those that inhibit mRNA decay (2, 5, 6).

In metazoans, several protein binding partners of PABC have been identified. These include the PABP-interacting proteins Paip1 and Paip2 and heterogeneous nuclear ribonucleoprotein E (or eCP1 and -2) as well as eRF3/GSPT (7–9). A number of potential interacting agents have also been identified in plants and yeast; they are Paip1-binding protein (Pbp1p), eIF4B, Rna15p, and a viral RNA-dependent RNA polymerase (4, 10, 11). We recently showed that a large number of potential binding partners can be identified by sequence analysis based on the presence of a consensus PABC recognition site (12). Finally, it is notable that in addition to poly(A)-binding proteins, PABC domains also occur in a subclass of ubiquitin E3 protein ligases that contain a HECT (homologous to E6-AP C terminus) domain. The function of the PABC domain in these ubiquitin ligases is unknown.

The structures of PABC domains from human PABP (hPABP) and HYD (a human ubiquitin ligase) have recently been determined by NMR spectroscopy and x-ray crystallography (12, 13). The two structures are largely similar and consist of 75 or 60 amino acid residues arranged as bundles of five or four α helices. Sequence conservation is highest in helices 2, 3, and 5, which correspond to the peptide-binding site determined by NMR spectroscopy (12).

Here we report the structure of the PABC domain from the yeast poly(A)-binding protein, Pab1p. The yeast sequence shows 40 and 57% identity with the domains from hPABP and HYD (themselves 52% identical). Together, the three proteins span much of the sequence variation in PABC domains. The yeast structure shows several distinct features that result in unique specificity and affinity of peptide binding.

The NMR assignments for this protein are available in the BioMagResBank (BMRB) database under BMRB accession number 10503 (www.bmrbr.org).
EXPERIMENTAL PROCEDURES

Sequence Comparison of PABC Domains—Forty sequences of PABC domains were obtained from a Ψ-BLAST search (14) of the NCBI non-redundant data base with the yPABC sequence (gi417441, residues 490–563) as query. These unique sequences were analyzed by ClustalW to generate an alignment and Neighbor Joining (NJ) tree (15). To simplify comparisons between different PABC domains, we have adopted a numbering scheme that is anchored on the RTPGMALLE motif common to all PABC domains. The PABC domain was defined to begin 34 residues before this motif (36 residues in the case of yPABC). The two additional residues in the loop between α helices 2 and 3 that are unique to the Saccharomyces and Caenorhabditis peptides were numbered 30a and 30b.

yPABC Expression and Purification—The C-terminal domain of Paip2 residues 491–577, was amplified by PCR using genomic DNA from Saccharomyces cerevisiae (a gift from Malcolm Whiteway) with primers PABYc-F (5’-CCCAACAAGTGGATCCCCAGAATTG-3’) and PABYc-R (5’-GGTATACATGATTCTTAGGCTGCATG-3’). The PCR product was cloned into the BamHI and EcoRI restriction sites of the vector pGEX-6P-1 (Amersham Biosciences). pPFC was transformed into Escherichia coli expression host BL21 Gold (DE3) (Stratagene) and grown at 37°C in Luria Broth or M9 media supplemented with 100 μg/ml ampicillin. Expression of the glutathione S-transferase–yPABC fusion protein was induced at 30°C by 1 mM isopropyl-1-thio-β-D-galactopyranoside for 3 h and purified by affinity chromatography using a glutathione-Sepharose 4B column (Amersham Biosciences). The N-terminal glutathione S-transferase tag was cleaved from yPABC by yPABC treatment for 20 h at 4°C with PreScission protease (Amersham Biosciences). The column was set at 2.5 units/mg of fusion protein and yielded a 92-residue protein fragment consisting of the 87 C-terminal residues of Paip1 plus a 5-residue (Gly-Pro-Leu-Gly-Ser) N-terminal extension. Glutathione-Sepharose was used to remove the PreScission protease.

The sequence composition of purified yPABC was confirmed by mass spectrometry. For NMR analysis, the protein was exchanged into NMR buffer (50 mM KHPO₄, 100 mM NaCl, 1 mM NaN₃, pH 6.3). The final yield of the 2.5 mg/ml dithiothreitol solution was 6 mg/liter culture in M9 media containing 6 g of NaHPO₄, 3 g of KH₂PO₄, 0.5 g of NaCl, 0.5 g of ¹⁵NH₄Cl (Isotec, Inc.), and 2 g of [¹³C₆]glucose (Cambridge Isotope Laboratory).

Peptide Preparation and Purification—Unlabeled peptides were synthesized by Fmoc (N-(9-fluorenylethoxycarbonyl) solid-phase peptide synthesis and purified by reverse-phase chromatography on a Vydac C₁₈ column (Hesperia, CA). The composition and purity of the peptides were verified by ion-spray quadrupole mass spectrometry.

The C-terminal domain of human Paip2, residues 106–127, was amplified by PCR using a plasmid template (a gift of Nahum Sonenberg) with primers P2C-F (5’-CTCTCTTCTTGAGGCATGGGGTCAGGAC-3’) and P2C-R (5’-CAGATGCAGCAGAAAATCTCATAATTTC-3’). The PCR product was cloned into the BamHI and EcoRI restriction sites of the vector pGEX-6P-1 (Amersham Biosciences) to make pP2C. An ¹³C-labeled peptide of this construct was made by expressing pP2C in E. coli expression host BL21 Gold (DE3) grown in M9 media containing ¹⁵NH₄Cl and purified the fusion protein as described previously for yPABC. Digestion with PreScission protease was performed in the same conditions as described above yielding a 27-residue peptide consisting of the 22 C-terminal residues of human Paip2 plus a 5-residue (Gly-Pro-Leu-Gly-Ser) N-terminal extension. The peptide was desalted using C₁₈ reverse-phase chromatography and then lyophilized. The composition and purity of the peptides was verified by ion-spray quadrupole mass spectrometry.

Peptide titrations were carried by adding either labeled or unlabeled Paip2 peptide into unlabeled or labeled yPABC, respectively. Titrations were monitored by ¹H,¹⁵N heteronuclear single quantum correlation spectroscopy (COSY) spectra of the labeled species (either peptide or protein) and were brought to a final protein concentration of 1 μM.

NMR Spectroscopy—NMR resonance assignments of yPABC were determined using standard triple resonance techniques on a 400-MHz ¹³C,¹⁵N-labeled sample (16) on a Bruker DRX500 NMR spectrometer. All NMR experiments were recorded at 303 K. Main-chain ¹H, N, and HN and side-chain ²⁷O resonances were assigned using HNCACB and CBCA(CO)NH experiments (17, 18). H N resonance assignments and ¹H,¹⁵N coupling constants were obtained from an HNHA experiment (19). ¹H,¹³C dipolar couplings were measured with an in-phase/anti-phase (IPAP)-heteronuclear single quantum correlation experiment on an isotropic sample (without phase) and on a sample containing 18 mg/ml P1 phage (20, 21). Two backbone and side-chain signal assignments were obtained from three-dimensional heteronuclear NOESY and total correlation spectroscopy experiments at 500 and 750 MHz and a homonuclear NOESY spectrum obtained at 500 MHz. The ¹H,¹⁵N heteronuclear NOEs were determined using standard triple resonance techniques on a 15N-labeled Paip2 (residues 106–577) acquired at 500 MHz, 1H971 NOEs were collected from homonuclear and ¹⁵N-edited NOESY experiments at 500 and 750 MHz respectively. The figure was generated with ClustalW (15) and TreeViewPFC (40).
give excellent quality spectra, and a large number of structural constraints were determined (Table I). The secondary structure and NOEs were very similar to human PABP, with the notable absence of the first α helix (Fig. 2a). In addition to NOE and dihedral angle constraints, a small set of 48 residual dipolar couplings (RDCs) was measured on a sample of 15N-labeled yPABC in Pf1 phage (Fig. 2b). These RDCs dramatically improved the precision of the structures, particularly in the region of helix 4. The backbone r.m.s.d. in the absence of RDCs was almost twice (0.61 Å) the final value for the 30 accepted structures (0.34 Å) calculated with RDCs. Inclusion of the RDCs also improved the Ramachandran plot statistics (Fig. 2).

The folded domain of yPABC includes ∼65 residues (502–567 of Pab1p) as a bundle of four helices (Fig. 3). The overall fold is similar to the recently determined PABC structures from human PABP (12) and HYD (13). The four helices (numbered 2–5) form a compact structure with a well packed hydrophobic core consisting of residues Leu-17, Leu-21, Val-25, Ala-32, Ala-33, Ile-36, Ile-40, Leu-43, Val-48, Phe-49, Leu-51, Leu-52, Phe-58, Tyr-62, Ala-65, Ala-68, and Tyr-69. yPABC contains a unique two-amino acid insertion that is accommodated in the loop between helices 2 and 3 (Fig. 1). The most unusual feature of yPABC is the strong bend in the last α helix. This helix shows a roughly 50° bend centered around Tyr-62 and terminates antiparallel with helix 3. Helix 5 contributes three aromatic residues (Phe-58, Tyr-62, and Tyr-69) to the hydrophobic core. The bend can be detected in the RDC data; parallel RDC experiments on hPABP confirm that this is a unique feature of the yeast domain.26 Surprisingly, all the ϕ/ψ angles in helix 5 fall in the most favored region of the Ramachandran plot for α helices (Fig. 2d).

As is the case for the HYD PABC domain, the yPABC domain is missing the first helix. Instead, the fourth helix in yPABC is raised and replaces a number of the contacts between helix 1 and 2 in hPABP (Fig. 3, d–f). The first N-terminal helix of PABC from hPABP is itself dispensable, and a shortened fragment (PABC residues 554–636) gave a 1H,15N correlation spectrum similar to that of the full-length domain (data not shown). Overall, the PABC domain from yeast PABP appears to be more closely related to the PABC domain from human HYD than human PABP. This is a consequence of the greater sequence relatedness of yPABC and HYD but is more clearly evident in the three-dimensional structures. A pairwise overlay of the most conserved Cα residues in the three proteins gives twice the r.m.s.d. for hPABP compared with HYD (Fig 3c).

Peptide binding studies were used to determine the specificity and position of the peptide-binding site on yPABC. The initial choice of peptides was based on the consensus binding sequence determined for the human PABC (12). The list of peptides studied is shown in Table II. Four peptides were found to bind to yPABC. The 22-residue C-terminal peptide from Paip2 demonstrated one of the highest affinities. Chemical shift mapping was used to identify yPABC residues that participate in peptide binding (Fig. 4). Residues with the largest chemical shift changes ((1H15N shift)2 + (1H13N shift × 0.2)2)1/2 on binding of Paip2 were Lys-35 (0.6 ppm), Tyr-22 (0.47), Glu-19 (0.45), Met-39 (0.39), Gln-20 (0.39), and Ile-40 (0.37). Only small chemical shift changes were observed in helix 5 (Fig. 3), in contrast to previous results with hPABP (12). Instead, almost all the chemical shift changes occur in helices 2 and 3 around the hydrophobic binding pocket, which is the presumed binding pocket for Phe-118 of Paip2. Additional changes occur at the N terminus of helix 2 and likely reflect interactions with the C-terminal portion of the peptide (see below).

Yeast does not have a protein homologous to Paip2. Using the previously published consensus for human PABC (Table III), we searched the S. cerevisiae genome for related sequences that might bind to yPABC. Among proteins known to interact with Pab1p, we identified residues 234–250 from Pan1p (29, 30), two regions from Ppb1p (residues 308–327 and 376–399) (11), and a peptide derived from the N terminus of RF3 (residues 106–122) (Table II). None of these peptides bound to yPABC, as determined by the absence of chemical shift changes in 1H,15N correlation spectra. Similar negative results were not observed for the S. cerevisiae genome.

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2 G. Kozlov, unpublished results.
obtained for a peptide derived from human Paip1. This was unexpected since Paip1 has been shown to bind to HYD (13). Of nine peptides tested, the four that bound were the Paip2 peptide, a peptide from the N terminus of human RF3, a peptide similar to *Pichia pinus* RF3, and a peptide from the *Drosophila* shuttle craft protein (Table II).

From titration experiments, we measured the dissociation constant of the Paip2 peptide-yPABC complex to be $1 \text{mM}$. Based on the similar amounts of line-broadening in spectra with other peptides, we estimate that the affinities of all the ligands tested are in the millimolar range. This is 3–4 orders of magnitude higher than that measured for Paip2/hPABP (7) and likely reflects the fact that the peptides do not interact with the C-terminal helix of yPABC.

We also monitored complex formation from the peptide side by cloning and expressing a $^{15\text{N}}$-labeled fragment of Paip2 (residues 106–127). The $^1\text{H},^{15\text{N}}$ correlation spectrum of the unbound peptide showed the small dispersion of signals characteristic of an unfolded peptide (Fig. 4c). The addition of unlabeled yPABC to the $^{15\text{N}}$-labeled peptide caused changes in roughly half of the signals. The complex was in intermediate exchange, so many of the NMR peaks broadened or disappeared upon the addition of yPABC.

We identified peptide residues involved in PABC binding by an $^1\text{H},^{15\text{N}}$ heteronuclear NOE (hNOE) experiment (Fig. 4d). The hNOE is a measure of the reorientation rate of the amide nitrogen-hydrogen internuclear vectors and, thus, of the mobility of the peptide residues. At 500 MHz, the hNOE varies between $-3.6$ and $0.82$ for mobile and immobile residues (22). For Paip2 residues Leu-103 to Leu-111 and Lys-123 to Ile-127,
the hNOE was negative, which indicates a lack of binding. Residues Asn-112 to Val-122 gave small or zero hNOEs and identified these residues as binding to yPABC. The absence of positive hNOEs is a reflection of the weak binding of Paip2 to yPABC. For several residues in the middle of the binding region, no hNOE signal could be detected. This was a consequence of exchange broadening and constitutes independent evidence for PABC binding by these residues. Residue Phe-118 of Paip2 showed the largest hNOE, which is consistent with its key role in complex formation.

Previous studies identified a 12-residue consensus PABC site between Ser-109 and Pro-120 of Paip2 (7). Our hNOE results suggest that this motif is shifted toward the C terminus and includes Gly-121 and Val-122. This agrees with ongoing studies with PABC from human PABP, which suggest that Paip2 binds hPABP as a series of β-turns.2 For yPABC, small negative hNOE values were observed for residues Ser-109 through Leu-111. These negative hNOEs likely reflect the differences in the structure and position of the last helix in yPABC and hPABP. Residues Ser-109 through Leu-111 do bind hPABP but via helix 5.2 These results suggest that the major specificity differences between PABC domains in human and yeast PABP occur in the N-terminal residues of the peptide ligands due to the altered structure of the terminal helices.

### TABLE II

**Peptides used in yPABC binding assays**

| NO. | PEPTIDE ORIGIN   | SEQUENCE                      | BINDING1 |
|-----|------------------|-------------------------------|----------|
| P1913 | Human RF3       | AF SRQLNVN AKPFVP NVHAAEFV PSFLR | +        |
| P1895 | Human Paip2     | VV KS NLNPNA KEFVP GV KY G N I | +        |
| P1934 | Shuttle craft protein | SKL QASA PEVF VN PFA KL | +        |
| P1954 | *Pichia* pinus RF3-related | SY I PNTAK AF VP GA PQ Y | +        |
| P1914 | Human Paip1     | VL MSK LSV NA PEVF P SGG Y S S S Y | -        |
| P1986 | *S. cerevisiae* RF3 | NNL QY QAG FQP QS Q GM | -        |
| P1933 | *S. cerevisiae* Panlp | EPL KPT ATGF VN SP ANN | -        |
| P1955 | *S. cerevisiae* Pbp1lp | SNS KPN SKN GRY VPPT LRQ | -        |
| P1956 | *S. cerevisiae* Pbp1lp | SL SKE AQ IE EEL KKF SEKF KP V Y D | -        |

1 Based on amide chemical shift changes in NMR titrations.

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*Fig. 4. Mapping the PABC-ligand interaction.* 

a, 15N,1H heteronuclear single quantum correlation of 15N-labeled yPABC in the absence (left panel) and presence (right panel) of a 22-residue Paip2-derived peptide (see Table II). b, plot of chemical shift changes in yPABC as a function of residue number. Residue numbering is as in Fig. 2 but includes the entire protein fragment studied by NMR. Residues Tyr-22 and Lys-35 in helices 2 and 5 showed the largest chemical shift changes. Helix 5 showed only minor changes. c, 15N,1H heteronuclear single quantum correlation of a 15N-labeled 27-residue Paip2-derived peptide in the absence (left panel) and presence (right panel) of unlabeled yPABC. d, 15N,1H heteronuclear NOEs of Paip2 peptide when bound to yPABC. The weak or absent signals between residues 9 and 23 of the peptide indicate that these residues interact with yPABC.
DISCUSSION

PABCs are highly conserved eukaryotic protein domains of 64–72 amino acids in length and sequence identities of 40% in interspecies comparisons. Three subfamilies can be distinguished in a phylogenetic tree of PABC sequences (Fig. 1b). The first group encompasses PABCs of animal origin, with overall pairwise identities of 80% or more (62% for C. elegans). Tissuespecific (testis) or inducible (activated platelets or T cells) isoforms have been described in humans (31–33), and these sequences show a slightly lower level of identity when compared with other forms. This is likely the result of subcellular or tissue specialization, with conserved but distinct specificity among the different PABC domains within one organism.

A second branch groups a family of more divergent PABC domains of vegetal origin with pairwise sequence identities of about 70%. PABC from the parasite Trypanosoma brucei is branched with its homologues in plants; this is supported by recent work that has hinted at a weak phylogenetic link between the euglenozoan lineage (to which trypanosomids belong) and plants (34). The third, most divergent group contains the PABC domains of the ubiquitin ligases of the hyperplastic (HYD) family as well as S. cerevisiae and Schizosaccharomyces pombe PABPs. The relationship between HYD and PABP proteins has not yet been established, but it hints at a role for ubiquitination in the regulation of protein synthesis. Structurally, the absence of the first α helix in yPABC and HYD seems to be a feature of the third group of PABC domains.

Secondary structure predictions using the multivariate linear regression combination (MLRC) software (35) as well as sequence conservation indicate the likely presence of helix 1 in yPABC and HYD among the different PABC domains within one organism.

Among the proteins/peptides that bind to yPABC (Table II), only RF3 occurs in yeast. In S. cerevisiae, RF3 was first identified as the stop codon suppressor mutations Sup35 and Sup2 (36, 37). More recently, this protein has received considerable attention as it mediates non-mendelian inheritance through a prion-like mechanism. The yeast [PSI+] prion phenotype results from self-propagating aggregation of RF3 through its N-terminal domain (38). This behavior is thought to be related to the large number of glutamine residues at the N terminus.

Comparison of RF3 sequences from 11 different yeast species allowed us to identify potential PABC binding sites in all but 4 species: S. cerevisiae, Zygosaccharomyces rouxii, Saccharomyces cerevisiae, and Kluyveromyces lactis (Table III). As is the case for human RF3, several of the RF3 proteins contain two or three potential PABC-binding sites. Yarrowia lipolytica RF3 contains three overlapping, putative PABC sites. It is unknown if all these sites are functional or if cooperativity exists between them. The absence of an evident PABC site in S. cerevisiae RF3 suggests that this interaction may be absent in baker’s yeast and related strains. The four species missing PABC sites are most closely related to each other based on phylogenetic grouping of yeast using 23 S RNA sequences, which suggests that the site was lost relatively recently (38, 39).

Mangus et al. (11) used the C-terminal portion of Pab1p as bait in a two-hybrid screen for interacting yeast proteins. Surprisingly, none of the proteins identified contain a consensus PABC site. Instead, mutagenesis studies indicate that the region preceding yPABC (Pab1p residues 406–494) is required for the binding of Pbp1p (11). This preceding region is not a structured part of the C-terminal domain of yPABC (12, 13). Although Pbp1p does not bind PABC, it is related to ataxin-2, the human protein responsible for type 2 spinocerebellar ataxia (SCA2), which does contain a PABC site (11, 12). Perhaps coincidentally, the origin of SCA2 is a polyglutamine expansion in ataxin-2 that leads to protein aggregation as for RF3.

In conclusion, the structure of the PABC domain from the yeast poly(A)-binding protein shows similarities to previous structures but contains a very different C-terminal helix (Fig. 3). This gives rise to a distinct binding specificity for yPABC, particularly toward the N terminus of the bound peptides (Fig. 4). A hydrophobic pocket between helices 3 and 5, which is unique to yPABC, could bind aromatic residues that occur in the N-terminal end of PABC sites in fungal RF3 proteins (Table III), but no PABC site was detected in RF3 from S. cerevisiae.
Future work will be directed toward understanding the function of yPABC in *S. cerevisiae* and in the identification of physiological binding partners.

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Solution Structure of the Orphan PABC Domain from *Saccharomyces cerevisiae* Poly(A)-binding Protein

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