Solution structure of the region 51–160 of human KIN17 reveals an atypical winged helix domain

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Abstract

Human KIN17 is a 45-kDa eukaryotic DNA- and RNA-binding protein that plays an important role in nuclear metabolism and in particular in the general response to genotoxics. Its amino acids sequence contains a zinc finger motif (residues 28–50) within a 30-kDa N-terminal region conserved from yeast to human, and a 15-kDa C-terminal tandem of SH3-like subdomains (residues 268–393) only found in higher eukaryotes. Here we report the solution structure of the region 51–160 of human KIN17. We show that this fragment folds into a three- α -helix bundle packed against a three-stranded β -sheet. It belongs to the winged helix (WH) family. Structural comparison with analogous WH domains reveals that KIN17 WH module presents an additional and highly conserved 3_{10} -helix. Moreover, KIN17 WH helix H3 is not positively charged as in classical DNA-binding WH domains. Thus, human KIN17 region 51–160 might rather be involved in protein–protein interaction through its conserved surface centered on the 3_{10} -helix.

Keywords: KIN17 protein; winged helix fold; NMR structure; nuclear metabolism

Supplemental material: see www.proteinscience.org

Maintenance of the genomic integrity is crucial for all living organisms. Since cells are continuously submitted to genotoxic stresses that induce DNA damages, they have evolved sophisticated mechanisms to detect, signal the presence of, and repair these lesions. In humans, the nucleotide excision repair pathway is an efficient way to remove DNA lesions induced by UV or ionizing radiation. The human gene *KIN17*, located in chromosome 10, participates in the general response to genotoxics. It is up-regulated following DNA damages produced by UV

or γ irradiation, and this response is strictly dependent on the presence of nucleotide excision repair proteins XPA and XPC (Masson et al. 2003).

The *KIN17* gene encodes a ubiquitously expressed nuclear protein that forms intranuclear foci in proliferating cells (Biard et al. 2002). Major features of the mammalian KIN17 protein are its ability to bind DNA and RNA in vitro and in vivo, to associate with multiprotein DNA replication complexes, and, when overexpressed, to inhibit the S-phase progression of the replication process (for review, see Angulo et al. 2005). Furthermore, the mouse KIN17 protein binds preferentially to curved DNA found at hot spots of illegitimate recombination in eukaryotic chromosomes (Mazin et al. 1994a). Taken together, these observations clearly indicate that KIN17 plays an important role in nuclear metabolism.

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Human KIN17 is a 45-kDa modular protein composed of a 30-kDa N-terminal region conserved from yeast to human, and a 15-kDa tail found only in higher eukaryotes. The recently solved crystal structure of its C-terminal domain (residues 268–393) reveals a tandem of SH3-like subdomain that contributes to RNA-binding of the whole protein (le Maire et al. 2006). Deletion of this C-terminal domain does not affect the DNA binding of KIN17 (Mazin et al. 1994b). The N-terminal region comprises a C₂H₂ zinc finger motif (residues 28–50), which exhibits DNA- and RNA-binding properties (Mazin et al. 1994b; le Maire et al. 2006), and a globular domain (residues 51–160) of unknown function. Interestingly, if deletion of the zinc finger motif reduces KIN17 DNA binding, the core of the protein (residues 71–281) which comprises the globular region 51–160, still binds DNA (Mazin et al. 1994b). Here, we report the high-resolution NMR structure of human KIN17 region 51–160 as an important step toward identifying the structural and biological functions of this domain.

Results and Discussion

Structure determination

The three-dimensional structure of human KIN17 region 51–160 was characterized using heteronuclear NMR and molecular modeling. As reported previously (Carlier et al. 2006), ¹H, ¹⁵N, and ¹³C chemical shift assignments were completed for 95% of the backbone atoms and 90% of the side-chain resonances (BMRB accession number 6938). The solution structure was calculated using 2743 NOESY-derived proton–proton distances, 18 hydrogen bonds, and 140 ϕ and ψ torsion angle values. Table 1 summarizes the structural statistics for the ensemble of the 12 best conformers that represent the solution structure of human KIN17 region 51–160. Analysis of this final ensemble shows that no distance violations larger than 0.5 Å are present and that the covalent geometry is respected. Atomic coordinates have been deposited in the RSCB Protein Data Bank under accession number 2V1N.

Structure description

A backbone superposition of the 12 best conformers is shown in Figure 1A as a stereo diagram. The first 14 N-terminal residues and the five last C-terminal amino acids (residues 51–64 and 156–160, respectively) are disordered, whereas fragment 65–155 adopts a well-defined α/β fold. The root mean square deviation (RMSD) calculated from the mean structure between residues 65 and 155 yields 0.43 Å for the backbone and 1.03 Å for the heavy atoms. The three-dimensional structure is constituted of four α -helices, H1 (residues 65–83), H2 (residues 91–99), H3 (residues 115–124), and H4 (residues 147–155); three β -strands, S1 (residues 88–90),

Table 1. Structural statistics for the ensemble of 12 final conformers

Number of nOe assigned	3413
Number of restraints	
Distance restraints	2743
Dihedral restraints	140
from TALOS prediction	136
from analysis of HNHA or HMQC-J	4
Hydrogen bonds	18
Number of violations	
nOe distance > 0.5 Å	0
Dihedral restraints > 10°	0
RMSD from idealized covalent geometry	
Bond (Å)	0.016 ± 0.0002
Angle (°)	3.3 ± 0.03
Improper (°)	2.7 ± 0.1
RMSD on restraints	
Distance (Å)	0.032 ± 0.0012
Dihedral (°)	1.1 ± 0.07
Coordinate precision (residues 65–155)	
Backbone (Å)	0.43 ± 0.08
Heavy atoms (Å)	1.03 ± 0.12
Ramachandran plot (residues 65–155)	
Most favored regions	88.6%
Additional allowed regions	10.1%
Generously allowed regions	0.8%
Disallowed regions	0.5%

S2 (residues 128–133), and S3 (residues 136–141); and one ₁₀-helix, H2.5 (residues 107–109), organized into an H1-S1-H2-H2.5-H3-S2-S3-H4 topology. Thus, the amino-terminal half of the domain is mainly α -helical, whereas the carboxyl-terminal half is dominated by two β -strands arranged in a twisted antiparallel β -sheet (Fig. 1B). The α -helices H1, H2, and H3 form a central orthogonal bundle. They are amphipathic, and their hydrophobic core is constituted by Met-65, Phe-72, Phe-76, Leu-77, Leu-79, Leu-80 (H1), Val-94, Tyr-95, Tyr-98 (H2), Leu-115, Phe-118, Trp-121, and Leu-122 (H3). The three-stranded β -sheet is packed onto the three-helix bundle via a hydrophobic interface in which Phe-76, Leu-77, Leu-80 (H1), Leu-115, Thr-119, Leu-122, and Gly-123 (H3) contact the hydrophobic β -sheet face composed of Cys-128, Val-130 (S2), Trp-137, Ile-139, and Tyr-141 (S3).

The three-amino-acid ₁₀-helix H2.5 is located in a highly conserved long loop (residues 100–114) that connects α -helices H2 and H3 (Figs. 1B, 2A). The presence of such a short ₁₀-helix in the unstructured region H2–H3 is supported by unambiguous assignment of several interresidue ¹H–¹H nOes, in particular two consecutive $d_{\alpha N}(i, i + 2)$ and one $d_{\alpha N}(i, i + 3)$ connectivities that involve residues 107–110 (Supplemental Fig. S1). In addition, ϕ and ψ dihedral restraints obtained for Met-107 and Asn-108 from TALOS prediction are consistent with a ₁₀-helix conformation (Supplemental Table S1). In the NMR structures, the ₁₀-helix H2.5 is stabilized by

Figure 1. Solution structure of human KIN17 region 51–160. Only the well-defined fragment (residues 65–155) is shown. (A) Stereoview of the superposition of the 12 best structures. The overall fold is indicated by the protein backbone (black), with side chains colored in blue (α -helices), pink (β -strands), or green (3_{10} -helix). (B) Ribbon representation of the lowest energy conformer.

a canonical hydrogen bond between Ala-109 and His-106 and by a hydrogen bond network that involves the backbone of Trp-112, the backbone of Met-107, and the side chain of Thr-110. Such a network is confirmed by the observation of the hydroxyl group resonance of Thr-110 at a typical chemical shift (5.60 ppm) in the ^{15}N -HSQC-NOESY spectra. The side chains of Ile-105, Met-107,

Thr-110, and Trp-112 make numerous van der Waals interactions with Phe-72 (H1), Leu-115, and Phe-118 (H3), and thus pack the 3_{10} -helix onto the central orthogonal bundle.

A ^{15}N - ^1H heteronuclear nOe experiment was performed in order to investigate the backbone flexibility. Figure 2B shows the values of $^1\text{H} \rightarrow ^{15}\text{N}$ nOe, which is essentially

Figure 2. (A) Multiple sequence alignment of five KIN17 proteins (Human, *Homo sapiens*; CAEEL, *Caenorhabditis elegans*; Drosophila, *Drosophila melanogaster*; Arabidopsis, *Arabidopsis thaliana*; Cerevisiae, *Saccharomyces cerevisiae*). The numbering scheme refers to human KIN17 sequence. Invariant residues are shown in black columns, highly similar residues are in gray columns, and weakly similar residues are shown in boxes. Secondary structure elements corresponding to the NMR structure of human KIN17 region 51–160 are indicated above the alignment. (B) $^1\text{H} \rightarrow ^{15}\text{N}$ heteronuclear nOe intensity ratio as a function of residue number. Proline amino acids or residues missing due to line broadening are indicated by an asterisk.

sensitive to rapid motions (i.e., picosecond to nanosecond timescale), as a function of residue number. Negative and small values (<0.25) are observed for the extremities 52–60 and 157–160, confirming the mobility of the N- and C-terminal parts of the domain. Intermediate values (between 0.35 and 0.6) are found for the C-terminal region 144–156, indicating partially restricted motions in the helical region H4. Consistently, only a small number of medium- and long-range ^1H - ^1H nOes were unambiguously assigned to residues 52–60 and 144–160 (Supplemental Fig. S1). Finally, almost all residues belonging to the three-helix bundle, the antiparallel β -sheet, and the long loop H2–H3 (i.e., from Met-65 to Asp-143) display a $^1\text{H} \rightarrow ^{15}\text{N}$ nOe value close to 0.8 characteristic of highly restricted rapid motions. This last region adopts a stable conformation on the picosecond to nanosecond timescale.

Region 51–160 of human KIN17 adopts a winged helix fold

The three-dimensional structure of human KIN17 fragment 65–155 was submitted to the DALI server (www.ebi.ac.uk/dali/). It is close to the three-dimensional structure of numerous proteins belonging to the winged helix family (WH), which is a member of the DNA-binding helix-turn-helix superfamily (Gajiwala and Burley 2000). The WH motif is a compact α/β fold consisting of three α -helices (H1, H2, and H3), three β -strands (S1, S2, and S3), and two loops called wings W1 and W2, organized in an H1-S1-H2-H3-S2-W1-S3-W2 topology. The WH domain of human KIN17 is very close to the canonical topology. The only difference occurs at the level of the H2–H3 loop, where an atypical well-defined 3_{10} -helix is observed. Analysis of the phylogenetic conservation of human KIN17 region 51–160 was achieved using the PSI-blast server (www.ncbi.nlm.nih.gov/BLAST/). Figure 2A shows that this region is particularly well conserved from yeast to human. Most residues from the hydrophobic core of the domain are conserved (31% sequence identity and 77% sequence similarity over 14 residues), as well as 8 of the 15 amino acids belonging to the long loop H2–H3. Such analysis suggests that all eukaryotic KIN17 proteins share a common WH domain at their amino-terminal region that is structurally similar to the human KIN17 region 51–160.

Possible functions of the human KIN17 winged helix domain

The WH module is mainly known for its ability to interact with nucleic acids and in particular with DNA. Interestingly, the DALI tool shows that human KIN17 region 51–160 displays structural analogy with the DNA-binding WH domain of BlaI (PDB code 1XSD, Z-score 5.1, sequence identity 13%), MecI (1OKR, Z-score 5.0, sequence identity

9%), and DP2 (1CF7, Z-score 4.8, sequence identity 16%), whose structures in complex with a DNA fragment have been solved by crystallography (Zheng et al. 1999; Garcia-Castellanos et al. 2004; Safo et al. 2005). In these structures, the recognition helix H3 penetrates DNA major groove to make base-specific contacts while the wing W1 interacts with the phosphodiester backbone of the minor groove to increase the binding affinity. This DNA recognition mode is typical of WH proteins (Gajiwala and Burley 2000). Superposition of the KIN17 WH domain onto the WH–DNA complex of BlaI, MecI, and DP2 reveals a remarkable structural similarity despite a low level of sequence identity (Supplemental Fig. S2). However, significant differences are observed in the region comprising the recognition helix H3 and the loop H2–H3. In KIN17, loop H2–H3 is longer by at least seven residues whereas helix H3 is about five amino acids shorter. Moreover, the presence of the additional 3_{10} -helix H2.5 in KIN17 loop H2–H3 results in a substantially different positioning of the recognition helix H3 that does not superimpose on that of BlaI, MecI, and DP2. Comparison of the electrostatic potential surfaces also shows structural differences between the WH domain of KIN17 and the DNA-binding WH proteins (Fig. 3A). In all the structures of WH–DNA complexes, basic residues belonging to helix H3 and/or wing W1 form a concave positively charged surface that is generally well conserved. In the case of KIN17, the corresponding surface is rather slightly negative. Moreover, analysis of a sequence alignment of 20 KIN17 proteins using the program ConSurf reveals that the conservation of this surface is not significant (consurf.tau.ac.il/). Considering these observations, we were convinced that the WH domain of KIN17 does not interact with DNA through the typical recognition mode of WH proteins. Southwestern blotting studies were further performed using different KIN17 fragments but no interaction was observed between the recombinant domain 51–160 and a double-stranded DNA fragment recognized *in vivo* and *in vitro* by the whole protein (data not shown).

Interestingly, three residues of helix H2 (Asn-92, Glu-97, and Ile-99) and five residues of loop H2–H3 (His-104, His-106, Asn-108, Ala-109, and Thr-114) constitute a highly conserved and neutral surface located on a face opposite to the H3–W1 face (Fig. 3B). This surface could be involved in protein–protein interactions as observed in the recently published structure of the RAP74–FCP1 complex, in which the WH domain of RAP74 uses its neutral H2–H3 surface to bind the FCP1 peptide (Nguyen et al. 2003). Since the KIN17 WH module (residues 65–143) is close to a zinc finger motif (residues 28–50), its conserved surface could also participate with intramolecular interactions with this zinc finger domain. Structural investigation of intramolecular domain interactions will now be carried out in order to provide additional clues on the function of KIN17 WH module.

Figure 3. (A) Electrostatic properties at the surface of WH proteins. (Top panel) Representation of the electrostatic potential at the surface of the WH domains of BlaI (PDB code 1XSD), MecI (1OKR), DP2 (1CF7), and KIN17. The domains are oriented so as to show the H3–W1 face. Blue, white, and red colors indicate positive, neutral, and negative electrostatic surface potential, respectively. (Lower panel) Ribbon representation of these structures in the same orientation as in the top panel. The canonical secondary structure elements are highlighted according to the following color code: dark blue, H1; light blue, S1; green, H2; yellow, H3; red, S2, S3, and W1. (B) A projection of the ConSurf results on the H2–H2.5 surface of the human KIN17 WH indicates the degree of conservation from dark blue (highly conserved) to red (variable).

Materials and Methods

Sample preparation

Region 51–160 of human KIN17 was overexpressed in *Escherichia coli* strain Rosetta DE3 transformed with a construct generated in pEXP-TH5 plasmid (Invitrogen). This vector encodes a 6xHis-tag, the Z-domain from Staphylococcal Protein A (ZZ), a TEV protease (Tobacco Etch Virus) cleavage site, and the KIN17 region. The recombinant protein was prepared from cells grown to an OD_{595 nm} of 1.2 at 37°C in a bacterial culture supplemented by 100 µg/mL ampicillin and 35 µg/mL chloramphenicol. Protein expression was then induced by addition of 1 mM isopropyl-1-thio-β-D-galactopyranoside (IPTG), and culture was further grown for 14 h at 20°C. The cells were harvested by centrifugation, resuspended in a Tris-HCl buffer (100 mM Tris-HCl pH 8.0, 150 mM NaCl, 5% glycerol, 1 mM EDTA, 1 mM PMSF), and lysed with an Eaton press (Rassant). The fusion protein was purified using IgG Sepharose Fast Flow (Amersham) and digested on-column with recombinant (His)₆-TEV protease. The cleaved KIN17 domain was further purified on nickel-nitriloacetic acid resin with a Ni-NTA column (Qiagen) to remove the (His)₆-TEV protease as well as the residual (His)₆-ZZ fragment. Because of the cloning strategy, the protein resulting from the cleavage contains the region 51–160 of human KIN17 plus an additional glycine residue at the N terminus. Uniformly labeled ¹⁵N protein was produced in minimum medium M9 containing 1 g.L⁻¹ of (¹⁵NH₄)₂SO₄ (Boehringer) as the sole nitrogen source. Uniformly labeled ¹³C/¹⁵N protein was produced in a rich medium prepared from uniformly labeled ¹³C/¹⁵N *Spirulina maxima* cyanobacteria. The resulting protein was characterized by electrospray ionization mass spectroscopy. NMR samples (~0.7 mM) were prepared in 50 mM phosphate buffer (pH 6.0) containing 150 mM NaCl, 1 mM EDTA, a protease inhibitor cocktail (Sigma), 1 mM TCEP, and 1 mM NaN₃ in either 90% H₂O/10% D₂O or in 100% D₂O. 3-(Trimethylsilyl)[2,2,3,3,3-²H₄] propionate (TSP) was added as an internal ¹H chemical shift reference. ¹³C and ¹⁵N chemical shifts were referenced indirectly to TSP, using the absolute frequency ratios.

NMR spectroscopy and structure calculation

All NMR experiments were performed at 30°C on Bruker AVANCE DMX-600 or VARIAN INOVA-800 spectrometers equipped with a triple resonance cryoprobe. ¹H, ¹⁵N, and ¹³C resonance assignment of human KIN17 region 51–160 has been described previously (Carlier et al. 2006). A ¹⁵N-¹H heteronuclear nOe experiment was carried out at 600 MHz using the classical pulse program (Farrow et al. 1994). Two spectra were acquired in an interleaved fashion with and without saturation (5s), respectively. Uncertainty in the ¹H → ¹⁵N nOe values were calculated from the peak intensity errors estimated from the root mean square baseline noise of both spectra. The ¹H-¹H nuclear Overhauser effect cross-peak volumes used for structure calculation were measured on three NOESY experiments (a ¹⁵N-HSQC-NOESY in H₂O with a 80-ms mixing time and a ¹³C-HSQC-NOESY in D₂O with a 100-ms mixing time recorded at 800 MHz, and a ¹³C-HSQC-NOESY in the ¹³C aromatic region recorded at 600 MHz with a 120-ms mixing time). ϕ and ψ torsion angle values were deduced either from the backbone chemical shifts using the program TALOS (Cornilescu et al. 1999) or from the analysis of the HNHA and HMQC-J experiments. Hydrogen-bond restraints were derived from slowly exchanging amide protons, identified by measuring the amide proton exchange rates from ¹H-¹⁵N HSQC spectra recorded at different times on a protein sample dissolved in D₂O (Supplemental Table S2). Oxygen atoms involved in hydrogen-bond restraints were deduced from the secondary structure determined by the TALOS program and from the β-sheet topology. All spectra were processed with the programs Xwinnmr (Bruker) or NMRPipe (Delaglio et al. 1995) and analyzed using Felix (Accelrys).

The solution structure of human KIN17 region 51–160 was solved on the basis of the analysis of 3413 nOe cross-peaks (1466 were picked on the ¹⁵N-HSQC-NOESY, 1919 on the aliphatic ¹³C-HSQC-NOESY, and 28 on the aromatic ¹³C-HSQC-NOESY, respectively). The semiautomated iterative assignment procedure INCA was applied for nOe assignment and three-dimensional structure construction (Savarin et al. 2001). Structures were calculated using a simulated annealing protocol in CNS 1.0 (Brunger et al. 1998). At the last step, 400 structures were generated using a total of 2743 distance

restraints, 18 hydrogen bonds, 136 ϕ and ψ torsion angle values obtained from TALOS prediction, and 4 ϕ angle values deduced from HNHA and HMQC-J experiments. The 12 best structures were selected and refined with a standard energy function (CHARMM22), including an electrostatic energy term. This term was calculated with no net charge on the side-chain atoms and with a distance-gated dielectric constant

Electronic supplemental material

Supplemental material includes an overview of the NMR restraints used for structure calculation of human KIN17 region 51–160 and a superimposition of this domain onto the X-ray winged helix–DNA structure of three analogous proteins.

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