A Novel S100 Target Conformation Is Revealed by the Solution Structure of the Ca\(^{2+}\)-S100B-TRTK-12 Complex*

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The Alzheimer-linked neural protein S100B is a signaling molecule shown to control the assembly of intermediate filament proteins in a calcium-sensitive manner. Upon binding calcium, a conformational change occurs in S100B exposing a hydrophobic surface for target protein interactions. The synthetic peptide TRTK-12 (TRTKIDWNKILS), derived from random bacteriophage library screening, bears sequence similarity to several intermediate filament proteins and has the highest calcium-dependent affinity of any target molecule for S100B to date (K\(_d\) <1 \(\mu\)M). In this work, the three-dimensional structure of the Ca\(^{2+}\)-S100B-TRTK-12 complex has been determined by NMR spectroscopy. The structure reveals an extended, contiguous hydrophobic surface is formed on Ca\(^{2+}\)-S100B for target interaction. The TRTK-12 peptide adopts a coiled structure that fits into a portion of this surface, anchored at Trp7, and interacts with multiple hydrophobic contacts in helices III and IV of Ca\(^{2+}\)-S100B. This interaction is strikingly different from the \(\alpha\)-helical structures found for other S100 target peptides. By using the TRTK-12 interaction as a guide, in combination with other available S100 target structures, a recognition site on helix I is identified that may act in concert with the TRTK-12-binding site from helices III and IV. This would provide a larger, more complex site to interact with full-length target proteins and would account for the promiscuity observed for S100B target protein interactions.

The S100 proteins are low molecular weight (10–12 kDa) members of the EF-hand family of calcium-binding proteins. Many of these proteins, including several of the S100s, the muscle contractile protein tropomin C, and the ubiquitous protein calmodulin act as signaling molecules by converting an influx of cellular calcium into a biological response. Calcium binding to these EF-hand proteins triggers a conformational change and allows the protein to interact with an appropriate target molecule. The S100 proteins are unique among this family because, unlike troponin C or calmodulin, they exist in solution as homo- or heterodimers. Each S100 monomer contains two helix-loop-helix calcium-binding motifs as follows: a basic N-terminal pseudo EF-hand comprising 14 residues (site I), and a canonical and acidic C-terminal EF-hand of 12 residues (site II). A central linker region joining the two EF-hands along with the extreme N and C termini of these proteins exhibit the most sequence divergence among family members and are therefore believed to provide specificity for target protein interactions. This feature, along with the dimeric state of the S100 proteins, likely indicates these calcium-signaling proteins have the distinctive ability to interact with more than one target molecule at a time.

S100B, a homodimer of 91-residue S100\(\beta\) monomers, is found primarily in glial cells and has been implicated in neurological diseases including Alzheimer's disease and Down's syndrome (1–3). More than 20 calcium-sensitive in vitro binding partners have been identified for S100B (4) including several cellular architecture proteins such as tubulin (5) and GFAP (6), where S100B can inhibit polymerization of these oligomeric molecules. Furthermore, S100B inhibits the phosphorylation of multiple kinase substrates including the Alzheimer protein tau (7, 8) and neuromodulin (GAP-43) (9) through 

The 12-residue peptide TRTK-12, derived from random bacteriophage library experiments, has been used in previous studies as a model for S100B-target protein interactions. Experiments utilizing this peptide have indicated that peptides containing the consensus sequence (R/K)L(I/V)WXXIL bind specifically to S100B in a calcium-sensitive manner (11). Furthermore, this consensus sequence is conservatively found in the cytoskeletal proteins tubulin, desmin, vimentin, and GFAP, shown previously to interact with Ca\(^{2+}\)-S100B (12). The TRTK-12 peptide competes with S100B target proteins including CapZ-\(\alpha\) and GFAP for Ca\(^{2+}\)-S100B binding (6, 11) and has the highest affinity (K\(_d\) ~260 nM) (13) of any known S100B target. Fluorescence studies (13) have shown that Trp\(^7\) of TRTK-12 is a key residue for the calcium-sensitive interaction with S100B becoming buried at the protein-peptide interface. In addition, deletion of residues 85–91 from S100B leads to a >2000-fold decrease in affinity for TRTK-12 indicating the C-terminal helix is an important site of interaction.

To date, only three structures are available for S100-target protein interactions. This paper is available online at http://www.jbc.org.

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The atomic coordinates and structure factors (code 1MQ1) have been deposited in the Protein Data Bank, Research Collaboratory for Structural Bioinformatics, Rutgers University, New Brunswick, NJ (http://www.rcsb.org/).

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The abbreviations used are: S100B, dimeric S100\(\beta\); GFAP, glial fibrillary acidic protein; TRTK-12, acetyl-TRTKIDWNKILS-NH\(_2\); NOE, nuclear Overhauser effect; MOPS, 4-morpholinepropanesulfonic acid.

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peptide complexes. In each case the target peptide adopts a 2.5-

turn α-helical structure that interacts via two distinct modes

with the S100 protein. The structures of human S100A10 and

S100A11 in complex with peptides from the binding regions of

annexin II and I, respectively, are nearly identical (14, 15) with

the annexin peptides bridging the two S100 monomers through

contacts in the linker region and C terminus of one monomer

and the N terminus of the other monomer. Surprisingly, the

similarity of interaction occurs despite little sequence similari-

ty between the annexin peptides. In contrast, the interaction

of rat S100B with a 23-residue peptide from the tumor suppressor

protein p53 shows each S100β monomer binds to a single peptide

through interactions with helix III and a portion of helix IV (16). This orients the α-helical p53 peptide about 90°

from that found for the annexin peptides with respect to their

S100 partners. These structural variations of the S100A10, S100A11, and S100B complexes indicate that recognition differ-

ences in the protein and the target must exist for S100 proteins.

In an effort to clarify these interactions, we present the

three-dimensional solution structure of Ca2+/S100B in complex with the TRTK-12 peptide. The amino acid sequence of

TRTK-12 does not correspond to a natural sequence for any

known S100 target. However, its unusually high affinity for

S100B may indicate that it contains structural determinants

that remain to be uncovered for recognition of an S100 binding

partner. The binding interaction of TRTK-12 is unexpected

with the peptide adopting an extended and reversed orienta-

tion compared with the p53 interaction. Furthermore, there is

no interaction with helix I of S100B as found in the S100A11-

S100A10 annexin structures thus providing a novel third mode

of recognition for an S100-target protein complex.

EXPERIMENTAL PROCEDURES

Sample Preparation—Human S100B protein was expressed in

Escherichia coli (strain N99) and purified as described previously (17). Uniformly 15N-labeled or 15N/13C-labeled S100B was prepared using M9 minimal media containing 1 g/liter 99% 15NH4Cl or 1 g/liter 99%

13C-glucose. Uniformly 15N-labeled S100B was prepared in M9 minimal media containing 1 g/liter 99% 15NH4Cl and 2 g/liter 15C-glucose. Uniformly 15N-labeled S100B and 13C-labeled S100B were synthesized by the Queen

Peptide Synthesis Lab at the University, Kingston, Canada). Purity was confirmed using specifically labeled TRTK-12. Spectra were processed and

assignments for the two isoleucine residues (Ile 5 and Ile10) were con-

firmed using the NMRDraw (24), and Pipp and Stapp (25) programs.

NMR Spectroscopy—NMR experiments were performed at 35

°C on Varian 500-, 600-, and 800-MHz spectrometers with pulsed field gradi-

ent probes. Backbone resonances for Ca2+/S100B in the complex were sequentially assigned using HNCACB (18), CBCA(CO)NH (19), and

HNC0 (20) experiments. Side chain assignments were made using C(CO)NH (21), HCC(CO)NH (21), 15N-edited TOCSY, and HCCH-

TOCSY (22) experiments. Some aromatic ring protons were assigned using HB/BC/GC/HD (23) and HCBC/GC/HE (23) experiments. TRTK-12 1H assignments were determined from homonuclear two-

dimensional NOEY and two-dimensional TOCSY experiments as well as from the C-terminal calcium loop. Several residues in the N-terminal calcium-binding loop have weak (Ser18, Glu21, His25, Lys26, Leu27, and Lys 28) or absent (Ser12, Asp15, Thr19, Lys20, Arg22, and Gly29) amide correlations in the 1H-15N-HSQC spectra. Several residues in the C-terminal calcium-binding loop may indicate that it contains structural determinants that remain to be uncovered for recognition of an S100 binding partner.

RESULTS

Binding of the TRTK-12 peptide has been monitored previ-

ously by NMR and fluorescence spectroscopy and found to have a $K_D = 260 \text{ nM}$ (13). In this work, formation of the complex was measured using a 15N-labeled S100B sample and monitoring the change in resonances as a function of added TRTK-12 peptide. Complex formation was complete at a ratio of 2:1 TRTK-12:S100B indicating that two TRTK-12 peptides bind to each S100B dimer protein. The resulting 1H-15N HSQC spectrum of this complex showed a single set of resonances in the NMR spectra for most residues (Fig. 1) indicating the arrange-

ment of the Ca2+/S100B-TRTK-12 complex dimer is symmet-

ric. Exceptions were noted for residues Ser1, Leu5, Lys6, Ser11, and His22, and which have duplicate peaks resulting from the pres-

ence of formyl and desformyl N-terminal methionine S100B species as observed previously for apo- and Ca2+/S100B (31).

Several residues in the N-terminal calcium-binding loop have

weak (Ser1, Glu3, His5, Lys8, Ser27, and Lys28) or absent (Gly22 and Asp29) amide correlations in the 1H-15N HSQC spectrum likely due to exchange with the H2O solvent. Gly36 shows a substantial downfield 1H shift characteristic of calcium binding to the C-terminal calcium loop. A comparison of this spectrum with that for Ca2+/S100B alone indicated that several residues including Ile47, Val51, Ala52, Ala53, and Cys64 had shifted upon

TRTK-12 binding.

To identify the specific interactions between TRTK-12 and human Ca2+/S100B, the solution structure of the complex (24 kDa) was determined using 2072 experimental distance re-

straints in combination with 536 dihedral and 136 hydrogen
bond restraints. This generated a family of 17 well defined structures (Fig. 2) based on the superposition of the 8 helices in the dimer (root mean square deviation 0.63 ± 0.07) (Table I). The TRTK-12 peptide was well defined between residues 4 and 12 forming a coil structure that folds back on itself. As observed in the rat S100B-p53 structure (16), each S100B monomer binds one TRTK-12 molecule.

Structure of Ca$^{2+}$-S100B in the Complex—Overall, the struc-
Table 1

NMR restraints and structure statistics

| No. experimental restraints (Å) | NOE | Total | 2072 |
|--------------------------------|-----|-------|------|
| Intraresidue                   | 788 |
| Sequential                     | 440 |
| Medium range                   | 406 |
| Long range                     | 292 |
| Intermolecular (dimer interface)| 32  |
| Intermolecular (S100B-TRTK-12 interface) | 56 |
| Dihedral                       | 268 |
| H-bond                         | 136 |
| Rmsd from experimental distance restraints | 0.017 ± 0.0114 |
| Rmsd from experimental dihedral restraints | 0.502 ± 0.1036 |
| Rmsd from idealized covalent geometry | Residues in favored regions | 93.2% |
| Bonds (Å)                      | 0.002 ± 0.0002 |
| Angles (°)                     | 0.435 ± 0.0191 |
| Improper (°)                   | 0.282 ± 0.0221 |
| Lennard-Jones potential energy (kcal mol−1) | −496.36 ± 50.95 |
| Rmsds to the mean structure (Å) | 0.71 ± 0.08 |
| All structured backbone        | 1.13 ± 0.10 |
| All structured heavy atoms     | 2.00 nm indicative of a random coiled structure.

Ca2+–S100B–TRTK-12 Structure

Structure of S100B in the TRTK-12 complex retains many structural features of the calcium-bound form alone (32). The dimer interface is characterized by antiparallel interactions between helices I and I’ (interhelical angle (Ω) = 164 ± 4°) and helices IV and IV’ (Ω = 172 ± 4°) forming an X-type four helix bundle (Fig. 2). Each S100β monomer consists of an N-terminal pseudo EF-hand motif (site I) comprising helix I (Leu10–Tyr17), calcium binding loop I (Ser38–Glu41), and helix II (Ser59–Glu62) and a C-terminal canonical EF-hand (site II) comprising helix III (Glu92–Leu106), calcium binding loop II (Asp111-Glu115) and helix IV (Phe123–Cys144). Calcium binding loops I and II are associated through a short antiparallel β-sheet (Lys36–Lys43 and Glu67–Asp89). The arrangement of helices I and II in site I (Ω = 129 ± 3°) is similar to that of Ca2+–S100B (Ω = 138 ± 4°) and calbindin D9k (Ω = 130 ± 2°), indicating that TRTK-12 binding to Ca2+–S100B results in little conformational change to this region. In contrast, significant changes are identified in site II. The helix III–IV interhelical angle (Ω = 104 ± 4°) is dramatically opened by more than 90° than found in apo-S100B (Ω = −166 ± 1°). Furthermore, the arrangement of helices III–IV shows distinct differences from human Ca2+–S100B (Ω = 148 ± 4°) being more similar to the III–IV arrangement found in the S100A11-annexin I complex (Ω = 103°) and more “open” compared with either the S100B-p53 (Ω = 110 ± 1°) or S100A10-annexin II (Ω = 117°) complexes. These observations suggest that the relative orientations of helices III and IV may be a governing factor for target specificity.

Structure of TRTK-12 in the Complex—Our previous studies (33) have shown that the TRTK-12 peptide is unstructured in the absence of Ca2+–S100B. Consistent with this, the circular dichroism spectrum of TRTK-12 (Fig. 3) showed an ellipticity minimum at 200 nm indicative of a random coiled structure. Upon binding, TRTK-12 assumes a coiled conformation that folds back upon itself (Fig. 2). The structure determination of TRTK-12 was aided by using a peptide having uniform13C-labeling at Ile5 and Ile10 and the N-terminal acetyl CH3 positions thus providing 13C markers throughout the peptide length. The coiled structure of TRTK-12 was supported by definitive NOEs between the side chains of residues Trp7–

Leu11, and peptide spectra were characterized by an absence of α-helical NOEs and α-proton (and αC) for Ile5 and Ile10 chemical shifts not consistent with α-helical structure. These findings are supported by CD spectra of Ca2+–S100B (50 μM) and TRTK-12 (100 μM) consistent with the binding of one TRTK-12 peptide for each S100β monomer.

Ca2+–S100B–TRTK-12 Interactions—The interaction between Ca2+–S100B and TRTK-12 is defined by several residues in
helix III (Val 52, Lys 55, Val 56, Thr 59, and Leu 60) and helix IV (Phe 76, Ala 80, Ala 83, and Cys 84). In particular, 13C-labeled Ile5 and Ile10 revealed definitive interactions to residues Thr82 in helix IV and Val52 and Val56 in helix III, respectively (Fig. 4). Furthermore, residues Lys9, Ile10, and Leu11 in the C terminus of TRTK-12 have multiple contacts in helix III, and Thr1, Thr3, and Lys4 are in close proximity to Ala83 in helix IV. These interactions position the N terminus of the TRTK-12 peptide near helix IV and the C terminus near helix III resulting in a peptide orientation opposite to that observed for the S100B-p53 complex. Although 13C labeling of the N-terminal acetyl group in TRTK-12 was used, no observable peptide-protein cross-peaks resulting from this label were observed in 13C-edited NOE spectra, indicating the extreme N terminus of TRTK-12 is exposed to solvent and does not interact with residues in helix I as the annexin peptides do in the S100A10 and S100A11 structures. A large hydrophobic cavity exists on Ca2+-S100B alone and in complex with TRTK-12 shows the side chains of Val56, Thr59, and Ala63 decrease their surface exposure by 86, 96, and 99%, respectively, upon TRTK-12 binding. Similarly, residues Trp7 and Ile10 of TRTK-12 have more than 84 and 90%, respectively, of their surface area buried in the complex. Recent fluorescence studies of the S100B-TRTK-12 interaction have indicated that deletion of the C-terminal 7 residues in S100B results in a drastic decrease in TRTK-12 binding affinity (13). This was attributed to a loss in α-helical structure near Ala83 in the truncated S100B protein. Presumably this would considerably alter the arrangement of residues Val80, Ala83, and Cys84 resulting in a significantly reduced affinity.

DISCUSSION

Examination of the structure of Ca2+-S100B-TRTK-12 and comparison to the existing structures of S100A10-annexin II, S100A11-annexin I, and S100B-p53 allows a distinction to be made between target recognition by these S100 proteins. Further
thermore, the TRTK-12 sequence was identified from random bacteriophage peptide selection and therefore may contain unique binding features in comparison to the natural sequences for the annexin and p53 peptides. In the current structure, the TRTK-12 peptide lies in a hydrophobic cleft formed between helices III and IV maximizing the interaction of the hydrophobic residues Ile6, Trp7, Ile13, and Leu11 with residues in both helices of S100B. Nearly all the interaction is hydrophobic in nature reaffirming earlier work that the S100B-TRTK-12 interaction is tighter at increased ionic strength (13).

The interaction is distinct from that of the rat S100B-p53 peptide (16), likely due to the sequence differences of the interacting peptides. The target sequence for p53 (SRHKKLMFKT) bears little similarity to TRTK-12 containing a highly positively charged C terminus that orients near the highly acidic N terminus of helix III (E1K1E1Q1E1). In contrast, the charged residues in TRTK-12 are more dispersed throughout its sequence and most are occupied through potential hydrogen-bonding interactions. Nevertheless, some similarities between the target peptide molecules exist. The anchoring residues for the p53 peptide are Leu13 and Phe16, spaced only one residue apart, as are Ile6 and Trp7 in TRTK-12. The distinguishing feature of these two residues in each peptide is their positions with respect to S100B. In the current work Trp7 is positioned in an analogous region to Leu13 in p53, whereas the side chain of Ile6 is located nearby that of Phe16 in p53, albeit somewhat shifted due to a different orientation. The reverse nature of these two interactions together with the differential charge balance in the peptides likely results in the reversal of orientation of TRTK-12 to p53 upon binding to S100B.

The regions of interaction of TRTK-12 and p53 differ significantly from that of both annexin I and II with S100A11 and S100A10, respectively. Both of the annexin peptides have interactions with several residues in the N-terminal helix I of these S100 proteins (Fig. 6A). An examination of the sequences and interactions reveals three key residues in the annexin peptides (Val9, Glu13, and Leu16) that have identical interactions with the N-terminal residues Glu13, Met12, Glu13, and Met12 in S100A10 (Glu13, Ile12, Glu13, and Ile16 in S100A11). This pattern in the target peptide, where two hydrophobes are separated by three residues, including a central acidic residue, is not found in either the TRTK-12 or p53 peptides. Furthermore, the side chain carboxylate of Glu13 in S100A10 (Glu13 in S100A11) has conserved hydrogen bonds to the Thr5 and Val3 amides in annexin II (Met2 and Val3, in S100A11). In S100B the position of Glu13 (Glu13) is held by a hydrophobe (Val9) removing its side chain hydrogen bonding ability. Interestingly, this position is among the least conserved within the S100 protein family. This sequence divergence in both the S100B and S100A10/S100A11 proteins and in the peptide motif is likely responsible for the different target peptide recognition sites between the proteins. Consistent with this, previous experiments have shown that TRTK-12 shows no observable interaction with S100A11 (33) when monitored by Trp7 fluorescence.

The interaction of Trp7 in TRTK-12 likely contributes to the tightest binding for any S100B target to date. It is also interesting that replacement of Phe16 in the p53 peptide with a Trp residue increases its affinity for rat S100B by about 5-fold (34). In addition, important similarities exist between the environments of Trp7 (TRTK-12) and Trp11 (annexin I) even though the orientation of the two target peptides is different with respect to the protein helices in each complex. A comparison of the anchoring Trp7 of TRTK-12 reveals side chain interactions (<6.5 Å) with Ile8, Val25, and Val26 in a majority of the NMR structures. The analogous interactions, involving Glu52, Val57, and Met51 exist for S100A11 (Fig. 6B). Despite this similarity, the differences of the peptide orientations for TRTK-12 and annexin I result in a significant hydrophobic surface for each protein that remains exposed, even in the presence of the bound peptide (Fig. 5A and Fig. 6C). This may occur simply because the target peptides presently used are too short or that the interaction can be modulated through a second region of interaction. As a result, it has been suggested recently (35) that S100 proteins may bind full-length targets using more than one site. The similarity of the locations for Trp7 (TRTK-12) and Trp11 (annexin I) would provide a unique bridging residue to encompass a larger, contiguous binding region that includes an α-helical annexin type interaction, utilizing the VEL residues found in annexin I and II, and an extended TRTK-12 type interaction based on hydrophobic interactions anchored by Trp7 (Fig. 6C). It is interesting that the recent structure of the calmodulin-calmodulin kinase kinase peptide complex displays exactly these features, where the N-terminal portion of the peptide forms an α-helical structure and the C-terminal region is more extended (36), folding back on the helix in addition to having important protein contacts. As in calmodulin, this larger interaction site would also provide a rationale for the promiscuity of S100B target interactions, including cellular architecture proteins such as tubulin, vimentin, desmin, GFAP, and caldesmon, which contain the TRTK-12 consensus motif (12). It remains to be seen whether the natural sequences for the interm-
ate filament proteins interact in a similar manner as TRTK-12 or via the α-helical mode found for either annexin or p53 peptides.

**Coordinates**—Chemical shift assignments for S100B and TRTK-12 in the complex have been deposited in the BioMagResBank (accession number 5377).

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