S100A16, an unknown member of the S100 family

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S-100 protein is a type of low molecular weight protein found in vertebrates characterized by two calcium binding sites of the helix-loop-helix ("EF-hand type") conformation. There are at least 21 different types of S100 proteins. The name is derived from the fact that the protein is 100% Soluble in ammonium sulfate at neutral pH. Twenty members have been identified so far, and altogether, S100 proteins represent the largest subgroup in the EF-hand Ca²⁺-binding protein family.

These proteins regulate intracellular processes such as cell growth and motility, cell cycle regulation, transcription and differentiation. Because of its abundance in the nervous system and owing to the limited sensitivity of the immunological methods in earlier sixties S100 (1) was regarded as a brain specific protein restricted to glial cells. Several members of this family were discovered and located having various cellular distribution such as glial cell of the central peripheral nervous systems, melanocytes, chondrocytes, adipocytes (S100B)(2-4), cardiomocytes, salivary epithelial cells, renal cells (S100A1) (2-4), lung and kidney (S100A2) (2-4), firoblasts (S100A4, S100A6, S100A10) (2-4), myoepithelial cells(S100A4) (2-4), tumor cells (S100B, S100A4, S100A6) (2-4), epithelial cells (S100A7, S100A8, S100A9, S100A12) (2-4), smooth ad heart muscle cells (S100A2, S100A4, S100A6, S100A11) (2-4), placentia (S100P) (2-4), epithelial lesions (S100A5).

All S100 proteins are composed of two EF-hand motifs flanked by conserved hydrophobic residues and separated by a linker region (4). The EF-hand loop closest to the C-terminus is 12 residues long and is referred to as the canonical EF-hand. This binding site has generally much higher affinity for calcium than the 14 residue N-terminal EF-hand loop, which is also called the variant EF-hand. The variant EF-hand is particular to the S100 proteins and is rich in basic amino acids (5). It is thought that calcium initially binds to the canonical EF-hand causing exposure of a C-terminal hydrophobic domain. Only at much higher calcium concentration, the variant EF-hand gets occupied, and this has been suggested to happen upon secretion of the proteins to the extracellular space (6). In the N-terminal EF-hand, calcium is primarily bound by main chain carbonyl oxygen’s, but this pattern in not conserved for all members of the S100 family, hence the name variant EF-hand. S100 proteins show a very divergent pattern of cell- and tissue-specific expression, of subcellular localizations and relocations, of post-translational modifications, and of affinities for Ca²⁺, Zn²⁺, and Cu²⁺, consistent with their pleiotropic intra- and extracellular functions. Up to 40 target proteins are reported to interact with S100 proteins and for S100A1 alone 15 target proteins are presently known. It is not unlikely that their biological activity in some cases is regulated by Zn²⁺ and Cu²⁺ rather than by Ca²⁺.

Despite the numerous putative functions of S100 proteins, their three-dimensional structures of, e.g., S100B, S100A6, and S100A7 (7-9) are surprisingly similar. They contain a compact dimerization domain whose conformation is rather insensitive to Ca²⁺ binding and two lateral a-helices III and III, which project outward of each subunit when Ca²⁺ is bound. Target docking depends on the two hydrophobic patches in front of the paired EF-hand generated by the binding of Ca²⁺. The selectivity in target binding is assured by the central linker between the two EF-hands and the C-terminal tail. It appears that the S100-binding domain in some target proteins contains a basic amphiphilic a-helix and that the mode of interaction and activation bears structural similarity to that of calmodulin. In many cases the interaction to an S100 protein with its target proteins and regulatory effects of an S100 protein on cellular activities were also observed to occur at free Ca²⁺ concentrations significantly lower than those at which half maximal binding of Ca²⁺ to an S100 protein in solution was detected. All these observations indicate to the occurrence of large conformational changes or variety of conformational states of different S100 proteins in presence of Ca²⁺ and target proteins. Despite of their immense importance in neurological disorders (S100B- Alzheimer disease, Down syndrome, and epilepsy) (10-11), inflammatory disorders (S100A8/A9 cystic fibrosis, arthritis and chronic bronchitis) (12-14), and certain cancers (S100A2/A4/A6) (15-17), in the control of cell growth and proliferation (18), cell cycle progression (19), and modulation of specific signal transduction pathways this particular family of proteins has not yet been studied to that extent. Several structures of S100 proteins has been already studied.
however many of them are undone and no information is available regarding their interaction to the target proteins.

Crystals of metal-free S100A16 have been obtained from PEG3350 solutions containing citrate anions of different metals. The morphology of the crystals is hexagonal (P63) and the resolution is generally around 2.0 Å. Several good datasets have been collected at BW7A at a standard remote wavelength trusting that molecular replacement would solve the phase problem. The best models available show only about 30% homology to S100A16 sequence; for this reason molecular replacement failed in giving a solution. So several derivative crystals have been grown and several SAD datasets have been collected at Hg, Cd, Zn and Cu edge. Data processing and structure solution is now in progress and from preliminary statistics it seems likely that it can be solved.

References