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The CBS Domain: Its Structure, Ligand Binding, and Emerging Role in Regulation

Review Article

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Abstract

Background: Cystathionine β-synthase (CBS) domains are structurally conserved motifs that are present in the proteomes of species from all kingdoms of life. Signifying their importance are the hereditary diseases resulting from mutations within the CBS sequence. They are usually encoded in tandem within a plethora of non-functionally related cytosolic or transmembrane proteins, often intramolecularly dimerizing to afford what is known as a CBS pair or Bateman module. It is also known that these CBS pairs can further multimerize to form higher-order assemblies, which have functions that remain to be elucidated. Moreover, a wide range of adenosyl ligands, divalent cations and nucleic acids have been documented to bind CBS domains and induce conformational changes to the larger protein in which they reside, thus suggesting their involvement in protein regulation in response to intracellular energy status.

Methods: This review was written based on the existing data currently available in the literature and included findings from 44 papers. Selection of papers was based on those that provided up-to-date information on the structural characteristics of CBS domains and their involvement in protein regulation.

Summary: This review aims to conceptualize the architectural characteristics of CBS domains, the structural basis of ligand binding, and its involvement in the regulation of protein function.

Introduction

Cystathionine β-synthase (CBS) domains are small, evolutionarily conserved motifs, consisting of approximately 60 residues associated in tandem repeats. (1) They are known to be widespread throughout all living species (InterPro IPR000644), either as independent proteins or as fusions with cytosolic, nuclear or transmembrane domains. (2) These proteins were initially identified in the archaebacterium *Methanococcus jannaschii* by Alexander Bateman in 1997, through a serendipitous discovery made from his investigation on the homocystinuria-causing enzyme cystathionine β-synthase, from which its name was conceived. (3) CBS domains have since been identified in numerous non-functionally related proteins, with 134,987 protein matches across all species within the EBI registry, as shown in Table 1. (2) They are considered to be adenosine oligophosphate-sensing modules, due to their capacity to regulate protein function in response to fluctuations in cellular energy levels; however, their specific function remains to be elucidated. (4) For instance, CBS domains have been noted to be involved in osmoregulation (5) and in the binding or transport of Mg^{2+} across membranes (6), as seen in several magnesium transporters, a few of which are the mammalian CNNMs (7), and the bacterial MgtE and CorC. (8) They are also known to be involved in the intracellular modulation of chloride channel trafficking (9), in nitrate transport, and as internal inhibitors of inorganic pyrophosphatases. (10)

To date, there are upwards of 120 solved crystal structures for the CBS domain, which all demonstrate an association between contiguous CBS motifs to form what is often referred to as a CBS pair or Bateman module. (11) Furthermore, CBS domains have been shown to bind adenosyl ligands and their derivatives with widely varying affinities and stoichiometries, often inducing conformational rearrangements depending on the construct being studied. (12) CBS modules are attributed with oligomerization into higher-order assemblies, an additional mode of regulation. This mode of regulation confers increased stability and solvent accessibility of certain interstices to ligands. (13) Interestingly, several hereditary diseases have been associated with mutations in the CBS sequence. For instance, mutations in inosine-5'-monophosphate dehydrogenase (IMPDH) lead to retinitis pigmentosa (14); chloride channel (ClC) mutations cause hypercalciuric nephrolithiasis, among other deleterious conditions (15); mutations within the γ-2 subunit of AMP-activated kinase (AMPK) lead to familial hypertrophic cardiomyopathy with Wolff-Parkinson-White syndrome; (16) homocystinuria is caused by mutations within the CBS enzyme; (17) and Bartter syndrome results from mutations within ClC-Kb, (18) osteopetrosis from mutations in ClC-7 (19), and Dent's disease from mutations within ClC-5. (20) This list of diseases emphasizes the (patho)physiological importance of CBS domains as a target for rational drug design. In this review, we aim to discuss the structural and functional characteristics of the CBS domain to better conceptualize their ligand binding and regulatory activity, which may provide useful insight into developing compounds of medicinal interest.

Table 1: Widespread Distribution of CBS Domains Across Various Phylae

Species	No. of Proteins With CBS Domains
Viruses	1
Prokarya	118,813
Archaea	6,654
Eubacteria	112,159
Escherichia coli (Strain K12)	9
Eukarya	16,174
Plantae	
Oryza savita (Asian rice)	99
Arabidopsis thaliana	76
Chordata	
Homo sapiens	87
Mus musculus (Mouse)	67
Danio rerio (Zebrafish)	57
Arthropoda	
Drosophila melanogaster	25
Nematoda	
Caenorhabditis elegans	39
Fungi	
Saccharomyces cerevisiae	10

*Data were obtained from http://www.ebi.ac.uk/interpro/entry/IPR000644/taxonomy.

Conserved Structural Characteristics of CBS Domain

Despite their low level of sequence homology, all CBS domains maintain oligomeric folds consisting of three-stranded β-sheets, where β1 and β2 run parallel to each other and antiparallel to β3, with two α-helices arranged in a β1-α1-β2-β3-α2 topology. (21) Its overall folding is somewhat irregular pyramidal, whereby the loop connecting β1-β2 defines the apex, and helices α1 and α2 make up its base. (22) Additionally, there is always a flexible linker that precedes β1, and most often contains at its N-terminus one turn of a helix, denoted by α0. (22) Tandem CBS motifs preferentially associate into a dimeric state forming what is referred to as a CBS pair or Bateman module, with pseudo-C_2 symmetry running parallel to the central β-sheets. (23) There are numerous examples of these CBS pairs undergoing further multimerization to form higher-order structures, thus emphasizing the many possible combinations that can be achieved and the consequent diversity of functions that arise from this variability. The flexible linkers containing the α0 helical turn are integrated well into the adjacent CBS motif due to the tight antiparallel association between the α-helices and β-sheets lining the dimerization interface. (22)

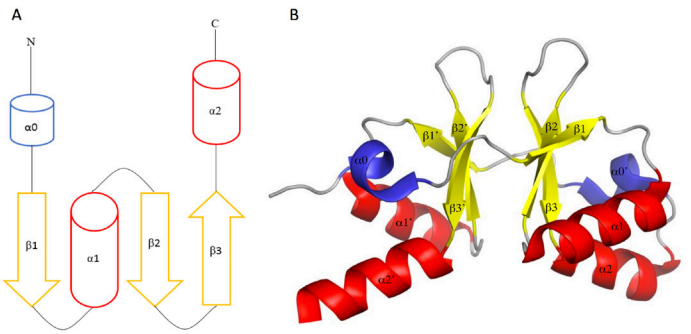

Fig. 1: The Structural Features of CBS Domains. (A) The topology of the CBS motif consists of an α0 helix (blue), helices α1 and α2 (red) and β sheets 1, 2 and 3 (yellow). (B) The CBS pair is represented with an irregular pyramid fold, where helices α1 and α2 make up the base and the loop connecting β1-2 denote the apex. PDB ID: 3KPC.

Crystallographic studies have revealed that CBS domains are not part of the catalytic core. Rather, CBS domains reside on the periphery of enzyme complexes, suggesting that they do not participate in enzymatic catalysis but rather in regulation. (24) Truncation experiments validated this assertion, whereby enzymes missing the CBS domain retained their catalytic activity, but lost their regulatory capacity. (25) Such examples include *Streptococcus pyogenes* IMPDH, which catalyzes the rate-limiting step in de novo guanine nucleotide biosynthesis, and consists of both a TIM barrel that embodies the catalytic framework and a CBS pair at its periphery. (26) The latter acts as an accessory domain that confers to the enzyme the ability to be *trans*-regulated by adenosyl ligands, thus coupling GTP/dGTP production to cellular energy status. (27) As shown in mutagenesis studies, deletion of the CBS domain does not impair the *in vitro* catalytic activity; however, it does result in loss of sensitivity to nucleotides. (22) The capacity of CBS domains to bind a wide variety of nucleotides may contribute to the number of effector signals that it is capable of transducing, emphasizing the importance in characterizing its ligands.

Ligans and Their Binding Site

CBS motifs have attracted considerable attention in recent years due to their regulatory role in enzyme complexes of pathological significance. Perhaps even more interestingly, CBS motifs have been documented to bind a myriad of adenosyl ligands in conserved locations, allosterically regulating the activity of the catalytic core. (28) Solved Bateman module crystal structures reveal a cleft at the CBS pair dimerization interface, which has been found to bear two ligand binding sites, S1 and S2, respectively. (29) Therefore, the number of binding sites is equal to the number of CBS motifs within the protein. (29)

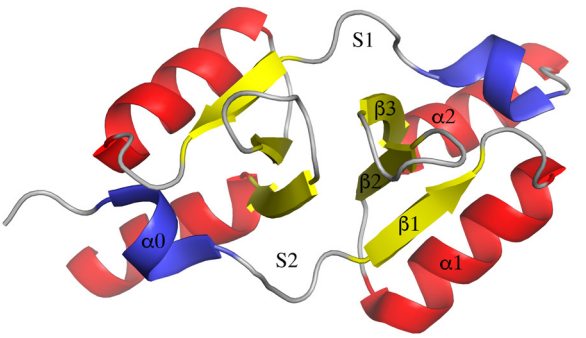

Fig. 2: An Apical View of the S1 and S2 Ligand Binding Sites within the CBS Pair. An apical view of the CBS pair is represented, indicating the positions of the two canonical ligand binding sites, S1 and S2. Shown in blue are α0, in red α1-2 and in yellow β1-3 for each CBS motif in the pair. PDB ID: 3KPC.

Each of these binding sites consists of three subsections, which confer ligand binding selectivity (i.e. preference for one base over another), sensitivity to ligand energy-charge (i.e. the number of appending phosphate substituents) and the orientation of the ligand within the cavity. The first section comprises the residues of the flexible linker region preceding β1, which has been found to show the most sequence diversity and inconsistency in terms of length across CBS-containing proteins. (22) The N-terminal α0 helix and the residues immediately preceding β1 within this flexible linker are well nested into the adjacent CBS motif and serve to maintain the hydrophobic contacts between residues at the dimerization interface. (22) Between these two points are several key residues. The first residue is a conserved serine or threonine that hydrogen bonds with the hydroxyl substituents of the ribose moiety. The second is centered in the middle of the linker and confers the selectivity of adenosyl derivatives over its guanine counterparts by orienting its main-chain carbonyl oxygen towards C2 of the adenine ring as to sterically hinder the recruitment of guanine, which contains an amino group at that position. (22) The third residue is positioned two residues further down the chain from the second key residue and also confers adenine selectivity through hydrogen bonding between its carbonyl oxygen and the N6-amino group. (22) The second section contains residues found within the loop between α1 and β2. This region bears hydrophobic residues that accommodate the purine ring through exclusion of water. (29) In some cases, the carbonyls of polar residues can interact with the exocyclic N6-amino group on the adenine ring. (29) The last section, making up the remainder of the interstice contact surface, includes the first two turns of α2 with the entirety of β3. (22) This section contains a G-h-x-S/T-x-S/T-D motif that functions in ribose-phosphate recognition, where h denotes a hydrophobic residue, x is any residue and G, S, T and D are their corresponding amino acids, respectively. (29) The highly conserved aspartate has been shown in some instances to be substituted by asparagine and instead functions in hydrogen bonding to the hydroxyl substituents of the ribofuranose moiety. (29)

Numerous research groups have documented that these cavities interact with a plethora of adenosyl derivatives with both varying affinities and stoichiometries. These derivatives include ligands such as AMP, ADP, ATP, diadenosine polyphosphate (ApnA), nicotinamide adenine dinucleotide (NAD), S-adenosyl methionine (SAM), 5'-deoxy-5'-methylthioadenosine (MTA), adenosine 5'-(β,γ-imido)triphosphate (AMP-PNP) and 5-amino-imidazole-4-carboxamide ribonucleotide (AICAR). (10,29,30) The structures of these ligands are provided in Fig. 3.

Additionally, CBS motifs have also been shown to bind divalent cations and nucleic acids. (31) In vitro studies reveal that Mg^{2+}, Mn^{2+} and Zn^{2+} are all found to accompany ATP within the binding cavity, serving to stabilize the anionic electrostatic repulsion between phosphate groups. (32,33) These cations have also been found to bind single-stranded DNA and RNA, and

in some cases have even been shown to associate with double-stranded DNA. (34) There is clearly much that has yet to be understood, presenting a new avenue of research in determining the many possible ligands and their modes of binding.

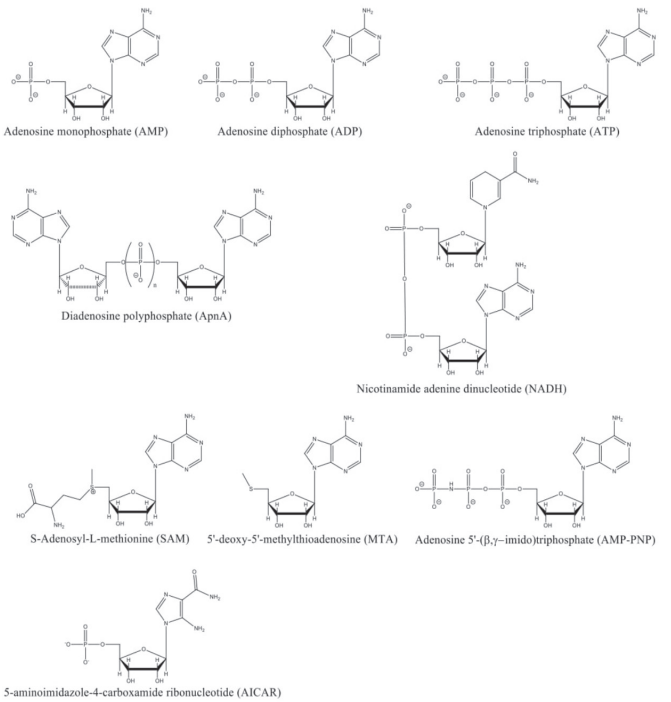

Fig. 3: The Structures of Adenosyl Derivatives known to bind CBS Motifs. The structures provided illustrate the wide variability of possible adenosyl-derived ligands that can bind CBS domains.

Dimerization/oligomerization modes of CBS pairs

Approximately 50-70% of all known protein structures self-assemble to form homomeric species, emphasizing its importance in functioning biological systems. (35) From an evolutionary standpoint, selection of the oligomerization property of proteins has allowed for increased stability, control over the solvent accessibility of certain sites, specificity of certain sites for ligands, and restriction of enzyme activity when necessary. In recent years, CBS pairs have also been found to associate with other such modules, forming higher-order assemblies. Studies conducted on the hyperthermophilic *Methanocaldococcus jannaschii* CBS-containing protein MJ0729 have proposed that its oligomerization state is pH-dependent. (36) MJ0729 is a 124 residue protein of 14.3 kDa that is thought to be involved in the regulation of the electron transport chain, although its specific function remains to be elucidated. (36) At a pH less than 2.5 and with the use of hydrodynamic and spectroscopic techniques in, the protein has been demonstrated to exist in a high oligomeric molten globular state. (36) At pHs within the range of 4.5-5.3, the species undergoes dissociation into an oblong tetrameric state. (36) This dissociation has been postulated to be caused by the titration of key aspartic acid or glutamic acid residues which provoke the switching between α-helix and β-sheet secondary structures, resulting in gain or loss of multimerization contact surfaces. At physiological pH, and even up to pH 9, the elongated dimeric species predominates. These findings are consistent with the observation that most proteins known to harbour a CBS domain exist predominantly in a dimeric state at physiological pH.

Certain eukaryotic proteins, including the γ-subunit of AMP activated protein kinase (AMPK), contain four contiguous CBS motifs within their primary sequence that associate to form two Bateman modules joined together by a linker of variable length. (37) This arrangement consequently only allows for the formation of parallel CBS modules, also referred to as a head-to-head orientation. (22) In 95% of cases, the linker is too short to accommodate an anti-parallel, or head-to-tail, orientation due to the physical strain which limits the potential reorientation of the Bateman modules, thus significantly favouring the abundance of the parallel species. (22)

Bacterial magnesium transporter MgtE is a notable example of how CBS pair oligomerization states regulate the transmission of an effector signal to the protein core. Under conditions of low Mg^{2+} concentration, the two CBS pairs associate to form a disc-like, flat-parallel module that suffers less compaction at its dimerization interface compared with the Mg^{2+} bound form. (38) This association is due to the repulsive electrostatic forces imparted by the α-helical acidic clusters within the ligand binding interstice that would otherwise be stabilized by a Mg^{2+} ion. Conversely, under conditions of high Mg^{2+} concentrations, the metal ion binds these clusters, effectively constricting the crevice, resulting in a transition from a flat-open to flat-closed conformation. This rearrangement causes movement of a long α-helix bridging the CBS and transmembrane domains which results in opening of the ion channel. The prevalence of these architectural features in which CBS domains confer regulation to larger proteins by forming higher-order assemblies emphasizes their versatility and indispensability in biological systems.

Cystathionine β-synthase regulation by CBS modulatory domains

To better conceptualize the molecular mechanisms involved in the regulation of enzymes by CBS domains, we turn to the example of Cystathionine β-synthase. Human CBS (*h*CBS) is a 61 kDa pyridoxal-5'-phosphate (PLP) dependent enzyme that catalyzes the condensation of L-serine with L-homocysteine to form cystathionine. (2) CBS therefore plays a pivotal role in mammalian sulfur metabolism, lying at the junction of the transsulfuration pathway whereby homocysteine is either converted to methionine or used in the production of cysteine. This positioning of the CBS domain proves to be a critical determinant in how sulfur is distributed endogenously. (39)

The *h*CBS enzyme consists of three structurally distinct domains: an N-terminal domain bearing a heme moiety which is thought to act in redox sensing; a central domain that confers PLP dependent modulation; and a C-terminal domain containing a Bateman module which allows for CBS pair homotetramerization *in vivo*. (40) The CBS pair domain has also been postulated to regulate enzyme function intrasterically and allosterically through the binding of S-adenosyl-methionine (SAM). (2) SAM was verified to bind with a dissociation constant (K_D) of 34 μM and to induce a conformational change that abates this subunit's association with the catalytic core, thus facilitating substrate binding and increasing enzyme activity approximately three-fold. (41) As depicted in Fig. 4, the binding of SAM brings both CBS pairs within close proximity at the internal axis of symmetry, consequently resulting in breakage of the hydrogen bonds formed between key residues T460, N463, S466, and Y484 with loop L191-202 residues R196, D198, S199, P200, and E201 on the catalytic core.

This conformational change relieves the occlusion at the entrance of the catalytic pocket and releases the autoinhibitory clamp on the protein core allowing for binding of substrate, as shown in Fig. 5. These crystallographic findings have been confirmed by mutagenesis studies on some of the key residues lining the pocket. For example, S466L, as reported by *Janosik et al.*, has been shown to compromise SAM sensitivity. (42) The overall fold of the protein core does not undergo any major structural rearrangements. This enzymatic reaction proves to be critical in the biosynthesis of cysteine by providing a regulatory control point for SAM. (42) At low concentrations of SAM, CBS pair activity is diminished, resulting in an accumulation of homocysteine which funnels toward the production of SAM. (43) Conversely, at high concentrations, CBS pair activity increases resulting in the clearance of homocysteine and the increase of cysteine production. (43)

In humans, there are currently 150 known loss-of-function mutations within the CBS gene that lead to homocystinuria, a marked accumulation of homocysteine manifesting itself in connective tissue defects, skeletal deformities, vascular thrombosis, and mental retardation. (44) Some of these CBS point mutations, including I435T, D444N, and S466L, can oc-

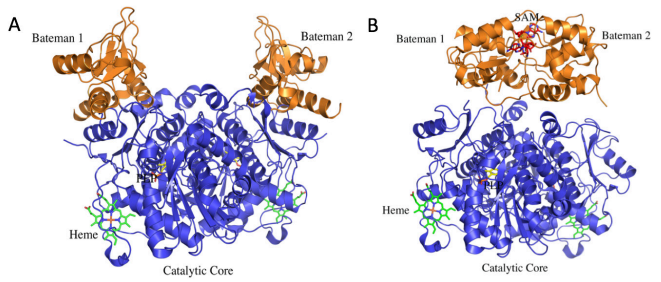

Fig. 4: The Structural Rearrangement of Human Cystathionine β-synthase upon Binding of SAM. The two CBS pair domains are featured in orange, and the catalytic core in blue. (A) In its unbound state, the two CBS pairs are distal from each other. PDB ID 4L0D. (B) When bound to SAM at its CBS module, the CBS pairs join at the central axis. The overall conformation of the catalytic core does not change. Shown in yellow is PLP, and in green are the heme moieties. PDB ID 4PCU.

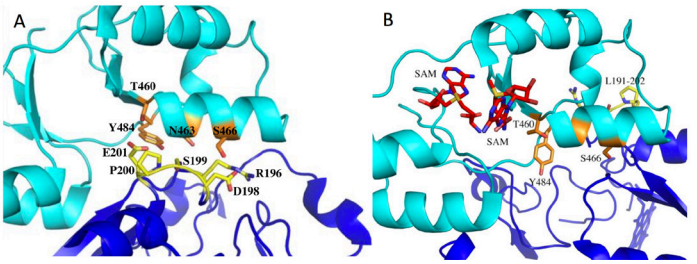

Fig. 5: Interaction between the CBS domain and the catalytic core within *h*CBS in the SAM bound state. (A) In the unbound state, key residues T460, Y484, N463 and S466 (orange) from the CBS domain interact with residues from the L191-202 loop (yellow), thus occluding the binding of SAM. (B) The binding of SAM causes a conformational change that disrupts the interactions between the residues on the CBS domain and L191-202, thus relieving the autoinhibitory clamp on the catalytic core.

cur in both domains and lead to either a dramatic decrease or complete loss of SAM activation. (42) Intriguingly, there are many other mutations that do not interfere with binding of SAM and still manage to impinge on enzymatic activation, suggesting that further studies are required to better understand this regulatory mechanism (42).

Conclusion

The current available information on the CBS domain reveals that its best-known feature is its tertiary structure. Indeed, these small motifs share poor sequence identity, yet have consistently shown through numerous examples of proteins from all kingdoms of life, to maintain a conserved three-dimensional structure. These motifs are often found in tandem, and associate to form what is known as a CBS pair or Bateman module. Furthermore, higher-order assemblies of CBS domains have been documented, and are thought to be peripheral units that relay signals from the intracellular environment to the protein core. Interestingly, careful studies of these domains reveal a cleft harbouring two ligand binding sites, S1 and S2. These canonical sites have been found to accommodate a wide variety of adenosyl derivatives as a means of sensing intracellular energy status, and in some particular cases have even been shown to interact with numerous divalent cations and nucleic acids. Indeed, there are many deleterious mutations within these domains that interfere with their ligand binding activity, consequently resulting in disease. Even though a relationship between the individual domains relaying signals and their larger protein structure has increased our understanding of the CBS domains, there is much that is still not understood. More investigation is required to decipher the rules governing the different modes of association of the Bateman modules, the identification and characterization of the chemical properties of their binding sites, and the structural effects induced by ligand binding. Once thought to be simple and obscure, CBS motifs have unveiled their involvement in certain pathologies, making them promising targets for therapeutic intervention.

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