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Large Conformational Changes and Molecular Recognition in Signal Transduction: Calmodulin and Active Transport/Chemosensory Receptors

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Calmodulin: very large conformation change of helix uncoiling, hinge-bending and domain rotation.

Calmodulin (CaM) is the principal Ca^{2+}-dependent regulator of a variety of important eukaryotic cellular processes. In many of these processes, calmodulin activates a plethora of target enzymes, and the calmodulin-binding domains in several targets have been shown to residue in a region of about 18-residue peptide segment. The domains have very little sequence identity or similarity. Synthetic target segments/peptides and natural peptide potent inhibitors have been shown to bind calmodulin in a Ca^{2+}-dependent manner with similar stoichiometry (1:1) and affinity (in the nanomolar range) as the native target enzymes/proteins.

We have determined 4x-ray structures of Ca^{2+}-CaM bound to different two target peptides from smooth muscle myosin light chain kinase (smMLCK) and brain CaM-dependent protein kinase II (CaMK II)and two natural peptides. These structures show how the central helix connecting the two domains in the native structures uncoils differently in order to position the two domains and engulf the peptides.

Receptors : hinge-bending motion between two domains.

These receptors, located in the periplasm or cell surface of bacteria, serve as initial component of active transport for a wide variety of nutrients and chemotaxis toward some nutrients.
Each receptor binds specific or very similar ligands with Kds in the micromolar range and interacts with cytoplasmic membrane proteins distinct for active transport or chemotaxis. These periplasmic

receptors (totaling about 50)lack sequence similarity and uniformity in size (25 KDa to 58 KDa). Nevertheless, the 14 structures of different receptors that have been determined are very similar. They consist of two similar globular domains (I and II) separated by a deep cleft or groove wherein the ligand binds. This structure is similar to those of hexokinase(as well as other kinases and dehydrogenases) and LacI family of repressors such as lactose repressor (LacR) and purine repressor (PurR).

We have determined the crystal structures of 9 different periplasmic receptors with bound ligands and several in ligand-free forms. In contrast to calmodulin, these receptors undergo a less elaborate hinge-bending motion in order:1) to enable the two domains to bind and sequester the ligand and 2) to form a ligand-stabilized 'closed' structure distinct from the 'open' ligand-free structure. The closed ligand-bound form is presumably recognized preferentially by the membrane components, thereby triggering nutrient transport or flagellar motion.

Molecular recognition: The structures further shed light on the ability of calmodulin to bind many targets with very tight affinity and, on the other hand, the high specificity but lower affinity of the receptors for small ligands.