Plausible binding mechanisms of Calmodulin for a spectrum of ligands

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Structural flexibility plays a key role in target recognition for a large variety of proteins, in particular, for the ubiquitous protein calmodulin (CaM). CaM is crucial because of its participation in calcium signaling pathways that regulate many essential biological functions in eukaryotic cells. Yet, it constitutes a good example for understanding the implications of protein flexibility and the relation between the conformational change and its function. Many processes are mediated by CaM through Ca$^{2+}$ dependent regulation of target enzymes. This broad specificity is manifested in the CaM binding regions of these target proteins, which differ significantly in their amino acid sequences. Also a variety of small organic compounds, with distinct chemical structures directly interact with calcium-loaded CaM. It is of utmost interest to find the domains or key residues controlling ligand binding and releasing mechanism in CaM because with a small conformational change, this protein can adapt itself to any ligand.

A new tool, termed perturbation-response scanning (PRS) has been introduced for the analysis of the remote control mechanisms in proteins. This method is based on linear response theory. By sequentially exerting directed forces on single-residues along the CaM chain, we record the resulting relative changes in the residue coordinates. When the ligand is integrated to the system in the holo form, only a few residues appear that are particularly successful in reproducing the experimental displacements. The bound form can be manipulated towards the unbound form, or the unbound form can be manipulated towards the bound form by either directly perturbing the ligand binding residues or the residues that are on the flexible linker region, or in the distant helices. We propose alternative mechanisms via which CaM mediates calcium-signaling processes.