Using molecular dynamics simulations to understand the specificity of protein-ligand interactions

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Relationship between the binding mode and the binding affinity of a ligand in complex with a protein is not always straightforward. Understanding the protein-ligand interactions at molecular level could explain why a specific compound has higher affinity and this knowledge has potential therapeutic applications in structure-based drug design. Although Protein Data Bank has several complex structures, it may well turn out to be a challenging task for some specific proteins to completely understand the binding affinities from the knowledge of complex structures alone. One such example is the Bcl-2 family of proteins which regulate the intrinsic pathway of apoptosis.

Bcl-2 family of proteins has both pro- and anti-apoptotic class and the interactions between them play a significant role in the process of mitochondrial outer membrane permeabilization. Bcl-2 family has BH1 to BH4 sequence domains. Experiments have shown that peptides derived from BH3 domain of pro-apoptotic protein is sufficient to induce the biological activity. Complex structures of several anti-apoptotic proteins in complex with BH3 peptides of pro-apoptotic partners are available. The complex structures of Bcl-XL and Mcl-1 show that the BH3 peptide reveal similar mode of binding in both the proteins. However, they exhibit different affinities. Examination of structures do not reveal clearly what gives rise to higher affinities for certain BH3 peptides while others show very low affinity.

Crystal structures represent a static view of an average ensemble of structures. We have carried out molecular dynamics (MD) simulations on Bcl-XL and Mcl-1 complex structures. Our hypothesis is that the peptide ligands with higher affinities will have stronger interactions with proteins and as a result they remain bound to the protein when we perform a long simulation. We have carried out 100 ns MD simulations on Bcl-XL and Mcl-1 complex structures. In this talk, I will present how the comparative MD simulations helped us to identify residues in the peptide that are involved in certain strong interactions which might be responsible for the higher affinity of peptides. Our results have implications in developing certain Bcl-2-specific anti-cancer drugs.