Mcl-1 structural dynamics from protein ensembles, enhanced sampling and pocket crosstalk analysis.

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Abstract

BCL-2 family proteins are known to govern the intrinsic pathway of apoptosis by a subtle interplay of protein-protein interactions between the members of this family[1]. Mcl-1 is a member of the BCL-2 family that exerts an anti-apoptotic function by inhibiting pro-apoptotic members. The ability of Mcl-1 to bind different partners is possibly linked to the large plasticity of its binding interface and hence to a wide conformational space accessible to this protein. We have developed recently in our laboratory a new family of original ligands able to bind to Mcl-1[2].

In this study, we explore Mcl-1 conformational space on the basis of the crystallographic data available within the Protein Data-Bank (PDB), but also by using metadynamics simulations (well-tempered metadynamics).

Two biasing schemes are used: (i) a global biasing scheme based on the essential dynamics captured by Principal Component Analysis (PCA)[3] allowed us to capture and enhance the rate of observing global conformational transitions. (ii) A more focused scheme using simple geometric collective variables is used to investigate the breathing motion observed at the binding interface of Mcl-1.

We successfully characterized Free Energy Surfaces describing the wide range of conformational states explored by Mcl-1 in water. A detailed analysis of Mcl-1 pockets cross-talk during the metadynamics simulations led us to discover the existence of an allosteric communication network between the canonical binding site of Mcl-1 and a distant binding site that might explain the allosteric inhibition of Mcl-1[4].

Bibliography

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