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Elucidation of Dynamics of Murine Double Minute 2 Shed Light on the Anti-cancer Drug Development

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Abstract : Coarse-grained elastic network models, namely Gaussian network model (GNM) and Anisotropic network model (ANM), are utilized in order to investigate the fluctuation dynamics of Murine Double Minute 2 (MDM2), which is the native inhibitor of p53. Conformational dynamics of MDM2 are elucidated in unbound, p53 bound, and non-peptide small molecule inhibitor bound forms. With this, it is aimed to gain insights about the alterations brought to global dynamics of MDM2 by native peptide inhibitor p53, and two small molecule inhibitors (HDM201 and NVP-CGM097) that are undergoing clinical stages in cancer studies. MDM2 undergoes significant conformational changes upon inhibitor binding, carrying pieces of evidence of induced-fit mechanism. Small molecule inhibitors examined in this work exhibit similar fluctuation dynamics and characteristic mode shapes with p53 when complexed with MDM2, which would shed light on the design of novel small molecule inhibitors for cancer therapy. The results showed that residues Phe 19, Trp 23, Leu 26 reside in the minima of slowest modes of p53, pointing to the accepted three-finger binding model. Pro 27 displays the most significant hinge present in p53 and comes out to be another functionally important residue. Three distinct regions are identified in MDM2, for which significant conformational changes are observed upon binding. Regions I (residues 50-77) and III (residues 90-105) correspond to the binding interface of MDM2, including (α2, L2, and α4), which are stabilized during complex formation. Region II (residues 77-90) exhibits a large amplitude motion, being highly flexible, both in the absence and presence of p53 or other inhibitors. MDM2 exhibits a scattered profile in the fastest modes of motion, while binding of p53 and inhibitors puts restraints on MDM2 domains, clearly distinguishing the kinetically hot regions. Mode shape analysis revealed that the α4 domain controls the size of the cleft by keeping the cleft narrow in unbound MDM2; and open in the bound states for proper penetration and binding of p53 and inhibitors, which points to the induced-fit mechanism of p53 binding. P53 interacts with α2 and α4 in a synchronized manner. Collective modes are shifted upon inhibitor binding, i.e., second mode characteristic motion in MDM2-p53 complex is observed in the first mode of apo MDM2; however, apo and bound MDM2 exhibits similar features in the softest modes pointing to pre-existing modes facilitating the ligand binding. Although much higher amplitude motions are attained in the presence of non-peptide small molecule inhibitor molecules as compared to p53, they demonstrate close similarity. Hence, NVP-CGM097 and HDM201 succeed in mimicking the p53 behavior well. Elucidating how drug candidates alter the MDM2 global and conformational dynamics would shed light on the rational design of novel anticancer drugs.

Keywords : cancer, drug design, elastic network model, MDM2
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