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Insight into interaction mechanism of the inhibitor pDI6W with MDM2 based on molecular dynamics

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Abstract. The p53-MDM2 interaction has been an important target of drug design curing cancers. In this work, Molecular dynamics (MD) simulation coupled with molecular mechanics/Poisson Boltzmann surface area method (MM-PBSA) is performed to calculate binding free energy of peptide inhibitor pDI6W to MDM2. The results show that van der Waals energy is the dominant factor of the pDI6W-MDM2 interaction. Cross-correlation matrix calculated suggests that the main motion of the residues in MMDM2 induced by the inhibitor binding is anti-correlation motion. The calculations of residue-residue interactions between pDI6W and MDM2 not only prove that five residues Phe19′, Trp22′, Trp23′, Leu26′ and Thr27′ from pDI6W can produce strong interactions with MDM2, but also show that CH-π, CH-CH and $\pi-\pi$ interactions drive the binding of pDI6W in the hydrophobic cleft of MDM2. This study can provide theoretical helps for anti-cancer drug designs.

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Key words: molecular dynamics simulation, cross-correlation matrix, p53-MDM2 interaction, binding free energy, MM-PBSA

1 Introduction

Currently, the tumor suppressor protein is a protein studied extensively, and it plays an important role in the regulation of the cell cycle and DNA repair[1]. The active p53 can well suppress oncogenesis and effectively protect host cell from cancer[2]. MDM2 can

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bind directly to p53 and inhibit the activity of p53. In fact, the overexpression of MDM2 occurs in almost 50% of cancers in the world[3, 4]. Thus, the inhibition of the p53-MDM2 interaction becomes a new approach for cancer therapy.

In order to disturb the binding of MDM2 to p53, a few groups have imitate the interactions of three residues Phe19, Trp23 and Leu26 from p53 with MDM2 to design some inhibitors with high affinity[5-7]. The inhibitor pDI6W designed by Phan J *et al.* can bind to MDM2 with binding constant Ki of 36 nmol[8]. Thus, insights into the molecular basis of the pDI6W-MDM2 interaction are helpful for the designs of anti-cancer drugs.

Recently, molecular dynamics (MD) simulation and molecular mechanics/poisson Boltzmann surface area method (MM-PBSA) have been successfully used to study the protein-protein interactions [9-18]. These two methods can efficiently understand the conformation changes of proteins induced by the inhibitor binding and explore the structure-function relation of proteins. At the same time, MD simulation can also provide important dynamic information for the rational designs of small molecule inhibitors.

In this work, the crystal structure (ID: 3JZR) from protein data bank (PDB) is used as the initial model for MD simulation[8], and Fig. 1 depicts the structure of the pDI6W-MDM2 complex. Cross-correlation matrix is computed to investigate the conformation changes of MDM2 induced by the inhibitor binding. The residue-based free energy decomposition is performed to calculate the residue-residue interaction. The results prove that the CH-π, CH-CH and $\pi-\pi$ interactions drive the binding of the inhibitor pDI6W in the hydrophobic cleft of MDM2.

2 Theory and method

2.1 MD simulation

The crystal structure (ID: 3JZR) taken from PDB is used for the starting structure for MD simulation. All crystal water molecules are kept in the starting model. All missing

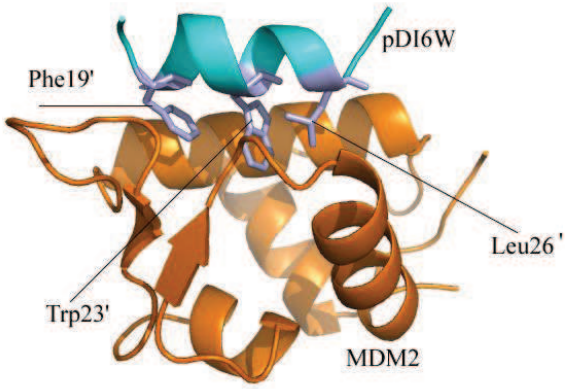

Figure 1: Structure of the pDI6W-MDM2 complex. MDM2 and pDI6W are showed in orange and cyan, respectively, the residues Phe19', Trp23' and Leu26' are displayed in stick mode.