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Computational investigation on the molecular interactions between MDM2 and its photoactivatable inhibitor

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ABSTRACT
The Murine Double Minute 2 (MDM2) protein is a crucial negative regulator of the tumor suppressor p53 molecule. In order to restrict p53 functioning, MDM2 molecules are overproduced in many human tumors. Thus, reactivating p53 in cancer cells using inhibitors, disrupting p53-MDM2 binding, can offer an effective approach for cancer therapy. Recently a photoactivatable MDM2 inhibitor, a photoremovable-protecting group (PPG) in complex with idasanutlin has been reported to exert no functional effect on cellular outgrowth but allows for the selective, non-invasive activation of antitumor properties due to the release of active inhibitor idasanutlin from the complex upon irradiation with 400 nm light. In this study, using molecular docking and Molecular Dynamics (MD) simulations, we have investigated the interaction of (i) PPG-idasanutlin complex and (ii) the active inhibitor idasanutlin with MDM2 at the molecular level. We noticed that the PPG-idasanutlin complex fails to fit into the binding cavity of MDM2. But the active inhibitor idasanutlin when it is free from PPG was found to fit perfectly into the binding cavity of MDM2. From the Dictionary of Secondary Structure of Proteins (DSSP) analysis, we found that the number of α-helices, which aid in the stability of protein, were found to be more in the MDM2-idasanutlin complex rather than in the MDM2-PPG-idasanutlin complex. Using the PDBsum server, we have compared the interaction profiles of MDM2-PPG-idasanutlin, MDM2-idasnautlin and MDM2-p53 complexes. From the interaction profile, we found the active inhibitor, idasanutlin free from PPG to bind to the region in MDM2 where p53 prefers to bind.. Our findings from this study would shed light on designing more potent photoactivatable MDM2 inhibitors.
Keywords: *photoremovable-protecting group; Molecular Dynamics simulation; active inhibitor idasanutlin.*

1. INTRODUCTION
At present, cancer is one of the most dominant causes of death across the world. Many different types of cancer treatment have been developed, but the type of treatment that an individual receives depends solely on two factors: (i) the type of cancer and (ii) the stage of cancer. These treatments can be either in a single formulation or in a combination, such as immunotherapy, targeted therapy, hormone therapy, and the most common method: surgery with chemotherapy and/or radiation therapy. But these methods come with certain drawbacks, wherein the inherent toxicity and the associated adverse effects account for the majority of the drawbacks in cancer chemotherapy. To overcome the problems concerning these selectivity issues, the focus has been now shifted to exploring the targeting pathways that are exclusive for cancer cells [1-3]. Therefore targeting the cancer cell-specific protein-protein interactions (PPIs) is an effective strategy for controlling these cellular pathways, , hence paving a way for a novel targeting strategy in anticancer treatment.

One of the most targeted proteins in developing anti-cancer therapy is p53, which functions as tumor suppressor protein and is well-known to exhibit a variety of PPIs. It plays an important role in many cell-regulating pathways like DNA repair, apoptosis, cell cycle control, and cellular stress responses [4,5]. p53, when activated by different kinds of stresses, can drive cellular senescence and at times leading to apoptosis. This property has deep involvement in cancer treatment because the upregulation of p53 protein expression can instigate senescence or apoptosis in the cycling cells [6-9].

The Murine Double Minute 2 (MDM2) is an E3 ubiquitin-protein ligase. MDM2 is well studied as the primary repressor of the p53 protein activity. The mechanism of repression includes the interaction of MDM2 with p53 by promoting its ubiquitination followed by subsequent degradation by the proteasome [10-12]. The other two mechanisms by which MDM2 inhibits p53 activity are either by directly binding to and blocking the N-terminal transcriptional activation domain of p53 or by promoting the export of p53 from the nucleus to the cytoplasm [13]. This regulation of the PPI between p53 and MDM2 can play a vital role in the development of anticancer drugs.

Recently, many classes of chemical compounds have been found to be effective as MDM2 antagonists, including Nutlin-Type Compounds, Imidazoles, Imidazothiazoles, Benzodiazepines, Spirooxindoles, Isoindolones, Indole-2-Carboxylic Acid Derivatives, Pyrrolidinones, Pyrrolidines, Isoquinolines and Piperidinones, Peptides and some miscellaneous compounds [14]. The antagonist that shows the maximum number of van der Waals interactions with MDM2 will effectively be able to inhibit the PPI between MDM2-p53 [15]. Among the mentioned compounds, ntlins have been found to be the most effective in modulating the tumor-suppressing pathway of p53 [16-18]. This function is achieved by the binding of MDM2 to p53, because of which the proteolytic breakdown of p53 gets inhibited. Once p53 gets stabilized, it stops the rapid cell division, leading to cell senescence [8].

Photopharmacological strategies [19,20] can be introduced for (i) increasing the selectivity of certain MDM2 inhibitors; and (ii) making them involved as research tools to understand MDM2−p53 interactions. In photopharmacological strategies, a drug can be modified with a photoswitch [19,20], or

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Article

Computational Investigation on the p53−MDM2 Interaction Using the Potential of Mean Force Study

Pundarikaksha Das and Venkata Satish Kumar Mattaparthi*

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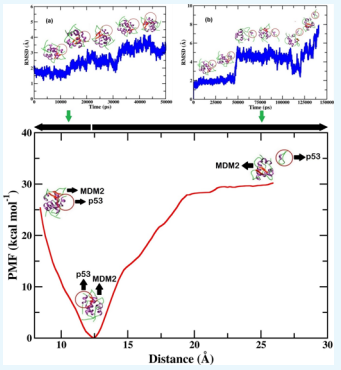
ABSTRACT: Murine double minute 2 (MDM2) proteins are found to be overproduced by many human tumors in order to inhibit the functioning of p53 molecules, a tumor suppressor protein. Thus, reactivating p53 functioning in cancer cells by disrupting p53−MDM2 interactions may offer a significant approach in cancer treatment. However, the structural characterization of the p53−MDM2 complex at the atomistic level and the mechanism of binding/unbinding of the p53−MDM2 complex still remain unclear. Therefore, we demonstrate here the probable binding (unbinding) pathway of transactivation domain 1 of p53 during the formation (dissociation) of the p53−MDM2 complex in terms of free energy as a function of reaction coordinate from the potential of mean force (PMF) study using two different force fields: ff99SB and ff99SB-ILDN. From the PMF plot, we noticed the PMF to have a minimum value at a p53−MDM2 separation of 12 Å, with a dissociation energy of 30 kcal mol^{-1}. We also analyzed the conformational dynamics and stability of p53 as a function of its distance of separation from MDM2. The secondary structure content (helix and turns) in p53 was found to vary with its distance of separation from MDM2. The p53−MDM2 complex structure with lowest potential energy was isolated from the ensemble at the reaction coordinate corresponding to the minimum PMF value and subjected to molecular dynamics simulation to identify the interface surface area, interacting residues at the interface, and the stability of the complex. The simulation results highlight the importance of hydrogen bonds and the salt bridge between Lys94 of MDM2 and Glu17 of p53 in the stability of the p53−MDM2 complex. We also carried out the binding free energy calculations and the per residue energy decomposition analyses of the interface residues of the p53−MDM2 complex. We found that the binding affinity between MDM2 and p53 is indeed high [ΔG_{bind} = −7.29 kcal mol^{-1} from molecular mechanics/Poisson−Boltzmann surface area (MM/PBSA) and ΔG_{bind} = −53.29 kcal mol^{-1} from molecular mechanics/generalized borne surface area]. The total binding energy obtained using the MM/PBSA method was noticed to be closer to the experimental values (−6.4 to −9.0 kcal mol^{-1}). The p53−MDM2 complex binding profile was observed to follow the same trend even in the duplicate simulation run and also in the simulation carried out with different force fields. We found that Lys51, Leu54, Tyr100, and Tyr104 from MDM2 and the residues Phe19, Trp23, and Leu26 from p53 provide the highest energy contributions for the p53−MDM2 interaction. Our findings highlight the prominent structural and binding characteristics of the p53−MDM2 complex that may be useful in designing potential inhibitors to disrupt the p53−MDM2 interactions.



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1. INTRODUCTION

Protein−protein interactions (PPIs) have a dominant role in the identification of huge number of biological processes as well as biomolecules.[1−3] Most of the essential biological processes such as enzyme catalysis, immune system modulation, gene expression, and adjustment of signal pathways depend crucially on the regulation of the PPIs.[4−6] Moreover, the designing of drugs is mainly based on the modification of PPIs. The current focus of the researchers is on studying the structure and function of proteins. This is because the root cause of many diseases is related to disorders present in proteins.

The tumor suppressor p53 plays a significant role in many essential biological processes, which include regulation of cell cycle, DNA repair, apoptosis, and senescence.[7−11] It has been found that p53 is among the commonly mutated proteins in human tumors because of its highly potent tumor suppressor role. Nearly 50% of human cancers have modifications in the p53 gene, causing inactivation or loss of p53 protein. Moreover, p53 function is effectively inhibited even in cancer cells retaining wild-type p53.[8,12] This type of p53 function inhibition is carried out by the murine double minute 2 (MDM2; HDM2 in humans) protein.

MDM2 is an oncoprotein, discovered by its overexpression in a spontaneously transformed mouse cancer cell line.[8,12−15] MDM2 is known to exhibit both p53-independent and p53-

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RESEARCH ARTICLE

Computational Investigation on the MDM2-Idasanutlin Interaction Using the Potential of Mean Force Method

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Abstract: ***Background*:** The Murine Double Minute 2 (MDM2) protein is a well-studied primary negative regulator of the tumor suppressor p53 molecule. Therefore, nowadays many research studies have focused on the inhibition of MDM2 with potent inhibitors. Idasanutlin (RG7388) is a well-studied small molecule, the antagonist of MDM2 with potential antineoplastic activity. Nevertheless, the highly significant information pertaining to the free energy profile, intermediates, and the association of receptor and ligand components in the MDM2-idasanutlin complex remains unclear.

***Objective*:** To study the free energy profile of the MDM2-idasanutlin complex in terms of the Potential of Mean Force (PMF) method.

***Methods*:** We have used the PMF method coupled with umbrella sampling simulations to generate the free energy profile for the association of N-Terminal Domain (NTD) of MDM2 and idasanutlin along with a specific reaction coordinate for identifying transition states, intermediates as well as the relative stabilities of the endpoints. We also have determined the binding characteristics and interacting residues at the interface of the MDM2-idasanutlin complex from the Binding Free Energy (BFE) and Per Residue Energy Decomposition (PRED) analyses.

***Results*:** The PMF minima for the MDM2-idasanutlin complex was observed at a center of mass (CoM) distance of separation of 11 Å with dissociation energy of 17.5 kcal mol^{-1}. As a function of the distance of separation of MDM2 from idasanutlin, we also studied the conformational dynamics as well as stability of the NTD of MDM2. We found that there is indeed a high binding affinity between MDM2 and idasanutlin ($\Delta G_{binding}$ = -3.19 kcal mol^{-1}). We found that in MDM2, the residues MET54, VAL67, and LEU58 provide the highest energy input for the interaction between MDM2 and idasanutlin.

***Conclusion*:** Our results in this study illustrate the significant structural and binding features of the MDM2-idasanutlin complex that may be useful in the development of potent inhibitors of MDM2.

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1. INTRODUCTION

P53 is a tumour suppressor protein made of 393 amino acids. It also acts as a transcription factor, which trans-activates a number of genes in response to different forms of genotoxic stress by binding to particular DNA sequences, thus halting the cell cycle, restoring damaged DNA, or inducing apoptosis as the cell fates [1, 2]. The structure of the p53 core DNA-binding domain (residues 94-312) binding directly to the DNA sequence was resolved by X-ray crystallography. Both X-ray crystallography and NMR analyses were used to deduce the structure of the tetramerization domain (residues 323–356) of the p53 protein [3-5]. Trans-activity of p53 is regulated either by post-translation mechanisms such as acetylation, phosphorylation, and isomerization of prolyls, or by Protein-Protein Interaction (PPI) [6-11]. p53 can pick a subset of target promoters through these mechanisms, by modifying its structure as well as the affinity to bind to the DNA sequences containing variations within the downstream genes. However, the mechanism responsible for downstream gene selectivity and the subsequent cell fate remains unclear [12].

Murine Double Minute 2 (MDM2) is a well-studied negative regulator of p53. The N-Terminal Domain (NTD) of

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