J. Chosun Natural Sci.
Vol. 11, No. 1 (2018) pp. 25 – 29
https://doi.org/10.13160/ricns.2018.11.1.25

Molecular Docking Analysis of Protein Phosphatase 1D (PPM1D) Receptor with SL-175, SL-176 and CDC5L

Thirumurthy Madhavan†

Abstract

Protein phosphatase manganese dependent 1D (PPM1D), a Ser/Thr protein phosphatise, play major role in the cancer tumorigenesis of various tumors including neuroblastoma, pancreatic adenocarcinoma, medulloblastoma, breast cancer, prostate cancer and ovarian cancer. Hence, analysis on the structural features required for the formation of PPM1D-inhibitor complex becomes essential. In this study, we have performed molecular docking of SL-175 and -176 and protein-protein docking of CDC5L with PPM1D. On analysing the docked complexes, we have identified the important residues involved in the formation of protein-ligand complex. Research concentrating on these residues could be helpful in understanding the pathophysiology of various tumors related to PPM1D.

Keywords: PPM1D, CDC5L, SL-175, SL-176, Molecular Docking, Protein-Protein Docking.

1. Introduction

Protein phosphatase, $Mg(^{2+})/Mn(^{2+})$ dependent 1D (PPM1D) also known as WIP1 (wild-type p53-induced phosphatase 1) which belongs to the PP2C family of Ser/Thr protein phosphatases[1] are known to be negative regulators of cell stress response pathways. It controls the feedback regulation of p38-p53 signaling which in turn activates the inhibition of growth and the suppression of stress induced apoptosis. PPM1D plays a crucial role in cancer tumorigenesis[2] and its overexpression has been observed in various human tumors, including neuroblastoma[3], pancreatic adenocarcinoma[4], medulloblastoma[5], breast cancer[6] and ovarian cancer[7]. It forms an integral component of ATM-dependent signaling pathway[8]. In a study by et al., the chance of identifying PPM1D as a novel biomarker for prostate cancer was studied[9]. Analysing the structural features involved in the PPM1D-inhibitor complex thus becomes essential. In a previous study, we have modelled the 3D structures of PPM1D using homology modelling[10]. In this study we have performed molecular docking of SL-175, SL-176 and protein-protein docking of CDC5L with the selected model of GPR54. The important residues involved in the interaction were identified and further studies on these residues could be helpful on the analysis of structural features of PPM1D/inhibitor interaction.

Department of Genetic Engineering, School of Bioengineering, SRM University, SRM Nagar, Kattankulathur, Chennai 603203, India.

†Corresponding author : thiru.murthyunom@gmail.com, thirumurthy.m@ktr.srmuniv.ac.in
(Received : January 22, 2018, Revised : March 16, 2018 Accepted : March 25, 2018)

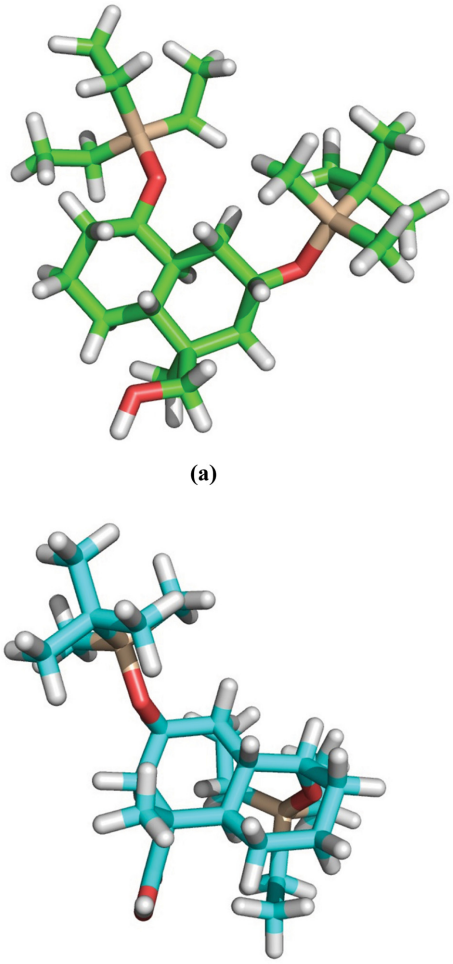
2. Material and Methods

2.1. Preparation of Protein Structure

The crystal structure of human PPM1D modelled in a previous study was study[10]. The structure was prepared using protein preparation tool in biopolymer module of SYBYL. Energy minimization was performed for 1000 iterations using Tripos force field, Gasteiger Huckel charge and Powell method.

2.2 Preparation of Ligand Molecules

In a study by Ogasawara et al., compounds SL-175 and SL-176 were studied for their potency of suppressing cancer cell proliferation by targeting PPM1D phosphatase. The chemical structures of both the antagonists were taken from the literature[11] and were sketched using sketch molecule function in SYBYL software[12]. The energy minimization of all the molecules was performed using Tripos force field and atomic charges



(a)

(b)

Fig. 1. Structure of antagonist molecules (a) SL-175 (b) SL-176.

were assigned using Gasteiger Huckel method. The structures of both the molecules are shown in Fig. 1.

2.3. Molecular Docking

Molecular docking was performed utilizing Surflex dock module of SYBYL. The antagonists were docked with PPM1D phosphatase. The docking algorithm in Surflex dock uses an idealized active site called protomol[13]. The protomol is the representation of intended binding site to which the ligand molecules were docked. Two parameters, such as threshold and bloat, determine the extent of a protomol. The protomol was generated using automated mode. Surflex dock uses an empirical scoring function to score the docked ligand conformation which takes into account several terms, including hydrophobic, polar, repulsive, entropic and solvation[14]. To evaluate the docking results, the docking scores are expressed in terms of $-\log_{10}K_d$ units, where K_d represents a dissociation constant of a ligand.

2.4. Protein-Protein Docking

Cell division cycle 5-like protein (CDC5L), a protein that interacts with PPM1D phosphatase is selected to perform protein-protein docking. The crystal structure of human CDC5L was downloaded from the Protein Data Bank (PDB ID: 2DIM). To perform protein-protein docking of CDC5L with PPM1D Phosphatase, ClusPro 2.0, the best web server to perform protein-protein docking, server was used[15,16]. It has performed well in the critical assessment of prediction of interactions (CAPRI)[17,18]. PIPER, a correlation method[19] identifies the docked conformation energy in a grid. The structures were clustered based on the pairwise RMSD as the distance measure and were optimized.

3. Results and Discussion

3.1. Molecular Docking

Molecular docking of SL-175, SL-176 with the model of PPM1D phosphatase was performed. 20 different conformations were generated for each molecule and the best conformation was chosen based on Surflex score and interaction with the residues. The docking score and H-bond forming residues for all the molecules are tabulated in Table 1. The binding mode of the antagonists with the receptor was represented in Fig. 2. On analyzing the docked complexes, residues ARG357, ARG359, GLN360 and ARG361 were identified to be involving in forming H-bond interactions with the antagonists.

Table 1. Docking scores and H-bond interaction of the antagonists

Compound No.	Sybyl score	No. of H-bonds	H – Bond Residues
SL175	4.48	2	ARG357, GLN360
SL176	4.33	2	ARG359, ARG361

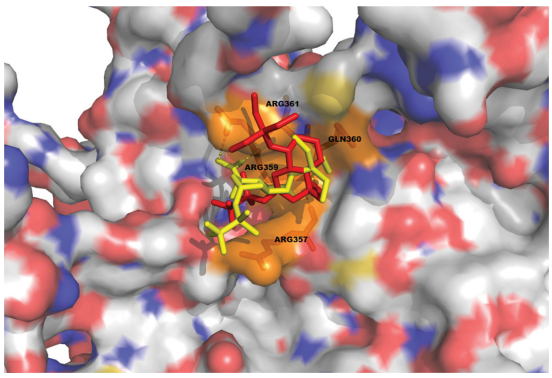


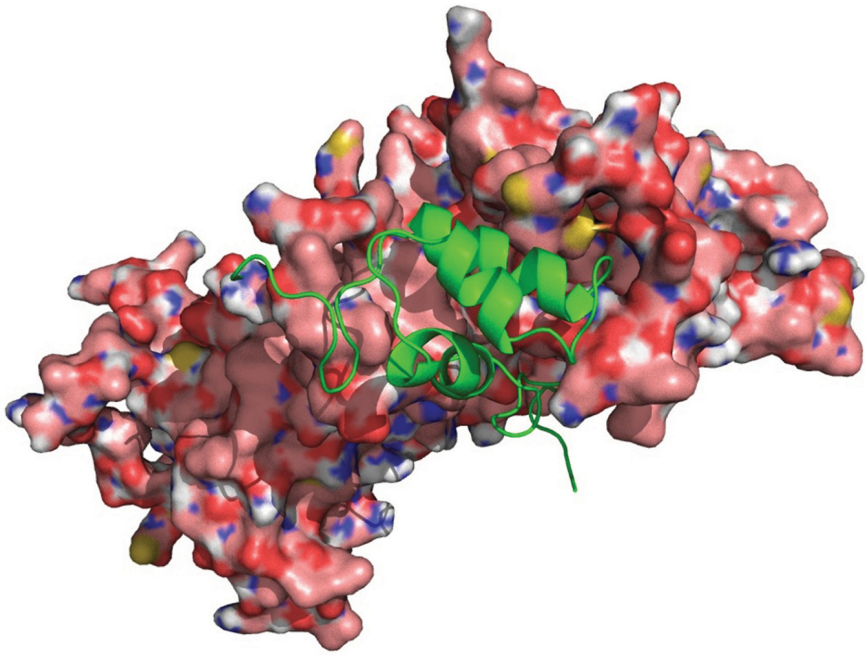
Fig. 2. Binding mode of SL-175 (yellow) and SL-176 (red) with PPM1D phosphatase.

3.2. Protein-Protein Docking

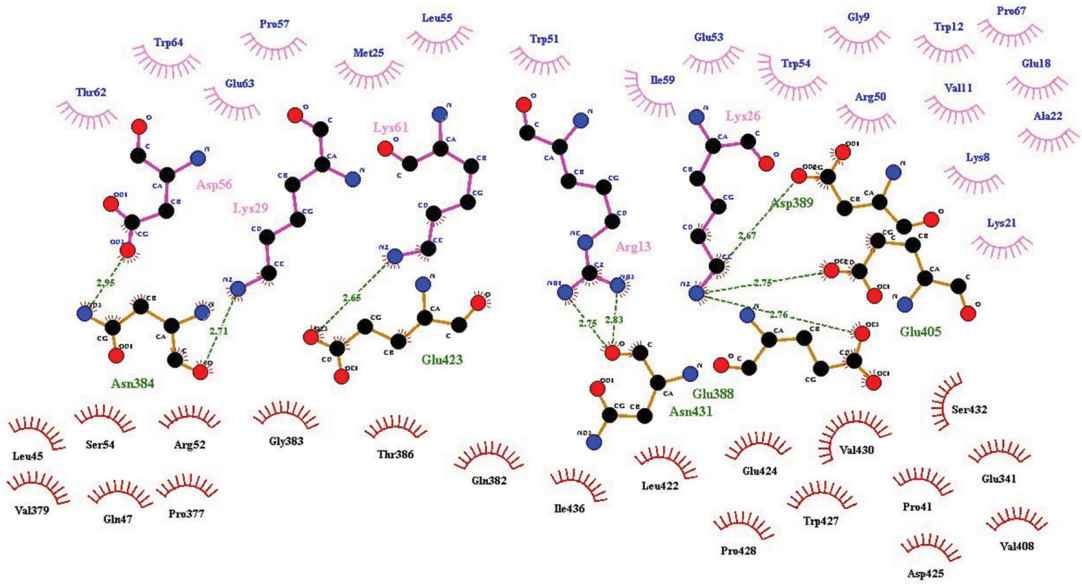
CLUSPRO 2.0 server was used to perform protein-protein docking to identify the important residues involved in the interaction. 29 different clusters of docked complexes were generated. The top cluster consists of 70 members, and lowest energy weighted score was -1033.8. On analysing the complexes, we have identified that residues ASN384, GLU388, ASP389, GLU405, GLU423 and ASN431 were forming H bond interaction with CDC5L. The cluster scores for both the complexes are represented in Table 2. The binding mode of CDC5L with PPM1D is represented in Fig. 3.

Table 2. Cluster scores developed using ClusPro server

Cluster	Members	Representative	Weighted Score
0	70	Center	-798.4
		Lowest Energy	-1033.8
1	64	Center	-850.0
		Lowest Energy	-896.4
2	58	Center	-778.8
		Lowest Energy	-976.7
3	49	Center	-986.3
		Lowest Energy	-986.3
4	38	Center	-808.6
		Lowest Energy	-853.6
5	37	Center	-806.0
		Lowest Energy	-889.4
6	36	Center	-952.6
		Lowest Energy	-952.6
7	34	Center	-791.4
		Lowest Energy	-905.8
8	31	Center	-795.4
		Lowest Energy	-943.0
9	27	Center	-1079.0
		Lowest Energy	-1079.0
10	27	Center	-929.0
		Lowest Energy	-929.0
11	26	Center	-821.7
		Lowest Energy	-995.0
12	26	Center	-818.2
		Lowest Energy	-829.7
13	22	Center	-950.2
		Lowest Energy	-950.2
14	22	Center	-837.2
		Lowest Energy	-837.2
15	19	Center	-881.9
		Lowest Energy	-881.9
16	18	Center	-905.1
		Lowest Energy	-1039.9
17	18	Center	-896.1
		Lowest Energy	-896.1
18	17	Center	-786.8
		Lowest Energy	-866.6
19	17	Center	-816.8
		Lowest Energy	-844.2
20	17	Center	-816.2
		Lowest Energy	-816.2
21	16	Center	-781.2
		Lowest Energy	-904.2
22	16	Center	-785.4
		Lowest Energy	-868.4
23	15	Center	-789.1
		Lowest Energy	-957.8
24	14	Center	-820.4
		Lowest Energy	-869.3
25	12	Center	-850.7
		Lowest Energy	-850.7
26	11	Center	-908.3
		Lowest Energy	-908.3
27	11	Center	-770.1
		Lowest Energy	-892.9
28	11	Center	-863.3
		Lowest Energy	-863.3
29	11	Center	-843.8
		Lowest Energy	-843.8



(a)



(b)

Fig. 3. (a) Binding mode of CDC5L with PPM1D phosphatase. (b) LigPlot of CDC5L and PPM1D phosphatase complex.

4. Conclusion

Molecular docking of PPM1D phosphatase with inhibitors SL-175 and SL-176 and protein-protein docking of CDC5L-PPM1D was performed. On analysis of the docking results, we have identified the important residues involved in the formation of H-bond interaction with the protein. Further studies on these crucial

residues could be useful in providing the important structural features involved in the formation of PPM1D-inhibitor complex.

References

[1] X. Lu, T. A. Nguyen, S. H. Moon, Y. Darlington, M. Sommer, and L. A. Donehower, "The type 2C phosphatase Wip1: an oncogenic regulator of tumor suppressor and DNA damage response pathways", Cancer Metastasis Rev., Vol. 27, pp. 123-135, 2008.

[2] H. Yang, X.-Y. Gao, P. Li, and T.-S. Jiang, "PPM1D overexpression predicts poor prognosis in non-small cell lung cancer", Tumour Biology, Vol. 36, pp. 2176-2184, 2015.

[3] F. Saito-Ohara, I. Imoto, J. Inoue, H. Hosoi, A. Nakagawara, T. Sugimoto, and J. Inazawa, "PPM1D is a potential target for 17q gain in neuroblastoma", Cancer Res., Vol. 63, pp. 1876-1883, 2003.

[4] P. Loukopoulos, T. Shibata, H. Katoh, A. Kokubu, M. Sakamoto, K. Yamazaki, T. Kosuge, Y. Kanai, F. Hosoda, I. Imoto, M. Ohki, J. Inazawa, and S. Hirohashi, "Genome-wide array-based comparative genomic hybridization analysis of pancreatic adenocarcinoma: identification of genetic indicators that predict patient outcome", Cancer Sci., Vol. 98, pp. 392-400, 2007.

[5] R. C. Castellino, M. De Bortoli, X. Lu, S. H. Moon, T. A. Nguyen, M. A. Shepard, P. H. Rao, L. A. Donehower, and J. Y. Kim, "Medulloblastomas overexpress the p53-inactivating oncogene WIP1/PPM1D", J Neurooncol., Vol. 86, pp. 245-256, 2008.

[6] M. B. Lambros, R. Natrajan, F. C. Geyer, M. A. Lopez-Garcia, K. J. Dedes, K. Savage, M. Lacroix-Triki, R. L. Jones, C. J. Lord, S. Linardopoulos, A. Ashworth, and J. S. Reis-Filho, "PPM1D gene amplification and overexpression in breast cancer: a qRT-PCR and chromogenic in situ hybridization study", Mod. Pathol., Vol. 23, pp. 1334-1345, 2010.

[7] J. Parssinen, E. L. Alarmo, S. Khan, R. Karhu, M. Vihinen, and A. Kallioniemi, "Identification of differentially expressed genes after PPM1D silencing in breast cancer", Cancer Lett., Vol. 259, pp. 61-70, 2008.

[8] S. Shreeram, O. N. Demidov, W. K. Hee, H. Yamaguchi, N. Onishi, C. Kek, O. N. Timofeev, C. Dudgeon, A. J. Fornace, C. W. Anderson, Y. Minami, E. Appella, and D. V. Bulavin, "Wip1 Phosphatase Modulates ATM-Dependent Signaling Pathways", Mol. Cell, Vol. 23, pp. 757-764, 2006.

[9] L. Jiao, D. Shen, G. Liu, J. Jia, J. Geng, H. Wang, and Y. Sun, "PPM1D as a novel biomarker for prostate cancer after radical prostatectomy", Anticancer Res., Vol. 34, pp. 2919-2925, 2014.

[10] S. Nagarajan and T. Madhavan, "Protein phosphatase 1d (ppm1d) structure prediction using homology modeling", J. Chosun Natural Sci., Vol. 9, pp. 35-40, 2016.

[11] S. Ogasawara, Y. Kiyota, Y. Chuman, A. Kowata, F. Yoshimura, K. Tanino, and R. Kamada, K. Sakaguchi, "Novel inhibitors targeting PPM1D phosphatase potently suppress cancer cell proliferation", Bioorg. Med. Chem., Vol. 23, pp. 6246-6249, 2015.

[12] SYBYL Software, Tripos Associates Inc, St. Louis, USA, 2002.

[13] A. N. Jain, "Scoring functions for protein-ligand docking", Curr. Protein Pept. Sci., Vol. 7, pp. 407-420, 2006.

[14] A. N. Jain, "Scoring non-covalent protein-ligand interactions: a continuous differentiable function tuned to compute binding", J. Comput. Aided Mol. Des., Vol. 10, pp. 427-440, 1996.

[15] S. R. Comeau, D. W. Gatchell, S. Vajda, and C. J. Camacho, "ClusPro: an automated docking and discrimination method for the prediction of protein complexes", Bioinformatics, Vol. 20, pp. 45-50, 2004.

[16] S. R. Comeau, D. W. Gatchell, S. Vajda, and C. J. Camacho, "ClusPro: a fully automated algorithm for protein-protein docking", Nucleic Acids Res., Vol. 32, pp. 96-99, 2004.

[17] D. Kozakov, D. Beglov, T. Bohnuud, S. Mottarella, B. Xia, D. Hall, and S. Vajda, "How good is automated protein docking?", Proteins, Vol. 81, pp. 2159-2166, 2013.

[18] M. F. Lensink and S. J. Wodak, "Docking, scoring, and affinity prediction in CAPRI", Proteins, Vol. 81, pp. 2082-2095, 2013.

[19] D. Kozakov, R. Brenke, S. R. Comeau, and S. Vajda S "PIPER: An FFT-based protein docking program with pairwise potentials", Proteins, Vol. 65, pp. 392-406, 2006.