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RESEARCH ARTICLE

INHIBITION OF CANCER BY TARGETING MMP9 THROUGH MOLECULAR DOCKING APPROACH

[1]Manaswini Jagadeb, [1]Chirasmita Nayak, *,[1]Rohit Pritam Das, [2]Sidhant Mohanty and [3]Rajesh Kumar Meher

[1]Department of Bioinformatics, Orissa University of Agriculture and Technology, India
[2]Department of Bioinformatics, B.J.B Autonomous College Bhubaneswar, Odisha, India
[3]Department of Biosciences and Biotechnology, Fakir Mohan University, Balasore, Odisha, India

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ABSTRACT

Now days among many serious diseases, cancer plays very important challenge to human society. To prevent this disease, many target proteins have identified. Among them MMP9 is playing very important role. Matrix metalloproteinase belong to the large family of protease known as the metzincin super family, These are zinc dependent endopeptidases. MMP have capacity to degrading all kind of extracellular metrix. Matrix metalloprotease 9 is a type iv collagenase is a class of enzyme belongs to the family of metalloproteinase involved in degradation of extracellular metrix. 20W1 is the available tertiary structure which was found in Protein Data Bank (PDB). The structure was taken for refinement by using PyMol and inhibitors were found from different literature study. The protein 20W1 was bound with some of its inhibiters and the binding energy, bond length with its interacting residues are studied.

INTRODUCTION

Cancer is a dreadful disease which has not permanent cure. There are many researches are going on to come across it. It is of about two hundred distinct types. These can be categorized to four main types: carcinomas, sarcomas, lymphomas and leukemia. The main cause of cancer is carcinogen Bernblum. There are different marker proteins associated with cancer disease. MMP9 was selected to target this disease. This protein digests decorin, elastin, fibrillin, laminin, gelatin and types IV, V, XI, XVI collagen. It activates growth factors like proGTFb and proTNFa. Physiologically MMP9 in coordination with other MMPs play a role in normal tissue remodeling event such as embryonic development, angiogenesis, ovulation, wound healing etc. The gelatinase B/MMP9 MMP9 and its inhibitors and address novel ways to inhibit gelatinase B/MMP9 involvement in tumors progression. (ref) So MMP9 was selected to target this disease. There are some inhibitors have identified having anticancer property and can inhibit MMP9. The MMPs are inhibited by specific endogenous tissue inhibitor of metalloproteinases (TIMPs), which comprise a family of four protease inhibitors: TIMP-1, TIMP-2, TIMP-3, and TIMP-4. It is a multidomain metallo enzyme, with a catalytic site composed of a metal binding domain separated from the active site by three fibronectin repeats such as elastin and denatured collagens. Within this region the amino acid Asp 309, Asn 319, Asp232, Tyr320 and Arg3076 are important for gelatin binding. The catalytic site is maintained inactive by an amino terminal propeptide PRCGXPD, with the cysteine coordinated with the catalytic Zn. The COOH terminus of gelatinase B/ MMP-9 contains a hemopexin domain that regulates substrate binding. Potential prooncogenic role for gelatinase B/MMP-9 have been reported, implicating gelatinase B/MMP-9 in neoplastic transformation,tumour initiation/promotion and genetic instability. Gelatinase B/MMP-9 localizes to the nucleus and nuclear gelatinase activity associated with increased levels of DNA fragmentation. Indeed, gelatinase B/MMP-9 binds the DNA damage heterodimer Ku 70/80, providing a potential mechanism for its nuclear translocation. Nuclear gelatinase B/MMP-9 has been reported in human glimas astrocytomas. Gelatinase B/MMP-9 also induce Rac1b alternative splice variant expression, which promotes chromosomal instability by increased reactive oxygen species levels and activating snail mediated transcription, resulting in increased oxidative DNA damage. Gelatinase B/MMP-9 has also been reported to promote liver tumors initiation by the proteolytic release and activation of matrix associated TGFβ and VEGF, and in human mammary epithelialcells induces cell surface expression of the HER2/Neu oncoprotein, inhibiting apoptosis and sifting normal mammary cells towards a transformed

Corresponding author: Rohit Pritam Das
Department of Bioinformatics, Orissa University of Agriculture and Technology, India

phenotype, in the presence of oestrogen. The objective is to predict the binding affinity, bond length with its interacting residues between the protein with its inhibitors. It may potentially applicable towards the design of new selective MMPs inhibitors

MATERIALS AND METHODS

Database used

- PDB
- Pubchem
- Pubmed
- **Tools used**
- Pymol
- Mod refiner
- Autodock

Protein preparation

- Target identification (20w1) from literature
- Download structure from PDB

Ligand preparation

- Download ligand 3d structure from pubchem
- Convert ligand sdf format to pdb format by pymol

Autodock setup

- Docking of 2ow1 with each ligands by taking 100 run and total grid(blind dock)
- Analyzed the result and found the region on protein, where ligand goes many times
- In second round docking, set the grid box there and docked again with 50 run
- Analysed the result (binding energy, KI value, H-bond interaction, interacting residues)

RESULTS AND DISCUSSION

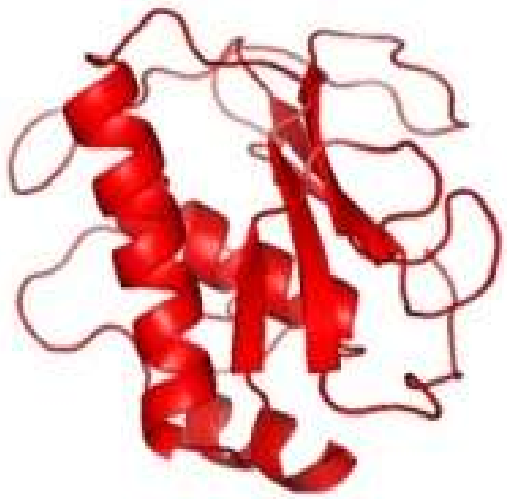

Fig 1. chain A of 2OW1 protein

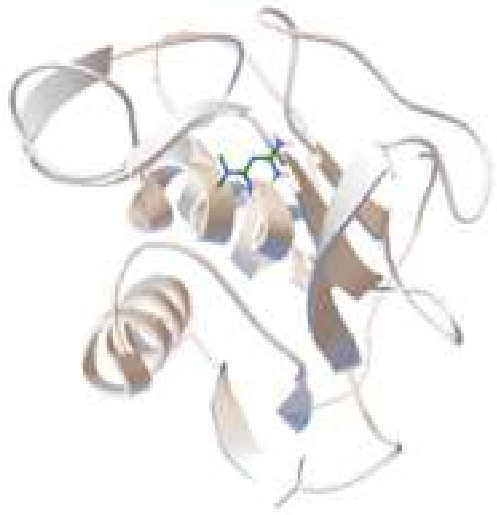

Fig 2(a). protein binding with inhibitor metformin.

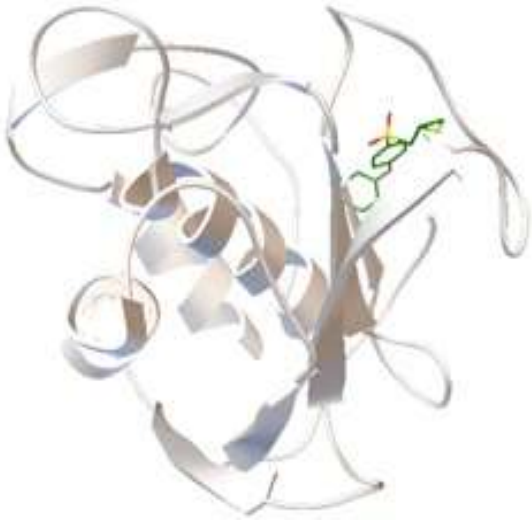

Fig 2(b). protein binding with inhibitor sb2.

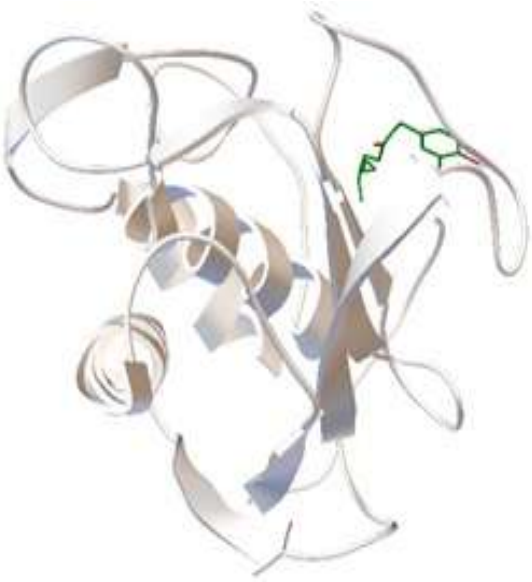

Fig 2(c). protein binding with inhibitor sho.

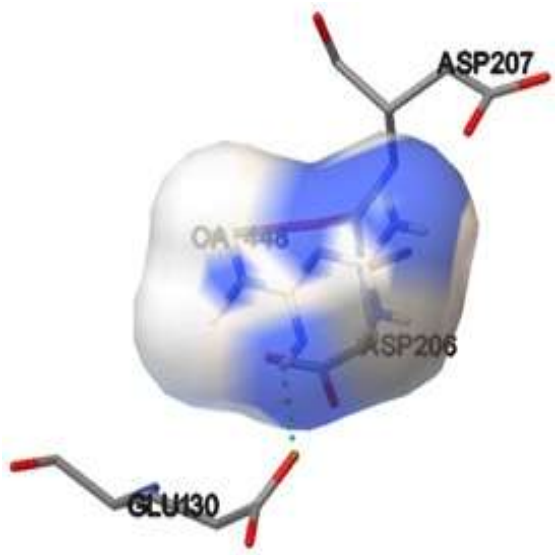

Fig 3(a). interacting residues and H-bond between protein-metformin.

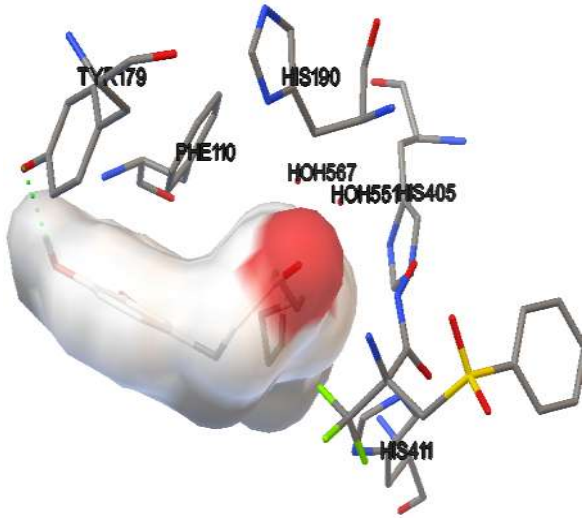

Fig 3(b). interacting residues and H-bond between protein-sho

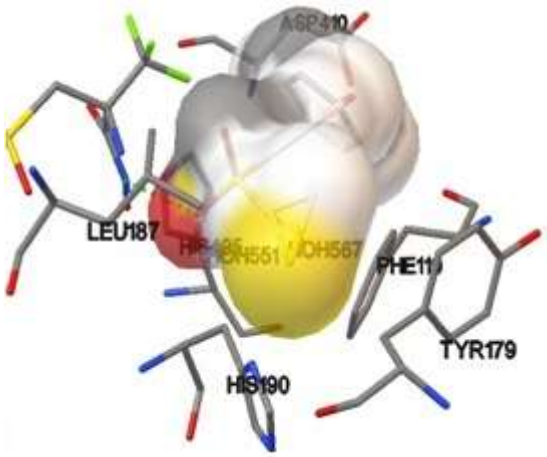

Fig 3(c). interacting residues and H-bond between protein-sb2.

Table 2. Protein-inhibitors interaction result by Autodock

Sl no.	Inhibitor name	Binding energy	KI value	Torsions energy	Interacting residues with H-bond
1	metformin	-7.3	4.48um	0.0	ASP207 GLU130 (O…H) ASP206 ASP410 LEU187 (N(H)…O)
2	Sb2	-7.26	4.77 um	1.49	HIS485 HIS190 PHE119 TYR179 PHE110 HIS190
3	sho	-6.34	22.41um	2.98	TYR179 (O…H) HIS405 HIS411

Conclusion

MMP9 is a suitable target for drug discovery, because of its high expression in human cancer tissue, tight correlation with the probability of patient survival and numerous invitro-invivo studies implicating MMP9 in tumor progression. The binding affinity, H-bond interaction with inhibitors and information about interacting residues may give a positive impact on future drug discovery and to fight against cancer.

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