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COMPARATIVE DOCKING STUDIES ON INHIBITORS OF ANTI-APOPTOTIC PROTEINS

A. Krishna Chaitanya*[1], I. Bhaskar Reddy[2], and DSVGK. Kaladhar[3]
[1, 2, 3] Department of Biochemistry & Bioinformatics,
GITAM Institute of Science, GITAM University, Visakhapatnam-530045, Andhra Pradesh, India
Email: chy2ak@gmail.com

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ABSTRACT

The anti-apoptotic proteins play a vital role in regulating the apoptotic signaling. The inhibition of apoptosis process can be mediated through these anti-apoptotic proteins. Understanding the signaling of apoptosis in cancer state of a cell leads to a new therapeutic approach by inhibiting the anti-apoptotic proteins. Once the anti-apoptotic proteins are deactivated, it leads to the proper activation of apoptosis in cancer cells which leads to the death of a cancer cell. Hence, in this work the anti-apoptotic proteins were identified through literature and their tertiary structures were predicted using automated servers named CPH Models 3.0 & 3D Jigsaw. Some of the structures are directly retrieved from PDB. The respective ligand molecules were retrieved from Drugbank. The docking studies were performed between selective anti-apoptotic proteins & their respective ligands using Molegro Virtual Docker (MVD) form which higher docking rerank score is taken in to consideration as an effective inhibitor / ligand molecule to the anti-apoptotic protein.

KEYWORDS: Apoptosis, Anti-apoptotic proteins, Docking, Inhibitors.

INTRODUCTION

Apoptosis is the process of cell death which is the main event to control or regulate the cellular processes during critical phases of a cell. The survival of a cell is maintained by a balance of pro-apoptotic and anti-apoptotic stimuli. The abnormality in the apoptosis mechanism leads to the development of cancer. But in many cases of

cancer the process of apoptosis is usually failed due to the improper signaling of apoptotic as well anti-apoptotic proteins. The anti-apoptotic proteins play a vital role in regulating the apoptosis. Their role is to inhibit the apoptotic process. This understanding of apoptotic signaling leads to the investigation of therapeutic activation of apoptosis in cancer cells as a potential anticancer strategy. For the effective activation of apoptosis, the anti-apoptotic proteins are needed to be inactivated.

Hence our present study is to focus on the anti-apoptotic proteins and their interactions with other proteins and their respective ligands which leading to their inactivation by binding with much affinity by performing the comparative docking studies of ligand(s) with anti-apoptotic proteins(s).

MATERIALS AND METHODS

Retrieval of 3-D protein structures & ligand molecules

The information about family of anti-apoptotic proteins are collected from the literature. For the selected number of proteins the 3D structures were retrieved using PDB (http://www.rcsb.org/pdb/home/home.do). The ligand molecules were retrieved from the Drugbank database (http://www.drugbank.ca/).

Tertiary structure prediction of anti-apoptotic proteins

The sequences for the anti-apoptottic proteins were retrieved from Uniprot/SwissProt database (http://www.uniprot.org/help/uniprotkb) and submitted to the 3D Jigsaw (http://bmm.cancerresearchuk.org/~3djigsaw/) & CPH models 3.0 (http://www.cbs.dtu.dk/services/CPHmodels/) homology modeling servers for the tertiary structure prediction. Both the servers are automated and comprising alignment accuracy measures, energy minimization algorithm to refine models and neural network based method respectively.

Anti-apoptotic proteins and their inhibitors docking studies

Selected anti-apoptotic proteins were docked with their respective ligand molecules using Molegro Virtual Docker (MVD). The best pose with the highest scores were considered among the docking poses generated for each ligand molecule. The Moldock along with Rerank scores are generated for each different docking pose.

RESULTS & DISCUSSION

Among the many proteins, five of the anti-apoptotic proteins were selected as they are mainly involved in mediating signal of apoptosis. The 3-D structures for some proteins are available in PDB and some were predicted using homology modeling servers. The clusterin, myxoma, livin are the proteins which are having the similarity with other proteins indicated in brackets in the table1.

Table 1: List of the Anti-apoptotic Proteins & their PDB IDs selected for Docking Studies.

S. No.	Protein	PDB ID	Length
1	Bcl-2 (isoform-2)	1gjh	166
2	Survivin	1xox	117
4	Clusterin (intimin – tir 90 complex)	2zwk	184
3	Myxoma (vaccinia virus protein)	2vvw	162
5	Livin (peptide antagonists of melanoma inhibitor)	1oxn	298

Table 2: Docking Scores for Anti-apoptotic Proteins with Selective Ligands.

Protein	Ligand	Moldock score	Rerank score
Bcl-2	**Cpm-1285**	**-123.16**	**-96.7891**
	Bh31-1	-104.08	-78.3841
	Terphenyl	-90.54	-78.8778
Survivin	Aspirin	-65.74	-61.92
	Folic acid	**-142.97**	**-121.98**
	Fusidic acid	-150.17	-101.266
	l- aspartic acid	-61.38	-52.92
	l-fusidic acid	-69.66	-62.99
	Leucovorin	-139.83	-118.03
	Vit-c(ascorbic acid)	-63.63	-60.83

	Salicylic acid	-50.95	-51.20
Clusterin	Alpha - methyl-n-acetyl-d-glucosamine	-65.20	-57.14
	di(n-acetyl-d-glucosamine)	**-81.81**	**-65.41**
	n-acetyl-d-glucosamine	-64.58	-54.40
Myxoma	Selenomethionine	-55.81	-51.78
	Choline	-36.51	-32.28
	Divalproex	-19.22	-18.56
	Glycodiazine	-80.71	-70.34
	Nitroprusside	-74..88	-65.76
	Oxybuprocaine	**-101.76**	**-82.69**
	Perchlorate ion	-39.07	-33.94
	Polysterene sulfate	-26.25	-22.05
	Sodium lauryl sulphate	-78.84	-70.13
	Valproic acid	-52.90	-47.37
Livin	Betamethasone	-96.511	-45.40
	Clobetasole	-38.20	-30.11
	Dexamethasone	-79.3992	-73.0383.
	Diflorasone	**-85.0075**	**-8.17999**
	Exemestane	-85.1632	-57.886

*The bold marked ligand molecules showing the appropriate score comparatively to other ligands.

The apoptosis process can be activated in cancer state by inhibiting the anti-apoptotic proteins. The families of IAPs (Inhibitors of Apoptosis) which inhibit the apoptosis process are Bcl-2, Survivin, Clusterin, Myxoma, Livin. By the comparative docking studies, for each anti-apoptotic protein the respective ligands disclosed their interaction energies. The highest score obtained for the ligand docking can be considered as an effector / inhibitor molecule.

CONCLUSION

By performing the comparative docking studies of ligands with anti-apoptotic proteins, the best scoring ligands were identified based on the best docking scores. The identified ligands can be further explored to generate more potential drug candidates through ligand-based drug design approaches. These docking studies also provide

in-depth understanding of the interactions at the binding sites of ligand groups and receptor site. The structural details of the docking surface areas and ligand groups activity can be further studied to enhance the much better inhibitor molecules to deactivate the anti-apoptotic proteins thereby leading to the activation of apoptosis in cancer cells.

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Corresponding Author:
A. Krishna Chaitanya
Dept. of Biochemistry & Bioinformatics,
GITAM University,
Email: *chy2ak@gmail.com*