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COMPUTATIONAL PREDICTIVE ANALYSIS OF MULTIDRUG RESISTANCE-ASSOCIATED PROTEIN5

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ABSTRACT: *Multiple Drug Resistance is a major cause of problems occurring in treatments of various diseases such as cancer. Getting over this problem will lead us to better cure and prevention. Various protein sequences (Multidrug Resistance associated Protein family) involved in causing these different drug resistances have been identified.MRP5 is found to be involved in many cases of drug resistance.In silico prediction of the structure of MRP5 would serve as a good platform for further dynamics of its response. If we analyze it in every aspect, it would be very helpful in further treatments. Structure of a protein is a very essential feature for function prediction. In order to get accurate assumption, we need to have perfect structural data. Getting virtual model for the MRPs which have no three dimensional structure reported, would help us in future In Silico analysis by using several modeling algorithms.*

Keywords— Multidrug Resistance,ABC Transporters,Homology Modeling

1. INTRODUCTION

Multidrug resistance proteins are members of the ATP-binding cassette (ABC) superfamily of membrane transporters that mediate the ATP-dependent transport of various substrates across biological membranes[1].MRPs are known for the broad spectrum of (anticancer) drugs that they transport out of cells, raising the possibility of their involvement in clinical multidrug resistance. MRP5 appears to be a nucleotide analogue pump. McAleer et al. found that cells transfected with an MRP5 gene construct are resistant to heavy metals (e.g., cadmium chloride and potassium antimonyl tartrate).The physiological function of MRP5 remains to be determined[2].Computational tools provide researches to understand physicochemical and structural properties of proteins. A large number of computation tools are available from different sources for making prediction regarding the identification and structure prediction of proteins. The amino acids sequence provides most of the information required for determining and characterizing molecule's function, physical and chemical properties. Computational characterization of the features of proteins found or predicted in completely sequenced proteomes is an important task in search for knowledge of protein function. Three dimensional structures for these proteins were yet not available. Hence to describe it structural features and to understand molecular function, the model structures for these proteins are essential requirement. Structure prediction experiments of MRP5 are carried out in our present work to move a step ahead in the area of molecular understanding of this protein and Multidrug resistance caused by it.

2. RELATED WORK

Multidrug Resistance –associated Protein (MRP)isoform 1 through 6 mRNA are expressed .In Caco-2 cells ,the expression of MRP-5 is found almost similar to MRP-1[3].MRP5,like MRP1 ,is expressed in almost every tissue tested[4] and along with MRP 4 and 6, MRP 5 has partially been characterized[5].MRP5 show ubiquitous expression and found to be over expressed in many tissues.There is no registered structure for MRP5 found on publicly available database.The In silico structure prediction of MRP5 would provide an important platform for further analysis.

3. MATERIALS AND METHODOLOGY

Sequence Acquisition and Analysis

Retrieval of the amino acid sequence and informations for Multidrug Resistance associated Protein 5 was carried out using different publicly available data sources[6].

Protein	Accession No.	Sequence Length
MRP5	BAA76608.1	1437

Table 1. Sequence information Used for the Analysis

Further Physicochemical properties and were analyzed using several computational applications available on Expasy server[6] and Peptide property calculator Physico-chemical properties of amino acids can be used to study protein sequence profiles, folding and function. Homology searches using heuristic method (BLAST) and secondary structure was predicted using web based servers such as SOSUI [7] and SOPMA [8].

Putative structure prediction using comparative modeling.

Predictive modeling was carried out using web based program SWISS-Model and a python based software Modeller [9].The structures on the basis of homology were selected as a template from pdb.Prediction of three dimensional structure using preferable template is performed with the use of Modeller.Then the respective structure is examined for quality using computer aided applications, such as Protein Structure Validation Software [10], WHATIF [11], and YASARA.

4. EXPERIMENTS AND OBSERVATIONS

Sequence of MRP5 was retrieved from NCBI and other information acquired are shown in Table1.Physicochemical Properties such as Isoelectric pH,Moalr absorbance coefficient (Extinction Coefficient),Instability index ,Aliphatic index, Grand average of hydropathicity (GRAVY) of a protein is essential to be checked for overall structural or functional prediction. These observations are shown in following Table.

Protein	MRP5
Instability Index	39.81
Molecular Weight	160614.29
pI	8.83
EC	142670
-R	150
+R	166
AI	99.42
GRAVY	-0.016

Table 2 Details of Physicochemical Features

Further for secondary structure prediction SOSUI and SOPMA were used. These web based prediction servers provide us the secondary structural features. The observation Table 3 and figure 1 shows the result for secondary structural features prediction.

Alpha helix	52.33%
310 helix	0.0%
Pi helix	0.0%
Beta bridge	0.0%
Extended strand	13.29%
Beta turn	4.66%
Bend region	0.0%
Random coil	29.71%
Ambiguous state	0.0%
Other state	0.0%

Table 3 Secondary Structure information

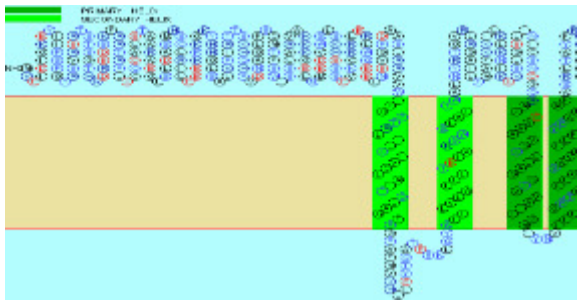

Fig. 1. Secondary Structural Features

For comparative modeling for the putative Three dimensional structure prediction of MRP5 was performed using MODELLER. Following figure shows the structure predicted and analyzed in PSVS for validation.

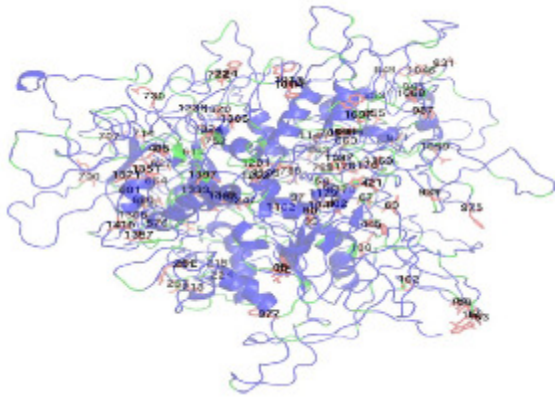

Fig.2. Three Dimensional Structure predicted in MODELLER and validated in PSVS.

Further energy minimization and checking the stereo chemical accuracy is carried out in YASARA which is shown in following figure.

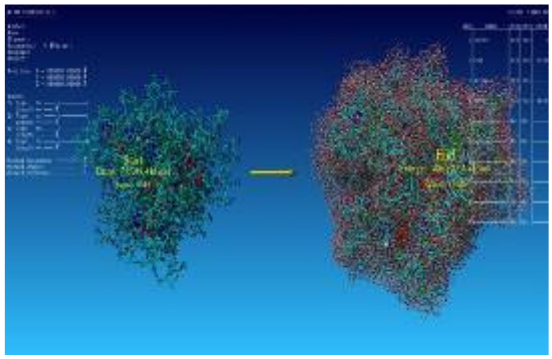

Fig. 3 Energy Minimization carried out in YASARA.

Table 4, 5(a) and 5(b) and Figure 4 shows the observations of stereo chemical validation for the predicted structure which were resulted using Ramachandran Plot and WHATIF.

Most favoured regions	Allowed regions	Disallowed regions
76.4%	17.3%	6.3%

Table 4 Ramachandran Plot Summary for the Predicted Structure

Program	ProsaII(-ve)	Procheck (phi-psi)	Procheck (all)
Raw score	-0.48	-1.35	-1.30

Table 5(a) Global Quality Score

Program	WHATIF
Z -score	-3.36

Table 5(b) Z score

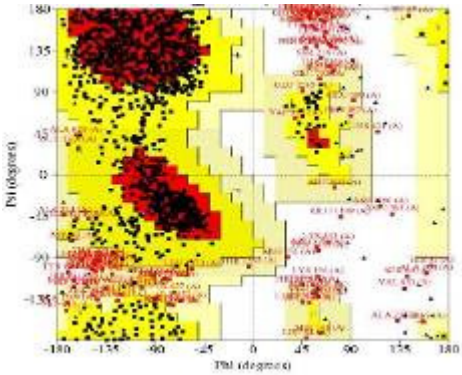

Fig.4 Ramachandran Plot for the Predicted Structure

5. DISCUSSION

Through predictive analysis of MRP5 using several computational applications, we got a putative three dimensional model.Such a model could be used to predict the dynamics and patterns of response of the MRP5 to different compounds, which would be useful in future work related to drug resistance occurring due to MRP5.In silico model availability would enhance the analytical practices and predictions which may provide good platform for further research in the area of multidrug resistance.

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