Research Article

Homology Modeling and Docking Studies on SEMA3A as a Receptor for Targeting Multiple Myeloma

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ABSTRACT

Conventional therapies have been useful in principle for the treatment of Multiple Myeloma; still there is no proper cure for the disease. Towards this quest, we aimed to utilize the computational resources to find out novel targets and their drug molecules. We found out that semaphorin 3A (SEMA3A) has a role in the progression of the disease and the complications associated with the disease. Further investigations into the problem, we established that there is no experimental structure available for the protein in the available data sources. Hence, our work stems from the building of a homology model of the receptor using SWISSMODEL workspace. We performed the model validation to verify the obtained model through which the results gave us a strong confidence level of our model. Further we performed the primary & secondary prediction to provide more insights into the selected receptor. The results identified the receptor as stable in nature. Docking studies were performed for the receptor, taking the available market drugs for multiple Myeloma as ligands. We included herbal ligands which have been shown to be effective against the treatment of the disease in literature. We took 11 available FDA approved drugs and 7 herbal compounds for the purpose of molecular docking. Our results clearly revealed that the herbal drugs are better lead compounds for the treatment of the disease. They also have minimal side effects when administered. The herb, GYNOSAPONIN with maximum negative energy showed good binding energy (-423.51). This can be subjected to experimental validation.

Keywords: SEMA3A, Multiple Myeloma, Homology Modeling, Docking.

INTRODUCTION

SEMA3A, also known as semaphoring 3A are defined as shot range proteins which are serving as inhibitory molecules. It basically acts as an important signaling link for precise neuron formation. Semaphorin 3A (SEMA3A) promotes the formation of dendrites and inhibits axon formation.[1,2] Multiple myeloma is commonly called as the plasma cell cancer. There have been years of continuous research still in the current scenario; the disease is treatable but not curable. A number of neurological complications have been associated with the disease after the treatment too. In order to minimize these complications, a signaling molecule such as SEMA3A has been considered as a receptor with the hope of generating a better response for the treatment of myeloma. SEMA3A is known to be a potential anti-angiogenic molecule. Binding of secreted semaphorin 3A (SEMA3A) to NRP1 induces the collapse of neuronal growth cones by activating the signal-transducing subunit(s) of the receptor complex, that is, class A plexins, a family of transmembrane proteins whose cytoplasmic domain is endowed with an R-Ras GAP activity that inhibits integrin function.[3] SEMA3A is an important element for the progression of the disease. Hence, our work treats it as a receptor to target the drugs for better treatment of the disease. Through various computational searches, it was established that SEMA3A has not been crystallized experimentally and 3D structure is not available. Hence, we resorted to the establishment of its 3D structure through homology modeling which is an established approach for predicting structures.[4] Here we present our work; SEMA3A is used as a receptor against the available drug targets for the disease. According to the literature, it has also been observed that Multiple Myeloma can be treated with the help of herbal targets. To explore this, we also took herbal compounds which have been reported to help cure the disease. We took a total of 11 available FDA approved drugs and also took 7 herbal compounds for the purpose of molecular docking. Docking of PDB structure of the receptor and ligands were done by using HEX8.0.0.0Cuda[5]. Our results clearly indicate that the herbal drugs are better lead compounds for the treatment of the disease. Also, they have minimal side effects when administered. Docking of PDB structure of the receptor and ligands were done by using HEX8.0.0.0Cuda. The herb, GYNOSAPONIN with maximum negative energy showed good binding energy.

MATERIALS AND METHODS

Sequence Retrieval

The amino acid sequence of Semaphorin-3A from human was retrieved from a protein knowledge database UniProt[6] having accession no. Q14563.

Primary and Secondary Structural Characterization

The amino acid composition and physico–chemical properties like theoretical isoelectric point (pI), molecular weight, total number of positive and negative residues, extinction coefficient[7], half-life,[8,9] aliphatic index,[10] instability index[11] and grand average hydropathicity

(GRAVY)[12] of Semaphorin-3A were computed using the ExpasyProtParam server.[13] The secondary structural features were predicted using Self Optimized Prediction Method from alignment (SOPMA).[14,15]

Tertiary Structure Prediction and Evaluation

The tertiary structure of Semaphorin-3A was not present in PDB. It was generated through homology modelling approach using Swiss Model Workspace[16,17]. The generated structure was validated using Verify3D by generating Ramachandran plot.

Active Site Prediction

Active Site prediction of the generated 3D structure of Semaphorin-3A was carried out by Schrodinger package.[18]

Molecular Docking

Eleven drugs and seven natural herbs related to the treatment of multiple Myeloma were identified. Their chemical structures were retrieved from Pubchem[19] in SDF format. The SDF format was converted into PDB format by using OpenBabel.[20] Docking of PDB structure of the receptor and ligands were done by using HEX8.0.0.0Cuda.[5] The herb, GYNOSAPONIN with maximum negative energy showed good binding energy.

The interaction image of the receptor with this ligand was also obtained for better understanding.

RESULTS AND DISCUSSION

Physio-Chemical Characterization of SEMA3A: For the prediction of the physio-chemical parameter computation, PROTPARAM tool was used (Table 1).

The computed isoelectric point for SEM3A is 7.05. It suggested that the given protein sequence is slightly basic in nature. The computed value of instability index was 43.50 which is indicating that the SEM3A is slightly unstable.[13] The extinction coefficient of the SEM3A protein was 115835 and the aliphatic index was 71.17. The aliphatic index denotes to the relative volume of a protein that is engaged by aliphatic side chains. Greater aliphatic index of proteins specified their structural stability.[13] A rise in the aliphatic index raises the thermo stability of enzyme. The calculated GRAVY was found -0.607. The grand average of hydropathy (GRAVY) value for a peptide or protein is calculated as the sum of hydropathy values of all the amino acids, divided by the number of residues in the sequence.[22] This lesser range of value showed superior interaction with water.

Table 1: Physio-chemical characterization of sema3a using protparam

Protein	Sequence length	Mol Wgt (kDa)	pI	Ext. Coeff.	Instability index	Aliphatic index	GRAVY	-R	+R
Q14563	771	88889.3	7.05	115835	43.50	71.17	-0.607	99	97

Table 2: Parameters of predicted Secondary growth structure generated by SOPMA

Protein	α-helix	β-sheet	γ-Turns	Disulphide bridge
Sema3a	197	169	67	-

Table 3: Active Site Prediction using Schrodinger

Protein Name	D-Score	Site (Amino Acids)
SEMA3A	1.026 (SITE3)	1,325,341,342,415,416,417,419,420,421,438,445, 446,447,449,462,463,464,465,469,470,472

Structural Analysis: The secondary structure prediction was carried out for the protein using the SOPMA tool. The predictions are summarized in Table No. 2. According to the SOPMA, the secondary structure displays Alpha helix (197), Extended strand (169) and Beta turn (67) in the protein. The results revealed that alpha helix dominated among secondary structure elements, followed by extended strands, which shows that amino acid sequence of this enzyme is hydrophilic in nature and have better interaction, which can be further facilitates the drug discovery process.

Homology Modeling of SEMA3A: Since, there is no experimental data available for the SEMA3A structure, the homology modeling was carried out for predicting the 3-D structure of the protein using Swiss Model Workspace (Figure 1). The protein sequence of SEMA3A

was retrieved from the UniProt Database and then it was used for model building. Out of total three models we chose the first, because of having the maximum QMEAN score. The QMEAN Score of the chosen model is 0.67, which signified 67% confidence on the structure.
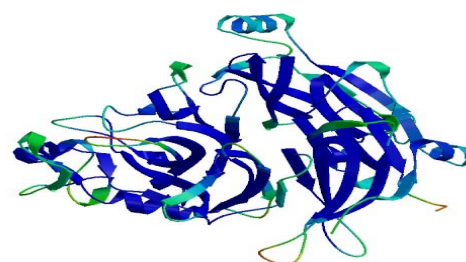
Figure 1: Homology Model of SEMA3A using SWISSMODEL workspace having a QMEAN score of 0.67 signifying 67% confidence on the structure.

MODEL VALIDATION: Quality of generated models was evaluated with PROCHECK8 server by Ramachandran plot analysis. Validation of generated models was further done by VERIFY 3D. The results obtained are shown in figure 2. The Ramachandran Plot of SEMA3A showing 96.36% of the residues are present in the allowed region.
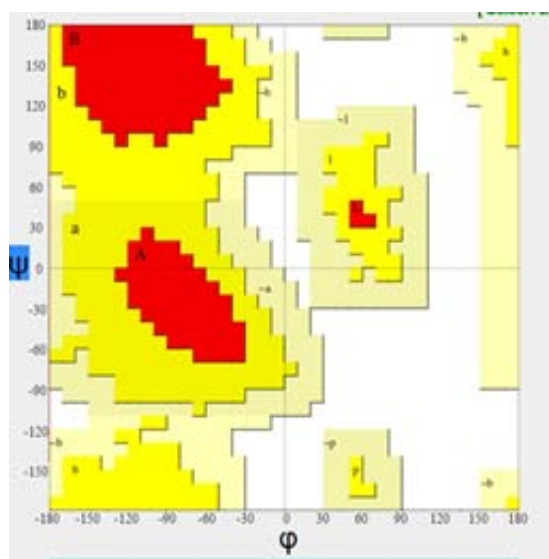
Figure 2: Ramachandran Plot of SEMA3A showing 96.36% of the residues being in the allowed region.

Active Site Prediction: The functional characterization was performed using the active site prediction module in Schrodinger (Table 3). Out of total five active sites we chose the third one. As it is having the best D score value which is also greater than 0.6.

Docking: Docking was carried out by using HEX. Table-4 and 5 shows the output of docking process. We took total 11 drugs and their 3 analogous from PubChem for docking (Table 4). Then we moved on to the natural herbs. Through literatute search we took total 7 herbs in which the herb Gynosaponin is showing the best docking result with the target (Table 5). It is having the minimum energy which is double in comparision to the rest ligands (Figure 3, 4). So in a summarised way we can say that, the target protein-Gynosaponin complex has the best score of -423.51. The experimental validation can be done using this herb.

Table 4: Docking Score for chemical drugs

Ligands	Etotal
carfilzomib	-208.12
carmustine	-245.53
cyclophasphomide	-337.21
lenalidomide	-252.23
melphalan	-280.74
mozobil	-252.23
pomalidomide	-327.68
predinosine1	-256.23
thalidomide	256.23
vincristine	-220.01
carfilzomib	-208.12

Table 5: Docking Score for Natural Herbs

Ligands	Etotal
astagaloside	-340.41
berb	-268.99
gynosaponin	-423.51
turmeric	-308.13
Cyclophasphomide analogue1	-288.62
Cyclophasphomide analogue2	-250.37
Cyclophasphomide analogue3	-250.17
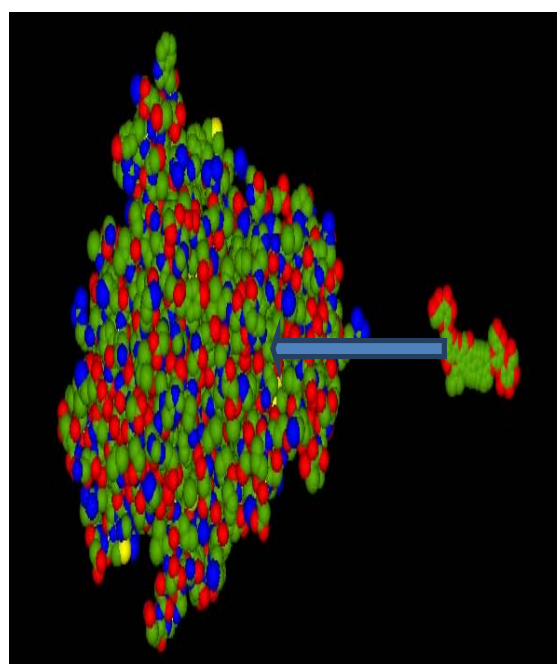
Figure 3: Depicting the docked location of the ligand.

CONCLUSION

SEMA3A is known to be a potential anti-angiogenic molecule. It basically acts as an important signaling link for precise neuron formation. SEMA3A is an important element for the progression of the disease. It has been considered as a receptor with the hope of generating a better response for the treatment of myeloma. Hence, in our study we treated it as a receptor to target the drugs for better treatment of the disease. According to the literature, it has also been observed that Multiple Myeloma can be treated with the help of herbal targets. So, we also took herbal compounds which have been reported to help cure the disease. In total We took 11 available FDA approved drugs and 7 herbal compounds for the purpose of molecular docking. Our results clearly revealed that the herbal drugs are better lead compounds for the treatment of the disease. They also have minimal side effects when administered.

The herb, GYNOSAPONIN with maximum negative energy showed good binding energy. The experimental validation can be done using this herb.

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