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Structure Prediction of Gasdermin a Receptor by Homology Modelling

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Abstract

The gasdermins are a family of recently identified pore-forming effector proteins that cause membrane permeabilization and pyroptosis, a lytic pro-inflammatory type of cell death. A role in the regulation of cell proliferation and/or differentiation is suggested by the differentiation status-specific expression of gasdermin proteins in epithelial tissues. One of the GSDM protein is Gasdermin A (GSDMA), which decreased in stomach and esophageal cancers, suggesting a tumor suppressor role. GSDMA receptor antagonists have been researched as potential treatments for inflammatory diseases and baldness. GSDMA's significance in a wide range of disorders makes it an important therapeutic target. As a result, homology modelling of the GSDMA receptor was undertaken in the current study using the crystal structures of Mus musculus (GSDMA3), Human gasdermin D (GSDMD), and Murine gasdermin D (murine GSDMD). The best model was chosen based on the validation results after 20 models were developed utilising single template-based approaches. The generated structures can be used for further binding site and docking studies in the future.

Keywords: GSDMA, Inflammatory disorders, Homology modeling, Model validation.

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1. Introduction

Gasdermins (GSDMs) are a conserved family of functionally diverse proteins which are mainly expressed in the gastrointestinal (GI) tract, skin and immune cells. Gasdermin protein family encoded with six paralogous genes includes Gadermin A (GSDMA), Gasdermin B (GSDMB), Gasdermin C (GSDMC), Gasdermin D (GSDMD), Gasdermin E (GSDME) and DFNB59 (Pejvakin) in humans and GSDMA1-3, GSDMC1-4, GSDMD, GSDME and DFNB59 in mice[1]. Gasdermin A is one of the gasdermin protein which regulate programmed cell death. It's triggered by caspases which activates by inflammasomes through external stimuli or internal dysfunction[2]. Gasdermin A have tumor suppressor activity which can act as a therapeutic target for various diseases[3]. Hence it has many properties, its structural and functional information is still not clear[4]. Because of the enormous time necessary to

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produce protein for crystallization, the number of experimentally resolved protein structures lags behind the sequence data available. Homology modelling is one of the computer-based methods for predicting the 3D structure of a protein from its amino acid sequence. It is regarded as the computational structure prediction method with the highest level of accuracy. It comprises of a number of simple steps and easy to apply. For homology modelling, there are numerous different programme and servers that are used. Maximizing the quality of homology modelling is essential because the functioning of the model depends on the calibre of the created protein 3D structure. As a result, using 3D structures of proteins created using homology modelling, protein interactions have been clarified. This aids in the discovery of fresh medication prospects. The crystal structure of Gasdermin A receptor does not available in protein database bank (PDB), hence in this study the 3D structure of GSDMA was predicted by single template - based homology modeling. Number of models were generated and validated using Ramachandran plot and ERRAT values. The predicted model would be useful for the development of new drugs for the GSDMA based diseases.

2. Materials and methods

2.1. Template selection

Gasdermin A receptor (accession No: Q96QA5) amino acid sequence was retrieved from the Uniprot database. BLASTp search was carried out to find the templates for homology modelling. Based on sequence identity, query coverage and E-value templates were selected. It has been statistically proven that if the level of sequence identity is above 30%, then up to 90% of the poly-peptide conformation tends to be modelled well. Below 30% identity models are unreliable due to increasing alignment errors[5].

2.2. Modelling and validation of GSDMA receptor

The three dimensional structures of GSDMA were modelled using EasyModeller 4.0 which uses MODELLER 9.12 and Python 2.7.1 in the backend[6]. Single template based approaches were carried out using four different templates. The predicted models were assessed and validated using the RMSD values. Later, the validation by programmes such as Ramachandran plot and ERRAT was carried out. Using SAVES server[7], Ramachandran plot is plotted for each of the predicted models which depicts the percentage of amino acids in favoured region. ERRAT is a protein structure verification algorithm that is especially well-suited for evaluating the progress of crystallographic model building and refinement. The SWISS-MODEL web server automatically calculates the QMEAN scoring function for the estimation of the local and the global model quality based on the geometry, the interactions and the solvent potential of the protein model. ProSA (Protein Structure Analysis) evaluates and compares the submitted structure against high-resolution structures deposited in PDB[8].

3. Results and discussion

3.1. Template selection

The templates such as crystal structure of

Table. 1. The query coverage and identity values of the templates obtained from blast search.

PDB ID	Max Score	Total score	Query Coverage %	E Value	Identity %
5B5R	627	627	99 %	0.0	73.26 %
6N90	186	186	99 %	3e-53	32.92 %
6VIE	180	180	98 %	5e-51	32.40 %
6N9N	174	174	98 %	1e-48	31.10 %

Mus musculus (5B5R), crystal structure of human gasdermin D (6N9O), crystal structure of Murine gasdermin D (6N9N and 6VIE) were selected for modeling[9]. The top templates obtained from blast search are shown in (Table. 1.).

3.2. Model generation and validation

Model was generated using single template - based approaches. In this study, the model generation was done using Easy Modeller 4.0. Five models were developed of the four templates (5B5R, 6N9O, 6VIE, and 6N9N) independently. As a result, 20 models were generated for this investigation. At first, RMSD was calculated between the generated models and the templates. The effectiveness of the generated models was assessed using ERRAT and Ramachandran plot analysis. (Table. 2.) contains a summary of all the validation outcomes. The best model within each template-based model was selected based on criteria such low RMSD, a high percentage of residues in favoured and allowed regions, and a high ERRAT quality value and Qmean score[10]. No model was selected using 6N9O as template, as it contained large RMSD and low ERRAT quality. Three models were selected as final model and they are represented in Fig. 1. and their RC plot is shown in Fig. 2. and ERRAT plot in Fig. 3. The RMSD between these three selected models was found to be 1.436, 0.336, and 2.296.

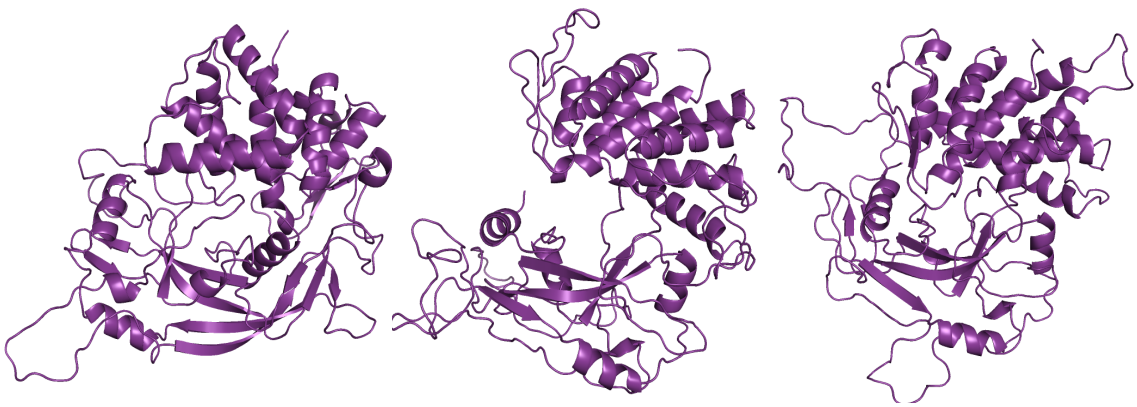
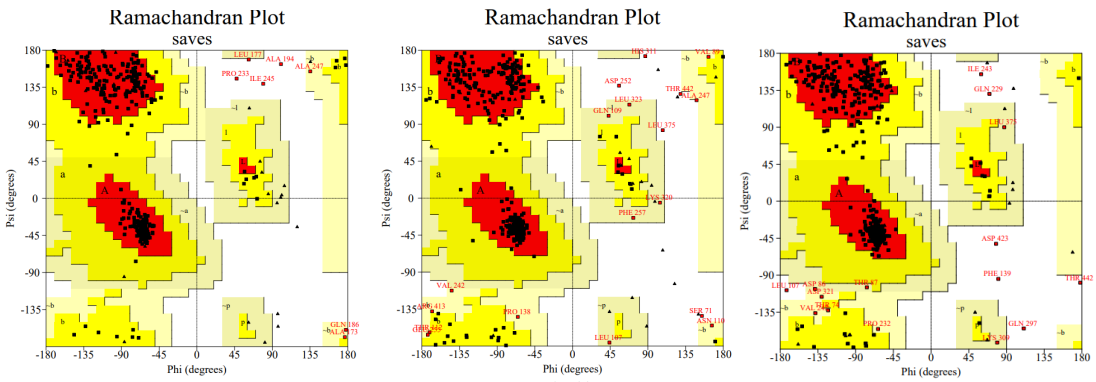


Fig. 1. Selected models for the Gasdermin A receptor were generated using various templates. (A) Homology model of GSDMA using the template 5B5R (Model 1). (B) Homology model of GSDMA using the template 6VIE (Model 13). (C) Homology model of GSDMA using the template 6N9N (Model 19).

Table. 2. Validation of the Gasdermin A generated models using the SAVES server.

MODEL	TEMPLATE PDB ID	RAMACHANDRA PLOT NUMBER OF RESIDUES IN			RMSD	ERRAT – overall quality factor	QMEAN global score	ProSA web Z – score Overall model quality
		Favoured (%)	Allowed(%)	Disallowed(%)				
	5B5R	**90.5**	**7.9**	**0.8**	**1.436**	**62.90**	**-3.35**	**-9.17**
		91.3	7.9	0.5	1.306	59.72	-3.35	-8.66
		90.5	7.4	1.0	1.387	65.90	-3.35	-9.42
		92.3	6.4	0.5	1.357	64.90	-3.20	-9.28
		91.8	6.9	0.3	1.356	64.20	-3.12	-9.17
	6N9O	86.2	12.0	0.5	1.300	45.88	-6.41	-5.85
		85.7	11.8	0.5	1.423	47.75	-6.41	-6.48
		85.9	11.5	0.5	1.315	43.63	-6.70	-5.8
		86.2	10.7	0.8	1.302	40.82	-6.95	-6.23
		86.2	12.0	0.0	1.297	36.07	-6.77	-5.62
	6VIE	83.9	11.3	2.0	0.548	40.13	-7.22	-6.91
		85.4	11.8	0.8	0.388	47.23	-7.14	-7.51
		85.4	**10.2**	**1.5**	**0.336**	**45.11**	**-7.55**	**-7.2**
		84.9	11.3	1.0	0.482	43.90	-7.92	-6.68
		85.2	11.5	1.5	0.670	43.35	-6.85	-6.21
	6N9N	85.7	11.8	1.5	2.708	37.97	-7.54	-5.71
		86.4	11.8	0.8	2.411	41.05	-6.43	-5.82
		85.2	11.0	1.8	2.450	39.30	-7.08	-5.71
		85.4	**11.0**	**1.8**	**2.296**	**45.19**	**-6.63**	**-5.6**
		85.9	11.0	1.3	3.224	37.70	-6.87	-5.84



(A) (B) (C)

Fig. 2. Ramachandran plot for the selected models using SAVES server.

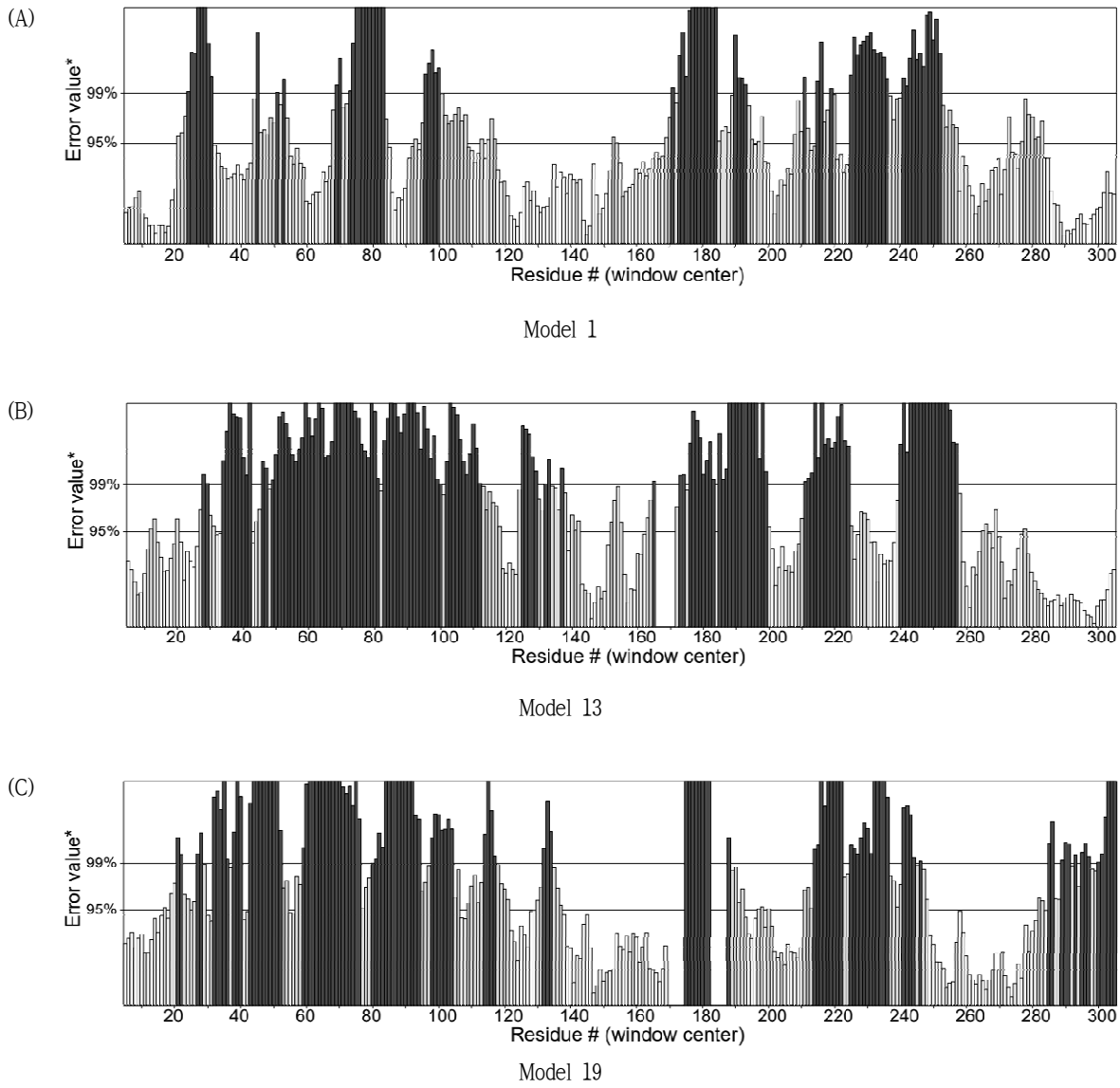


Fig. 3. ERRAT plot for the selected models using SAVES server.

4. Conclusion

Three dimensional models for Gasdermin A receptor (GSDMA) were generated using single template based approaches. Models generated using 5B5R, 6N9N and 6VIE are found to be reliable. Additionally, these models could be utilized for docking and binding site studies, which could be beneficial for disorders linked to GSDMA.

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