Biomedical Letters ISSN 2410-955X– An International Biannually Journal

Research article
2020 | Volume 6 | Issue 2 | Pages 204-208

ARTICLE INFO

Received
April 02, 2020
Revised
May 19, 2020
Accepted
June 28, 2020

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Keywords
Parkinson's disease
PRKN
Parkin
Structure prediction
Protein-protein interaction

How to Cite
Nasir BA, Nasir MA, Ikram MF, Waqas M, Razaq R. Comparative Modeling and Protein-Protein Docking analyses to reveal the Potential Binding Pockets of Parkin: a Candidate Parkinson disease. Biomedical Letters 2020; 6(2):204-208.

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Special Issue: Computational drug designing and molecular docking analyses

Open Access

Comparative Modeling and Protein-Protein Docking analyses to reveal the Potential Binding Pockets of Parkin: a Candidate Parkinson disease

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Abstract

There has been progressive improvement in computational drug design from last decade. Numerous computer aided compounds has been reported against neurodegenerative disorders. Parkinson disease is a common neurodegenerative disease in humans associated with *PRKN* encodes Parkin. Parkin is involved in tumor repressing, prevents cells from cancers as growing and dividing exponentially uncontrolled. Almost 200 *PRKN* mutations have been identified leads to cause Parkinson disease having symptoms of cancers, loss of memory and postural instability. In this research article, 3D structures of parkin were predicted by using comparative modelling approach. The predicted structures were evaluated by using different evaluation tools and 80.600% of overall quality factor. Molecular docking analyses of Parkin and PINK1 were conducted by using PatchDock. The least global energy of -45.35 Kcal/mol was observed having the interacting residues in the binding pocket. The reported interacting residues may help for target specific drug design against parkin. This research article can be a major initiative to predict the therapeutic drug targets against Parkinson disease.

Introduction

PRKN is an associated gene of human Parkinson disease (PD). PRKN encodes 'Parkin' protein consists of 465 amino acids. Parkin is involved in the degradation of damaged protein. Ubiquitin is a degrading molecule which serves as a signal to move damaged proteins to proteasomes.

Parkin is known to be involved in maintaining the quality of mitochondria. However, its exact mitochondrial function is not known yet. It has been reported that the activity and configuration of parkin have several significant activities. Parkin is involved in tumor repressing activity leads to prevent the cells from cancers as growing and dividing exponentially uncontrolled [1].

The *PRKN* is located at chromosome 6 named as FRA6E. FRA6E is a fragile area as it is un-stable to rearrangement and breakage. Due to decrease in parkin protein activity, parkin helps the cells to grow and divide in an uncontrolled manner leads to tumor formation [2].

There are almost >200 *PRKN* mutations identified that may cause Pdiseased. The symptoms are movement and balance issues, cancers, loss of memory and postural instability. The mutations in PRKN lead to an abnormally small parkin that is nonfunctional and rapidly degradable. Other mutations may cause change in DNA building blocks leading to a defective version of the parkin [3].

The cause of mutations in *PRKN* leads to PD is still vague. The loss of parkin activity caused by mutations may lead to degradation of ubiquitin leads to accumulation of damaged proteins in cell. The damaged proteins disturb the normal function of cell.

PINK1 protects the mitochondrial dysfunction during cellular stress by phosphorylating mitochondrial proteins. It involves in the clearance of damaged mitochondria through selective autophagy (mitophagy) by mediating activation and translocation of PRKN [4].

PD is a complex neurodegenerative disorder leads to rigidity, postural instability and onset usually before 40. It differs from classic PD by early DOPA-induced dyskinesia, diurnal fluctuation of the symptoms, sleep benefit, dystonia and hyper-reflexes. Pathologically, the patients show loss of dopaminergic neurons in the substantia nigari, similar to PD just like schizophrenia [5]. However, lewy bodies (intraneuronal accumulations of aggregated proteins) are absent. The majority of the cases are sporadic suggesting a multifactorial etiology based on environmental and genetic factors [6]. However, some patients present with a positive family history for the disease. Familial forms of the disease usually begin at earlier ages and are associated with atypical clinical features [7]. The current work is an initial step towards the prediction of therapeutic drug targets for the treatment of PD. In this study, the binding domain of parkin was predicted by using protein-protein interaction analyses. Computational analyses help to solve the biological problems by utilizing the statistical and mathematical models [8] [9, 10].

Materials and Method

Sequence retrieval

The protein sequence of Parkin was retrieved through UniProt KB [11, 12] having accession number O60260. It was observed that the 3D structure of parkin has not been reported through X-ray crystallography and NMR techniques [13]. The stereo-chemical properties of parkin was calculated by Protparam [14]..

Structure prediction

After sequence retrieval, 3D structure of parkin was predicted through homology modeling, threading and *ab initio* approaches. Various tools were used for 3D structure prediction. Homology modelling is performed by LOMETS [15] and an offline standalone homology modeling program MODELLER [16]. The query sequence was subjected to BLASTp against PDB to obtain a suitable template for homology modelling. A template with 95% query coverage and 90% of sequence similarity was observed. The extra chains and ligands were removed from template by using UCSF Chimera [17]. 3D structure prediction was performed by using MODELLER for homology modeling approach. Threading approach was also utilized to predict the 3D structure of parking. The online tools including QUARK and CE-threader were also utilized for structure prediction [18, 19]. I-Teaser was also used for 3D structure prediction [18, 19]. HHpred was used to predict the secondary structure of the protein [20, 21].

Structure Evaluation

The predicted structure was evaluated to check the integrity of the predicted structure. Numerous tools were used to evaluate the different parameters of the

predicted structure. All the generated models were evaluated by using Rampage evaluation tool which draws a Ramachandran plot. Comparative graph comprises of favored region, allowed region and outliers was generated. All the generated models were evaluated by Rampage to verify the phi and psi angels [22, 23]. ERRAT was used to calculate the non-bonded interactions of residues and overall quality factor of the predicted structures [24]. WhatCheck was employed to evaluate the predicted models [25]. Verify3D was used to evaluate the hydrogen bond estimation [26]. ProCheck was used to verify the streo-chemical properties of the predicted structures [27].

Protein-Protein Docking

The interacting partner of parkin was observed by using String online database [28]. PINK1 was involved in clearance of damaged mitochondria through selective autophagy (mycophagy) by mediating activation and translocation of *PRKN* [29]. The protein-protein molecular docking analyses was performed by using PatchDock and Clustal-Pro [30]. All the generated complexes were further refined by using FireDock. The interactional residues were analyzed by UCSF Chimera [31-33].

Results and Discussion

Various structure prediction tools were used to predict the 3D structure of parkin. Various structure evaluation tools were used to evaluate the generated models. The final selected structure was visualized by UCSF Chimera (**Fig. 1).**

The selected model has more efficient results as 80.600% quality factor by ERRAT was observed. 92.26% Verify3D value, What-Check 85%, Rampage shows 95.66 favored region and Procheck predicts that protein has 90% optimizes physiochemical properties.

Protein-protein docking was performed by using PatchDock and interacting residues were observed (**Fig. 2**).

39 interacting residues of parkin were observed interacting with 42 active residues of PINK1. Ile-162 was interacting with Gln-63 and Gln-64, Glu-172 showed interaction against Gly-93 and Gly-94. Similarly, Thr-545 showed interaction with Cys-449 and Cys-451. All active residues from both the proteins were observed in the binding domains. The docked complex showed least global binding energy of -45.35 Kcal/mol.

Gly159, Gln160, Ser161, Ile162, Gly163, Lys164, Glu172, Pro201, Gly202, Gln205, Glu206, Arg207, Ala208, Pro209, Pro215, Pro289, Gly290, Val293, Asp294, Asn320, Tyr321, Pro322, Cys323, Gln327, Asn332, Thr333, Pro334, Ser335, Leu372, Asp373, Asp375, Gly376, Cys377, Arg543, Thr545, Glu546, Lys547, Cys548 And Glu551 interacting residues were observed in the docked complex as an active binding domain.

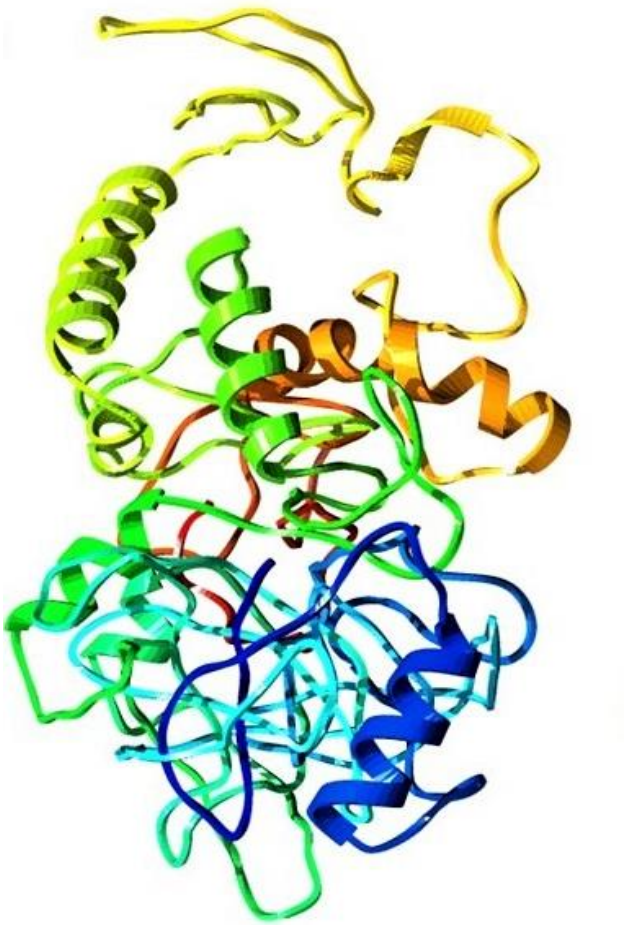

Fig. 1: 3D structure of parkin.

Conclusion

In this article, comparative modelling approach was used to predict the 3D structure of parkin. Various evaluation tools were utilized to evaluate the quality of the predicted structure. Protein-protein molecular docking was performed to generate the parkin and PINK1 docked complex to understand the interactive phenomenon more effectively, which may help to understand the nature insights of PD. This research can be a major initiative towards the development of effective drug targets against PD by targeting parkin.

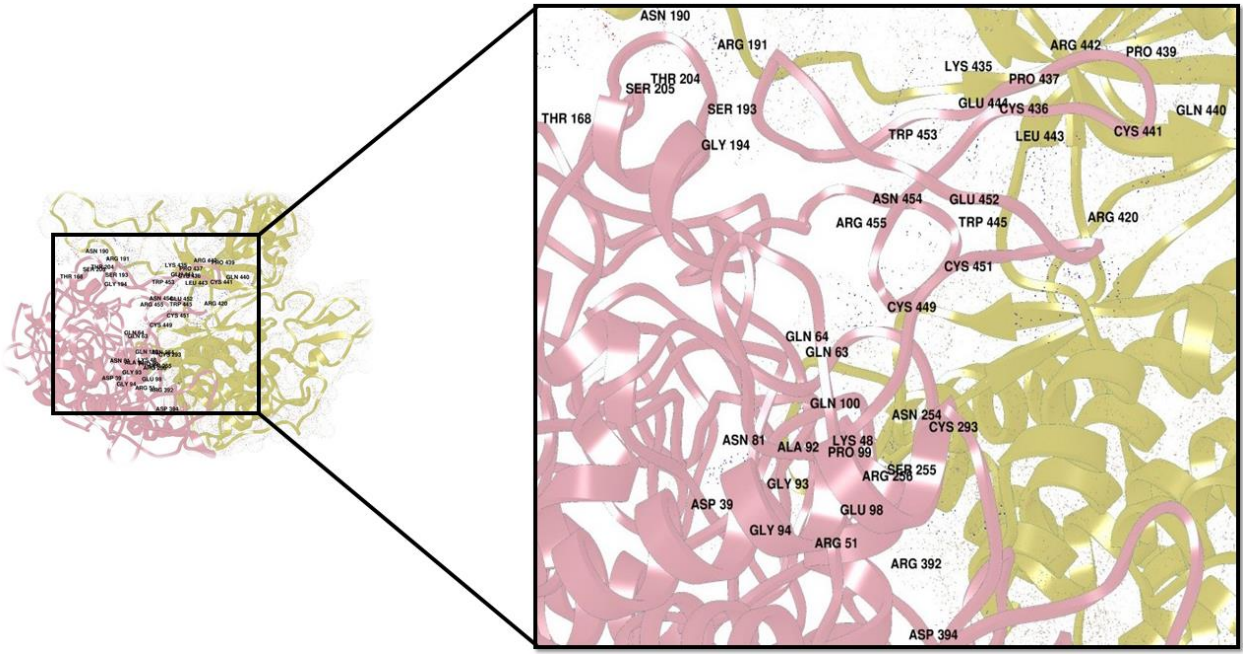

Fig. 2: The interacting residues of Parkin (Golden) and PINK1 (Pink) docked complex.

In future, targeted docking will be carried out against several ligands to check the efficiency of novel ligands against PD.

Acknowledgments

Authors are very thankful to GCUF for providing us a platform for this work.

Conflict of interest

Authors have no conflict of interest.

Authors' contributions

All authors contributed equally to this work.

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