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Computational investigation on the conformational dynamics of C-terminal truncated α-synuclein bound to membrane

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ABSTRACT

Accelerated progression rates in Parkinson's disease (PD) have been linked to C-terminal domain (CTD) truncations of monomeric α-Synuclein (α-Syn), which have been suggested to increase amyloid aggregation *in vivo* and *in vitro*. In the brain of PD patients, CTD truncated α-Syn was found to have lower cell viability and tends to increase in the formation of fibrils. The CTD of α-Syn acts as a guard for regulating the normal functioning of α-Syn. The absence of the CTD may allow the N-terminal of α-Syn to interact with the membrane thereby affecting the normal functioning of α-Syn, and all of which will affect the etiology of PD. In this study, the conformational dynamics of CTD truncated α-Syn (1–99 and 1–108) monomers and their effect on the protein–membrane interactions were demonstrated using the all-atom molecular dynamics (MD) simulation method. From the MD analyses, it was noticed that among the two truncated monomers, α-Syn (1–108) was found to be more stable, shows rigidness at the N-terminal region and contains a significant number of intermolecular hydrogen bonds between the non-amyloid β-component (NAC) region and membrane, and lesser number of extended strands. Further, the bending angle in the N-terminal domain was found to be lesser in the α-Syn (1–108) in comparison with the α-Syn (1–99). Our findings suggest that the truncation on the CTD of α-Syn affects its interaction with the membrane and subsequently has an impact on the aggregation.

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1. Introduction

The development of intracellular aggregates of fibrils of the intrinsically disordered protein α-Synuclein (α-Syn) is the main characteristic feature of PD that distinguishes it from other neurodegenerative disorders (Breydo et al., 2012; Eisenberg & Jucker, 2012; Stefanis, 2011). The involvement of fibrillation of α-Syn in neuronal cell death in PD is now well-known (Singh et al., 2017; Wong & Krainc, 2017). The N-terminal region (residues 1–60), which is primarily involved in membrane binding (Zarbiv et al., 2014), the non-amyloid β-component (NAC) domain (residues 61–95), which is essential for amyloid formation (Waxman et al., 2009), and the highly charged C-terminal region (residues 96–140), which is known to interact with polyamines, metal ions, and cellular protein (Eliezer, 2013). The remarkable capacity of truncated CTD α-Syn to aggregate and convert into pathological fibrils has led to the detection of many types of truncated CTD α-Syn in both normal and PD brains (Anderson et al., 2006; Bhattacharjee et al., 2019; Delcourt et al., 2018; Li et al., 2005; Muntané et al., 2012). *In vitro*, truncated CTD α-Syn speeds up the development of oligomers and fibrils in comparison to full-length protein (Games et al., 2014; Levitan et al., 2011; Ma et al., 2018; McGlinchey et al., 2019; Ni et al., 2019; Terada et al., 2018; Van der Wateren et al., 2018). When full-length α-Syn and truncated CTD α-Syn are co-expressed, full-length α-Syn pathologically accumulates more quickly (Daley et al., 2011; Sorrentino et al., 2018; 2020; Ulusoy et al., 2010). Up to residues 85–90, when the NAC domain starts, deletion of C-terminal residues speeds aggregation (Iyer et al., 2018; Murray et al., 2003). Because the NAC region functions as the core of amyloid fibrils, further truncation reduces the chances of aggregation (Giasson et al., 2001; Murray et al., 2003; Stephens et al., 2020). Since truncated CTD α-Syn is more toxic than full-length α-Syn, cells expressing it are more susceptible to oxidative stress (Bassil et al., 2016; Kanda et al., 2000; Ma et al., 2018; Stefanova et al., 2001). According to studies, the charges in the positive N-terminal and negative C-terminal regions help to partly protect the NAC domain (Bertoncini et al., 2005). However, α-Syn has dynamic conformations with a significant degree of compactness that are stabilized by long-range interactions (Bertoncini et al., 2005). Due to the impact of electrostatic and hydrophobic contacts that may hinder aggregation, these interactions take place between the NAC area and the C-terminal region as well as between the N-terminal and C-terminal regions (Bertoncini et al., 2005). Additionally, it has been stated that the membrane-sensor

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Computational investigation on the effect of the peptidomimetic inhibitors (NPT100-18A and NPT200-11) on the α-synuclein and lipid membrane interactions

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ABSTRACT

Parkinson's disease (PD) is associated with α-synuclein (α-Syn), a presynaptic protein that binds to cell membranes. The molecular pathophysiology of PD most likely begins with the binding of α-Syn to membranes. Recently, two peptidomimetic inhibitors (NPT100-18A and NPT200-11) were identified to potentially interact with α-Syn and affect the interaction of α-Syn with the membrane. In this study, the effect of the two peptidomimetic inhibitors on the α-Syn-membrane interaction was demonstrated. DFT calculations were performed for optimization of the two inhibitors, and the nucleophilicity (N) and electrophilicity (ω) of NPT100-18A and NPT200-11 were calculated to be 3.90 and 3.86 (N); 1.06 and 1.04 (ω), respectively. Using the docking tool (CB-dock2), the two α-Syn-peptidomimetic inhibitor complexes (α-Syn-NPT100-18A and α-Syn-NPT200-11) have been prepared. Then all-atom molecular dynamics (MD) simulation was carried out on the α-Syn (control), α-Syn-NPT100-18A and α-Syn-NPT200-11 complex systems in presence of DOPE: DOPS: DOPC (5:3:2) lipid bilayer. From the conformational dynamics analysis, the 3-D structure of α-Syn was found to be stable, and the helices present in the regions (1–37) and (45–95) of α-Syn were found to be retained in the presence of the two peptidomimetic inhibitors. The electron density profile analysis revealed the binding modes of NAC and C-terminal region of α-Syn (in the presence of NPT200-11 inhibitor) with lipid membrane are in the close vicinity from the lipid bilayer centre. Our findings in this study on α-Syn-membrane interactions may be useful for developing a new therapeutic approach for treating PD and other neurodegenerative disorders.

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1. Introduction

Parkinson's disease, dementia with Lewy bodies, and multiple system atrophy are together known as synucleinopathies, and it is thought that progressive buildup of the synaptic protein α-Syn (encoded by SNCA) plays a significant role in the pathogenesis of these diseases. There is presently no disease-modifying medication for the approximately 10 million people around the world who suffer from synucleinopathies (McKeith et al., 2005; Prasad & Hung, 2021; Spillantini et al., 1997; Wakabayashi et al., 1998). Although the exact mechanisms leading to pathological accumulation of α-Syn remain unclear, there is evidence to suggest that changes in the rate of synthesis play a role (Farrer et al., 2001; Fujioka et al., 2014; Singleton et al., 2003; Tan & Skipper, 2007). Accumulation and aggregation of α-Syn cause toxic oligomers to develop, which may spread from cell to cell in a manner similar to prion diseases (Brundin et al., 2010; Crews et al., 2010; Dehay et al., 2013; Kruger et al., 1998; Lashuel et al., 2002, 2013; Lee et al., 2010; Luk et al., 2012; Polymeropoulos et al., 1997; Xilouri et al., 2016). Neurodegeneration may be facilitated by oligomers of α-Syn that vary greatly in size, shape, and conformation. Oligomers of varied sizes have been suggested to be harmful in certain investigations, whereas greater molecular weight aggregates have been suggested in other studies (Bucciantini et al., 2002; Bartels et al., 2011; Conway et al., 2000; Cremades et al., 2012). In recent studies, Molecular dynamic simulation and biophysical investigations have shown that α-Syn binding and subsequent penetration of the neuronal membrane are significant steps in this process, supporting the possibility that higher order α-Syn aggregates are hazardous (Bernal et al.,2020; Bortolus et al., 2008; Masaracchia et al.,2018; Tsigelny et al., 2008; Van Rooijen et al., 2010). Thus, it is suggested that interactions between α-Syn and lipids in the neuronal cell membrane constitute a crucial step in the oligomerization and cytotoxicity processes (Beyer, 2007; Tsigelny et al., 2012). As a result, methods for removing α-Syn from the membrane, accelerating breakdown and clearance, avoiding aggregation, or reducing α-Syn formation may be effective therapeutic approaches. In earlier research, antibodies (Games et al., 2013), proteolytic enzymes (Spencer et al., 2013), and small compounds (Toth et al., 2014) that reduce α-Syn fibrillation or aggregation were used to target α-Syn aggregates. A library of 34 peptidomimetic analogues was

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Conformational dynamics of A30G α-synuclein that causes familial Parkinson disease

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ABSTRACT

The first gene shown to be responsible for autosomal-dominant Parkinson's disease (PD) is the SNCA gene, which encodes for alpha synuclein (α-Syn). Recently, a novel heterozygous A30G mutation of the SNCA gene associated with familial PD has been reported. However, little research has been done on how the A30G mutation affects the structure of α-Syn. So, using atomistic molecular dynamics (MD) simulation, we demonstrate here the key structural characteristics of A30G α-Syn in the free monomer form and membrane associated state. From the MD trajectory analysis, the structure of A30G α-Syn was noticed to exhibit rapid conformational change, increase in backbone flexibility near the site of mutation and decrease in α-helical propensity. The typical torsion angles in residues (Val26 and Glu28) near the mutation site were observed to deviate significantly in A30G α-Syn. In the case of membrane bound A30G α-Syn, the regions that were submerged in the lipid bilayer (N-helix (3-37) and turn region (38-44)) found to contain higher helical content than the elevated region above the lipid surface. The bending angle in the helix-N and helix-C regions were noticed to be relatively higher in the free form of A30G α-Syn (38.5^0) than in the membrane bound form (37^0). The A30G mutation in α-Syn was predicted to have an impact on the stability and function of the protein based on ΔΔG values obtained from the online servers. Our results demonstrate that the A30G mutation in α-Syn altered the protein's α-helical structure and slightly altered the membrane binding.

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KEYWORDS
A30G mutation; α-synuclein; molecular dynamics; Parkinson's disease; membrane dynamics

1. Introduction

Parkinson's disease (PD) is the most common movement disorder and the second-most prevalent neurodegenerative disease, and it is marked by a number of non-motor symptoms in addition to its cardinal motor symptoms (Balestrino & Schapira, 2020). Degeneration of nigrostriatal dopaminergic neurons and the widespread development of Lewy bodies, aberrant neuronal cytoplasmic inclusions primarily made of aggregated α-synuclein (Syn), a widely expressed protein produced by the SNCA gene, are the clinical hallmarks of Parkinson's disease (PD) (Chen et al., 2020; Mahul-Mellier et al., 2019; Shahmoradian et al., 2019; Spillantini et al., 1998). Seven distinct missense mutations (A30P, E46K, H50Q, G51D, A53T, A53E, and A53V) have been found to be linked to PD (Nishioka et al., 2017; Steward et al., 2008), and SNCA was the first gene to be identified as causing autosomal dominant PD (Fusco et al., 2018; Fusco et al., 2016; Gonzalez-Garcia et al., 2021; Grey et al., 2015; Kulenkampff et al., 2021; Loov et al., 2016; Man et al., 2021; Musteikytė et al., 2021; Newberry et al., 2020; Theillet et al., 2016; Thompson et al., 2016; Zhang et al., 2019). Among the seven distinct missense mutations, the A53T mutation was the first missense mutation found in SNCA and most common in families with Greek or Italian roots (Galvagnion et al., 2015). In case of H50Q mutation, since there was no evident case of PD as compared to controls in large databases, so it was considered to be not pathogenic (Appel-Cresswell et al., 2013; Blauwendraat et al., 2018; Campioni et al., 2014; Galvagnion et al., 2016; Klein & Westenberger, 2012; Proukakis et al., 2013). Other SNCA missense mutations (E46K (Zarranz et al., 2004; Pimentel et al., 2015), G51D (Kiely et al., 2015 Fusco et al., 2014; Lesage et al., 2013) and A53E (Martikainen et al., 2015; Pasanen et al., 2014)) have been identified in a number of families and/or cases, but A30P was only discovered to co-segregate in five affected individuals of one German family (Rejko et al., 1998). Many other studies have highlighted that multiple amino acid substitutions at the position 30 in wild type (WT) α-Syn may represent a potential pathological site in association with Parkinson's disease (Burre, 2015; Cascella et al., 2019; Liu et al., 2021; Perlmutter et al., 2009; Stok & Ashkenazi, 2020; Ulmer & Bax, 2005; Ulmer et al., 2005). In a recent study, five affected people from three unrelated Greek families were found to have a new heterozygous A30G mutation of the SNCA gene where the clinical, functional characteristics and genetic findings of A30G

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Screening of druggable conformers of α-synuclein using molecular dynamics simulation

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ABSTRACT

Intrinsically disordered proteins (IDPs) are becoming an engaging prospect for therapeutic intervention by small drug-like molecules. IDPs structural binding pockets and their flexibility exist as a challenging target for standard druggable approaches. Hence, in this study, we have performed and identified the most probable druggable conformers from molecular dynamics simulation on α-synuclein based on the structural parameters: radius of gyration (R_g), solvent accessible surface area (SASA) and the standard secondary structure content. We found the conformers showing lower solvent accessible surface area and higher secondary structure content of α-helical are defined to be suitable binding pockets for druggability.

Keywords: *α-synuclein; druggability; intrinsically disordered proteins; molecular dynamics.*

1. INTRODUCTION

Intrinsically disordered proteins (IDPs) exhibit prevalent key roles in the biological processes of all diversified living organisms. IDPs are broadly involved in crucial cellular activities, including regulation and signal transduction [1] and are also linked with a number of human diseases [2-4] such as in expression of cancer related proteins (p53, breast cancer protein BRCA-1/2) and other neurodegenerative disorders including the α-synuclein and tau protein in Alzheimer's disease [5]. IDPs structural attributes of high flexibility and lack of stable secondary and tertiary structures, often engaged themselves at the hubs of protein-protein interaction networks and consequently associates with multiple partners [6-8]. The primary step of fibrillogenesis of IDPs requires the stabilization of monomeric or oligomeric partially folded conformations as they are devoid of a stable structure. As Statistically stated, 79% of malignancy related proteins and 57% of the distinguished cardiovascular disease-related proteins are anticipated to contain shorter regions which are disordered and no longer than 30 residues in length [9-10]. Therefore, IDPs can be perceived as active drug targets and to play a significant role in drug design [11-25]. However, prior to drug design on a specific protein it is crucial to evaluate its possibility to be a decent drug target. Also, presence of binding cavities of appropriate geometrical shape for ligand binding ("druggability"), acts as a crucial assessment problem in drug discovery [26]. Therefore the drug design strategy for IDPs are yet in their early stages [27] in comparison with the ordered proteins for which there exists well-developed drug design pipelines[28]. In IDPs, the number of binding cavities were predicted to be more in number than in the case of ordered proteins of similar length. In addition, from the literature review studies, it is evident that the cavities of IDPs exerting greater surface areas and larger volumes shows higher druggability than those of ordered proteins. In addition, IDPs must possess important biological roles and establish their association with the specific disorder, which aids in drug designing towards IDPs. The obstacles along with the possible measures in designing the drugs for IDPs have been been reported [5]. Although there are few limitations developed during drug designing targeted IDPs of which major defaults were lack of efficient experimental screening strategies and determining specificity that impacts ligand-protein interactions. The enzymes and cell surface receptors become the target of the most of the drugs by regulating their functions, wherein the small molecules can mimic the interactions made by their natural substrates [29]. Even though enzymes possess a certain degree of flexibility, their structures tend to fluctuate around equilibrium positions, making it easier to identify binding pockets and subsequently design drugs to fit in them. On the other hand, IDPs exist as large ensembles of structures, where their amino acid chains can rapidly form multiple conformations, sometimes within microseconds. They exhibit large conformational fluctuations and no evidence of permanent binding pockets. This type of conformational feature does not present suitable cavities for small drug-like molecules to form stable interactions [13-14, 30-31]. IDPs are frequently striking different postures. Allowing their highly dynamic nature into consideration, we have performed Molecular dynamics simulation on α-synuclein protein, a typical IDP, to get a better sampling of conformers. The compactness of a protein which is measured as Radius of gyration (R_g) is known to affect the stability and folding rate of proteins [32]. In addition to this, recent studies have reported the use of compactness to define the binding pockets in a protein [33-35]. Some of the studies have highlighted the idea of considering compactness (R_g) of the protein or protein-ligand complexes for binding site prediction [33,35]. Recent studies suggest that lower the R_g, the compactness of the ligand-protein complex is higher, causing the interactions between ligand and protein to be stronger [34] . Also, R_g depicts the significance of a more compact well-docked protein-ligand complex to be a better therapeutic agent [36]. Structure-based prediction of ligand

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Effect of ethanol as molecular crowding agent on the conformational dynamics of α-synuclein

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ABSTRACT

The functions of many proteins have been directly connected to their conformational changes. The macromolecular crowding environment inside the cell is known to have a significant impact on the equilibria and transition rates between different conformations of the protein. Here we demonstrate the effect of ethanol as crowders on the conformational dynamics of α- synuclein protein, a primary component of the fibrillar neuronal inclusions, and known as Lewy bodies that are diagnostic of Parkinson's disease. We observed the α-synuclein protein to experience stronger crowding effects with an increase in concentration of ethanol, the crowding agent. The findings that we obtained from this simulation study would serve as valuable guides for expected crowding effects on conformational dynamics of α- synuclein.

Keywords: *Parkinson's disease; Macromolecular crowding; presynaptic, aggregation.*

1. INTRODUCTION

In the recent past, many research studies have highlighted the importance of the protein dynamics as a valuable platform to understand the association between the structure and function [1-6]. The protein dynamics leads to the sampling of alternative conformations. Because of ligand binding [7] and post-translational modifications like phosphorylation [8], the conformational changes in the protein molecule gets initiated. As a result, the protein molecule adopts different conformations at varying functional states.

From these structures, the conformational changes at atomistic level can be studied. We generally see that biophysical characterizations of conformational changes in protein have been studied mostly under dilute and lesser densed medium. But the proteins perform their biological functions inside the cell which is highly crowded with macromolecules. For example, the cytoplasm of Escherichia coli contains high concentration of macromolecules (about 300–400 g/l and 30% of the total volume occupancy)[9]. Because of crowding in cell membranes, membrane proteins occupy a similar level of the total surface area [10]. However, the impact of crowding environment in cell on the equilibria and transition rates of diverse conformations of proteins are not understood well. The macromolecular crowding in the cell also likely to alter the energy landscapes of conformational changes in a protein resulting in more compact structures over more open structures [11]. Such effects of crowding have been verified experimentally [8].

Molecular Dynamics (MD) simulations have also been used as a tool to investigate the energy landscapes of a number of proteins in a crowding environment, in the context of either conformational change [12] or folding-unfolding transition [13-15]. In our study, we have investigated the consequences of ethanol as a crowding medium on the conformational dynamics of α-synuclein. We have found the crowding environment to affect the secondary structure content of α- synuclein to a greater extent.

2. MATERIALS AND METHODS

The initial 3-D structure of α-synuclein was taken from Protein Data Bank (PDB). In order to study the effect of different concentrations of ethanol, the crowding agent on the conformational dynamics of α-synuclein, we have employed MD simulation using the explicit solvent model. MD simulations were performed using periodic boundary conditions. In carrying out this experiment, cubic simulation boxes were filled with different proportions of water-ethanol mixtures using Packmol. In all these cases, the protein molecule was placed at the center of the simulation box using Leap module of AmberTools 14 program.

The protein molecules are then overlaid by equilibrated triple point charge (TIP3P) boxes in order to solvate the molecule of interest in the respective cubic simulation boxes. In addition, positively charged Na+ counter-ions were added into the system to neutralize the negative charge on the protein molecules. The volume occupied by ethanol was set up to about 0%, 5%, 10%, 20%, 50% and 100% of total volume. To study the structural dynamics of intrinsically disordered proteins (IDPs), MD simulations have been extensively in use. The AMBER14 package was used to perform MD simulation while protein and water molecules are described by parameters from ff99SB force field and TIP3P water molecules in the system. In each system, the charge of the protein was neutralized by adding Na+/Cl- counter ions. An isobaric–isothermal ensemble was applied using Langevin dynamics [16] along with Berendsen- thermostat [17] for temperature control. The system was subjected to one stage minimization to ensure the stability of the structure. The integration time step was set to 1 fs. To further take the system to

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ORIGINAL ARTICLE

Identification of FDA-approved drugs with triple targeting mode of action for the treatment of monkeypox: a high throughput virtual screening study

Varshita Srivastava[1] · Biswajit Naik[1] · Priya Godara[1] · Dorothy Das[2] · Venkata Satish Kumar Mattaparthi[2] · Dhaneswar Prusty[1]

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Abstract

According to the Center for Disease Control and Prevention, as of August 23, 94 countries had confirmed 42,954 Monkeypox Virus cases. As specific monkeypox drugs are not yet developed, the treatment depends on repurposed FDA-approved drugs. According to a recent study, the Monkeypox outbreak is caused by a strain with a unique mutation, raising the likelihood that the virus will develop resistance to current drugs by acquiring mutations in the targets of currently used drugs. The probability of multiple mutations in two or more drug targets at a time is always low than mutation in a single drug target. Therefore, we identified 15 triple-targeting FDA-approved drugs that can inhibit three viral targets, including topoisomerase1, p37, and thymidylate kinase, using high throughput virtual screening approach. Further, the molecular dynamics simulation analysis of the top hits such as Naldemedine and Saquinavir with their respective targets reveals the formation of stable conformational changes of the ligand–protein complexes inside the dynamic biological environment. We suggest further research on these triple-targeting molecules to develop an effective therapy for the currently spreading Monkeypox.

Keywords Monkeypox · Drug repurposing · Molecular docking · Molecular dynamics

Introduction

The Monkeypox outbreak, caused by a DNA virus named monkeypox virus [1], may affect many nations in both endemic and nonendemic regions [2]. The virus is studied to show nosocomial and household human-to-human transmission [3]. Infections with human Monkeypox can result in several medical issues, including fever, rash, and lymphadenopathies that ultimately lead to consequences like pneumonia, encephalitis, sight-threatening keratitis, and recurrent bacterial infections [4]. Despite a low transmission rate and a mild clinical course, the virus threatens the mass [5]. Due to the rapid increase in the number of cases related to the disease, there is an immediate need for therapeutic solutions. Computer-aided drug discovery can help in cost-effective decision-making before the expensive process of drug synthesis starts [6]. Therefore we conducted high throughput virtual screening (HTVS) of 1612 FDA-approved drugs against three therapeutic targets of MPVX, namely p37, topoisomerase1, and thymidylate kinase(TMPK), using CLC Drug Discovery Workbench 3.02.

P37 is a cellular cargo that interacts with Rab9 and TIP47 to build a virus-specific wrapping complex necessary for the enveloped virus, contributing to the multiplication of viral particles. There are no homologs of this protein in humans [7]. Topoisomerase1 is associated with DNA replication, repair, transcription, and other biological functions [8]. The enzyme TMPK plays a direct role in the metabolism of thymidine 5'-triphosphate(TPP); hence, it is a potential molecular target for developing antiviral drugs [9]. Fig. 1 clearly explains the functional significance and necessity of these three target proteins in the successful survival of the MPXV pathogen. Our HTVS study revealed 1612, 23, and 837 FDA-approved drugs with better binding affinity for the active/catalytic

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An *In Silico* Study for the Identification of Novel Putative Compounds Against the Wild and Mutant Type Penicillin Binding Protein 2 of *Neisseria Gonorrhoeae*

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Abstract: Penicillin-binding protein 2 (PBP2) is an enzyme crucial for cell wall biosynthesis during cell proliferation of *N. gonorrhoeae*. In the present work, the crystal structures of wild and mutant type PBP2 were analyzed to identify structural changes leading to antibiotic resistance. Other than these two targets, three other targets were generated by analyzing possible hot spots for mutations in PBP2. By using a reverse screening approach, fifteen molecules were screened and processed for ligand binding analysis with all five targets. The analysis of the above studies suggested that two compounds Guanosine 5'-diphosphate and Thymidine 3', 5'-diphosphate show the good binding affinity than Ceftriaxone and other compounds. Further, we have generated ten novel compounds using Ceftriaxone, Guanosine 5'-diphosphate, and Thymidine 3', 5'-diphosphate. To identify the novel findings, all novel compounds were docked against aforesaid five targets. The studies resulted in the finding of three best molecules that may be considered as suitable, potent, and generic inhibitors against *N. gonorrhoeae* other than Ceftriaxone.

Keywords: *Neisseria gonorrhoeae;* Ceftriaxone*;* Hot spot wizard; CUPSAT; Chimera; Designing; Molecular Docking.

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1. Introduction

Penicillin-binding protein 2 (PBP2) is a membrane-bound enzyme involved in the process of synthesizing cross-linked peptidoglycan, which is a major component of *N. gonorrhoeae* cell wall [1]. The biosynthesis of the bacterial cell wall has been extensively studied as a potential antibiotic target since membrane-based efflux pump systems play an important role in bacterial pathogenicity and antibiotic resistance in bacteria [2]. Till today, three classes of PBPs have been identified in *N. gonorrhoeae*: Class A (PBP1) and Class B (PBP2), high molecular mass transpeptidases, and Class C (PBP3 & PBP4), low molecular mass transpeptidases [3]. Previous studies have shown that Class C *transpeptidases* (PBP3 and PBP4) have a minor effect on the growth of the bacterium on deletion, whereas PBP1 & PBP2 are essential for cell viability and therefore a fatal target for carbapenems and other β-lactam antibiotics [4]. β-lactam antibiotics show less minimum inhibitory concentration (MIC) against PBP2 than PBP1, which makes PBP2 a primary killing target to fight *N. gonorrhoeae* [5]. β-

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An *In-Silico* Study of Stable and Environment-Friendly *Oryza sativa* Urease

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Abstract: Urea is one of the most extensively used fertilizers in agriculture but has a detrimental impact on the environment. One of the strategies to reduce this impact can be engineering modified plants containing urease enzyme with a considerably higher affinity for urea so that the urea applied in the fields can be significantly reduced. In this study, we have selected *Oryza sativa* Urease and generated stable mutants having a high affinity for urea. We modeled the 3D structure of the enzyme and identified the potential binding sites by analyzing the binding sites of similar proteins, i.e., 48 urea binding proteins. We found that mutation of Arg578 with Cys near the substrate-binding site of *Oryza sativa* Urease leads to a stable mutant protein that has a higher binding affinity for urea. This study will lead to a generation of environment-friendly, stable, genetically modified rice crop that consumes lesser urea, without compromising with crop productivity.

Keywords: *Oryza sativa* Urease; molecular docking; high urea affinity; molecular modelling; mutation analysis.

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1. Introduction

Plants suffice their nutrient requirements due to the presence of Nickel-dependent metalloenzyme- Urease (EC 3.5.1.5), present in various plant species as the housekeeper enzyme, playing a vital role in catalyzing the hydrolysis of urea, converting it to ammonia in the cytosol, which further acts as a substrate for Nitrogen assimilation in plants [1]. With an estimated production of 480.13 million metric tons in 2016-17, indicated by USDA (United States Department of Agriculture), *Oryza sativa* (Rice) is one of the predominantly grown cereal crops worldwide, crucially depending on urea as the main source of nitrogen fertilizer [2], which is accessible to plants, only after its hydrolysis, mainly by microbial urease, followed by plant ureases [3, 4].

Widespread application of urea for paddy growth has a detrimental impact on the ecosystem, due to the high activity of microbial ureases in the soil leading to ammonia volatilization, phytotoxicity, Nitrate accumulation, suspended seed germination [5], leaching, contamination of nearby water bodies, soil acidification, etc. [6,7]. Similar harmful effects of excess of another nutrient- Phosphorous, have been studied, and novel methods have been

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Computational Investigation on the Efficiency of Small Molecule Inhibitors Identified from Indian Spices against SARS-CoV-2 Mpro

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Abstract: Recently, small compounds from Indian spices (Carnosol, Arjunglucoside-I, and Rosmanol) have been identified as SARS-CoV-2 main protease (Mpro) inhibitors. The structural dynamics and characteristic features of binding of these small molecules to the SARS-CoV-2 Mpro are not well understood. Here, we have constructed the potential of mean force (PMF) for dissociating Mpro-small molecule inhibitor complexes from the umbrella sampling simulations using the weighted histogram analysis method. Mpro-small molecule inhibitor complexes exhibited relatively higher dissociation energy values than the alpha-ketoamide-Mpro complex (positive control) from the PMF calculations. We found that binding affinity between protein and ligand is higher in Mpro-Arjunglucoside-I complex [ΔG_{bind} = -19.74 kcal mol^{-1} from MM-GBSA and ΔG_{bind} = -9.13 kcal mol^{-1} from MM-PBSA] than in other three SARS-CoV-2 small molecule complexes. The MM-GBSA/MM-PBSA calculations revealed that the small molecule inhibitors studied in this work have substantially higher binding affinity for Mpro. We found the residues present in SARS-CoV-2 Mpro's binding pocket contributed the most binding free energy to SARS-CoV-2 Mpro-small molecule interactions. Our findings emphasize the structural and binding features of the identified small molecule inhibitors with SARS-CoV-2 Mpro, which could be relevant in developing therapeutic candidates to combat SARS-CoV-2.

Keywords: MM-GBSA; MM-PBSA; **the** potential of mean force; molecular dynamics; per residue energy decomposition; COVID 19.

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1. Introduction

A unique strain of SARS-CoV-2 coronavirus was first detected in Wuhan, a city in China's Hubei Province with a population of 11 million people, in December 2019, following a pneumonia outbreak with no clear reason. The virus has spread to more than 200 countries and territories around the world, and on March 11, 2020, the World Health Organization (WHO) declared it a pandemic[1, 2]. There was 288,767,991 laboratory-confirmed coronavirus disease 2019 (COVID-19) infection worldwide as of the 1st of January 2022, with 5,455,634 recorded fatalities. On 16 March 2020, outside of China, the number of cases and deaths surpassed those within the country [3]. SARS-CoV-2 belongs to the coronavirinae family of single-stranded RNA viruses, divided

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Effect of Double Mutation (L452R and E484Q) in RBD of Spike Protein on its Interaction with ACE2 Receptor Protein

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Abstract: The severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) caused coronavirus disease 2019 (COVID-19) pandemic has become a global health issue. Recently, the SARS-CoV-2 strain (B.1.617 double mutant variant) has raised alarms in India and other nations. B.1.617 variant was found to contain two key mutations (L452R and E484Q) in the RBD region of the spike protein. In this work, we have focussed on the effect of the double mutations in spike protein on its binding to the host cell receptor protein, angiotensin-converting enzyme 2 (ACE2). From the molecular dynamics simulation, we observed that the L452R and E484Q double mutant (DM) in spike protein utilizes unique strategies to achieve stable binding to ACE2 compared to the spike protein's wild type (WT). Using MM-GBSA/MM-PBSA algorithms, we found that the binding affinity between spike protein-containing DM and ACE2 is high (GB_{TOT} = -47.09 kcal mol^{-1}, PB_{TOT}= -19.93 kcal mol^{-1}) in comparison with spike protein WT and ACE2 (GB_{TOT} =-31.79 kcal mol^{-1}, PB_{TOT}= -6.33 kcal mol^{-1}). Stable binding of spike protein to ACE2 is essential for virus entry. They should understand interactions between them while designing drugs and treatment modalities to target or disrupt this interface.

Keywords: SARS-CoV-2; Coronavirus; ACE2 receptor; Double mutant, B.1.617; molecular dynamics; spike protein; COVID-19.

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1. Introduction

The ongoing spread of an infectious Coronavirus disease 2019 (COVID-19), caused by Severe Acute Respiratory Syndrome-Coronavirus-2 (SARS-CoV-2), an enveloped positive-stranded RNA virus into the community, poses exceptional challenges for the healthcare system due to high incidence and long incubation time [1]. SARS-CoV-2 is a novel coronavirus isolated on January 7, 2020 [2,3] by the Chinese Center for Disease Control and Prevention. The SARS-CoV-2 spike glycoprotein (spike protein) has gained significant attention since the outbreak of the COVID-19 pandemic due to its role in viral pathogenesis and immune response [4]. As of now, the vaccines that target spike protein, being used for COVID-19, provide host cells with a genetic transcript (mRNA or adenovirus) that ribosomes translate into a mutated spike protein. However, the nature and effect of mutations on the nascent spike protein remain

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A Computational Approach to Understand the Interactions Stabilizing the Aβ$_{1-42}$ Oligomers

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Abstract: Aβ peptide aggregation is known to be an important factor in the cause of Alzheimer's disease (AD). Smaller oligomers, the intermediates during the process of aggregation, are known to be more neurotoxic than matured fibrils. To gain the insight into the toxicity of low molecular weight Aβ$_{1-42}$ oligomers, it is essential to understand the course of its formation and the interactions involved. But the structural dynamics of Aβ$_{1-42}$ oligomers at the atomistic level and the interactions holding the monomeric units in the oligomeric structures still remain elusive. In this study, using molecular dynamics simulations, we have investigated the structural dynamics of the toxic Aβ$_{1-42}$ peptide intermediates and the interactions stabilizing the oligomers. From the structural dynamics of Aβ$_{1-42}$ oligomers, we observed the significant number of secondary structural transitions from α-helix to random coils in some of the monomeric units. From the interaction study, we noticed the involvement of hydrophobic contacts and inter-molecular hydrogen bonds in stabilizing the oligomers. Additionally, we subjected the equilibrated structure of the oligomers in the PDBSum server to examine the protein-protein interactions. The interaction results obtained from the PDBSum server was found to be consistent with the results obtained from the trajectory analysis.

Keywords: Aβ$_{1-42}$ peptide; Oligomers; Alzheimer's disease; Protein Aggregation; Protein misfolding.
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1. Introduction

Alzheimer's disease (AD), first described by the German psychiatrist, Alois Alzheimer, is categorized under a growing list of disorders [1] caused by β-sheet-rich insoluble filamentous deposits [2]. There is compelling evidence generated over the years that confirm Aβ peptides [3-5] to be the major stimulating factor of early onset of AD. These peptides are found in a variety of lengths, of which Aβ$_{1-42}$ is the most abundant and toxic in nature [6]. Structural investigations have reported that synaptic structure and function can be impaired even by the smallest Aβ oligomers and dimers [7-9]. Although the amyloid fibrils are not as toxic as the oligomers, they act as a reservoir of Aβ monomers. Under normal physiological conditions, small soluble oligomers are the most toxic species involved in aggregation, which leads to the formation of amyloid fibrils [10-12]. It has been shown that the characteristic soluble oligomers of Aβ$_{1-40}$ and Aβ$_{1-42}$ comprise of a mixture of dimer and tetramers which adopt secondary structure rich in β sheets and also denote the presence of oligomers consisting larger spherical particles with beta-strand structure [13-16]. The occurrences of Aβ$_{1-42}$ oligomers confined within plaques specify to the dynamic equilibrium between these species. In human neurons, Aβ$_{1-42}$ oligomers are found to be present intracellularly [17]. Determination of the

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Effect of Mutations in the SARS-CoV-2 Spike RBD Region of Delta and Delta-Plus Variants on its Interaction with ACE2 Receptor Protein

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Abstract: The outbreak of severe acute respiratory syndrome coronavirus 2 (SARS CoV-2) has undergone multiple significant mutations since its detection in 2019 in Wuhan, China. The emergence of new SARS-CoV-2 variants that can spread rapidly and undermine vaccine-induced immunity threatens the end of the COVID-19 pandemic. The delta variant (B.1.617.2) that emerged in India challenges efforts to control the COVID-19 pandemic. In addition to Delta, so-called Delta Plus sub-variants (B.1.617.2.1 and B.1.617.2.2) have become a new cause of global concern. Here we compare the interaction profile of RBD of the spike protein of the Delta and Delta-Plus variant of SARS-CoV-2 with the ACE2 receptor. From the molecular dynamics simulation, we observed the spike protein of Delta and Delta-Plus variant of SARS-CoV-2 utilizes unique strategies to have stable binding with ACE2. Using MM-GBSA/MM-PBSA algorithms, we found the binding affinity of spike protein of the Delta- variant-ACE2 complex is indeed high (GB_{TOT} = -39.36 kcal mol^{-1}, PB_{TOT}= -17.52 kcal mol^{-1}) in comparison with spike protein of Delta-Plus variant-ACE2 Complex (GB_{TOT} = -36.83 kcal mol^{-1}, PB_{TOT} = -16.03 kcal mol^{-1}). Stable binding of spike protein to ACE2 is essential for virus entry, and the interactions between them should be understood well for the treatment modalities.

Keywords: SARS-CoV-2; coronavirus; ACE2 receptor; Delta-Plus, B.1.617; molecular dynamics; spike protein; COVID-19.

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1. Introduction

Coronavirus disease 2019 (COVID-19), a disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has killed over 5.4 million people globally, making it the deadliest global health catastrophe since the 1918 influenza pandemic. The virus has continued to strike destruction since the World Health Organization (WHO) proclaimed it a global pandemic on March 11, 2020, with many countries seeing numerous waves of breakouts. Adaptive mutations can alter the pathogenic capacity of a virus in its genome. Even a single amino acid substitution can significantly impact a virus's ability to elude the immune system, making vaccine development difficult. SARS-CoV-2, like other RNA viruses, is prone to genetic evolution as it adapts to new human hosts, creating various variants with distinct characteristics from the ancestral strains. Periodic genomic sequencing of viral samples aids in the detection of new SARS-CoV-2 genetic variations circulating in populations, particularly in

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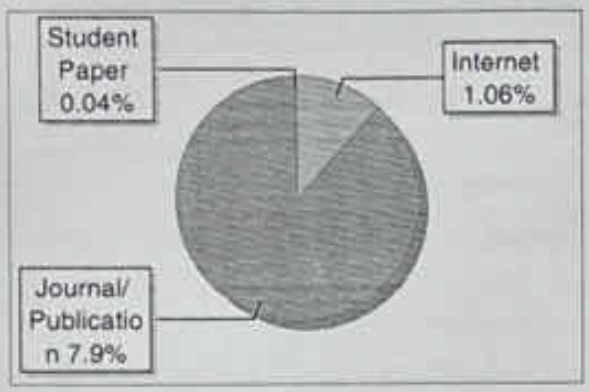

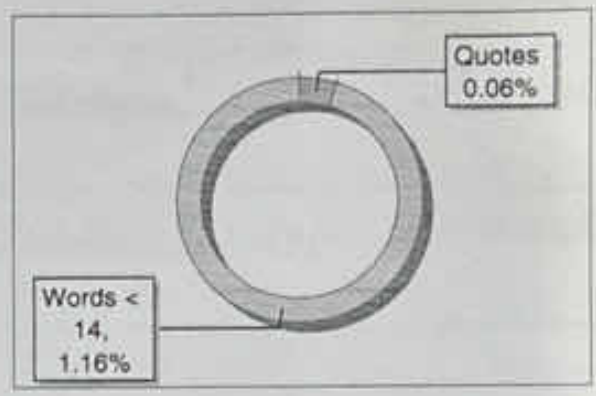

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