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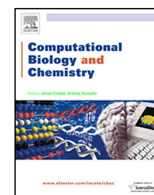

Research Article

Comparative homology model building and docking evaluation for RNA III inhibiting peptide of Multi drug resistant *Staphylococcus aureus* strain MRSA252

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ABSTRACT

Since last several years, infection caused by *Staphylococcus aureus* is challenging to cure using conventional antibiotics. The organism is a Gram-positive bacterial pathogen that can cause serious diseases not only in humans but also in animals, such as various skin infections, pneumonia, endocarditis and toxin shock syndrome. This bacterium causes such diseases by producing macromolecules such as hemolysins, enterotoxins, proteases and toxic shock syndrome toxin (TSST-1). This organism had developed the multidrug resistance by acquiring MEC-A gene. This account for made organism to come into the category of Superbug. Several studies showed that, the toxin production is induced by AIP and RAP via the phosphorylation of TRAP. TRAP is a 21 kDa protein and was believed to be associated with the membrane via SvrA Phosphoamino acid analysis revealed that TRAP is histidine phosphorylated in a signal transduction pathway that is activated by RAP. The inhibition of TRAP could be done by RIP (RNAIII-inhibiting peptide). The structure for RIP is still undiscovered to be used as inhibitor.

Present work has been carried out to get the structural insight with various online and offline homology modeling techniques such as SWISS-MODEL, MODBASE, GENO3D, CPHmodels and I-TASSER for getting unknown structural information target of RNAIII-activating protein from *Staphylococcus aureus* strain MRSA252 origin for their future exploration as a target in drug discovery process against MRSA.

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1. Introduction

The aim of comparative or homology protein structure modeling is to build a three-dimensional (3D) model for a protein of unknown structure on the basis of sequence similarity to proteins of known structure to be used as template(Bajorath et al., 1993; Bludell et al., 1988; Johnson, 1995; Sali, 1995). Comparative protein structure modeling remains the most accurate prediction method. The overall accuracy of comparative models spans a wide range, from low resolution models with only a correct fold to more accurate models comparable to medium resolution structures determined by crystallography or nuclear magnetic resonance (NMR) spectroscopy(Sánchez and Šali, 1997).

Staphylococcus aureus can cause disease through the production of toxins. Toxin production is autoinduced by the protein RNAIII-activating protein (RAP) and by the autoinducing peptide (AIP), and is inhibited by RNAIII-inhibiting peptide (RIP) and by inhibitory AIPs. RAP has been shown to be a useful vaccine target site, and RIP and inhibitory AIPs as therapeutic molecules to prevent and suppress *S. aureus* infections.

Staphylococcus aureus is a Gram-positive bacterial pathogen that can cause serious diseases in both humans and animals, such as various skin infections, pneumonia, endocarditis and toxin shock syndrome. This bacterium causes various diseases by producing virulence factors such as hemolysins, enterotoxins, proteases and toxic shock syndrome toxin (TSST-1) (Lowy, 1998; Torimiro et al., 2012). toxin production is induced by AIP and RAP via the phosphorylation of TRAP. In this signal transduction process, RIP (RNAIII-inhibiting peptide) was known to inhibit the phosphorylation of TRAP (Giacometti et al., 2003). TRAP is a 21 kDa protein and was believed to be associated with the membrane (Balaban et al., 2001) via SvrA (Garvis et al., 2002). Phosphoamino acid analysis revealed that TRAP is histidine phosphorylated in a signal transduction pathway that is activated by RAP(Gov et al., 2004). It is neccosry to find the effective drug target to treat such infections caused by MRSA. Present work has been carried out to get the structural insight with various homology modeling techniques for getting unknown structural

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information target of RNAIII-activating protein from *Staphylococcus aureus* strain MRSA252 origin for their future exploration as a target in drug discovery process against MRSA.

2. Material and methods

The process of elucidation of structure of TRAP is difficult task at time. The model building process includes multiple methods to get qccuraate model of protein.

2.1. Selection of protein sequence

Based on literature survey, sequence of Q6GFM2 (TRAP_STAAR) Protein, Target of RNAIII-activating Protein(TRAP) of *Staphylococcus aureus* strain MRSA252 origin was retrieved from UniProtKB/Swiss-Prot database. The availability of structural details was examined in not only using BLAST (Altschul et al., 1997) and Pfam based search but also carry out identification in PDB (Berman et al., 2000), MODBASE and SWISS-MODEL. Protein super classification was done by using on line web server http://supfam.mrc-lmb.cam.ac.uk/SUPERFAMILY/. The SUPERFAMILY hidden Markov model library representing all proteins of known structure predicts the domain architecture of protein sequences and classifies them at the SCOP superfamily level. (Gough, 2002)

3. Model building

All protein modeling were performed on standalone Discovery Studio platform (Accelrys Software, Inc.) and on line web server of SWISS-MODEL, MODBASE, GENO3D, CPHmodels and I-TASSER. Discovery studio is comprehensive package for drug discovery. Based on the target-template sequence alignment protocol, The sequence similarity and protein fold template was manually selected and given as input. Alignment of the Template and Target sequence was carried out by Align sequence Profiles Protocol with default parameters and instructions provided by supplier. Homology Modeling of TRAP protein generated in the Discovery Studio 2.1 (Accelrys Software, Inc.) of Build Homology model, side chain refinement and loop refinement protocol with default parameters. Also created TRAP protein modeled 3D model using same approach was carried out using default parameter needed for basic requirements for model building in online servers including SWISS-MODEL (Arnold et al., 2006), MODBASE (Eswar et al., 2001), GENO3D (Combet et al., 2002), CPHModels (Nielsen et al., 2010) and I-TASSER (Pandit et al., 2006). The process of model building was performed using standard instructions available on website respectively.

4. Model evaluation

4.1. Secondary structures analysis by Rasmol

Secondary structure details of all predicted structures were extracted by using protein visualizing software Rasmol 2.7.3 and Discovery Studio Visualizer. Secondary structure analysis was provided very littlebit amount of data to be used for the docking procedures.

4.2. Ramachandran plot analysis by Rampage

All Predicted structures assessment was analyzed by Ramachandran Plot with RAMPAGE (Lovell et al., 2003) in PDB format of the structure. This Method of Ramchandran Plot is quite easy to perform and carryout analysis. Results give favoured region, allowed region and outlier region.

4.3. Comparative protein (Profiles-3D) analysis

Profile 3-D protocol of discovery studio 2.1 was used for the verification of the all predicted structure and give the verification result in the scoring patent as verify score.The parameters used for the analysis was Explained in article for Homology modeling (Aparoy et al., 2008).

4.4. Comparison of protein health report

All predicted structures were analyzed by using protein health report tool in the discovery studio 2.1 for finding errors in the protein structures with the default parameters. Bond length, Bond angle, Main-Chain φ, ψ angles not allowed in Ramachandran region, Side-Chain conformation, Non planar Peptide Bond, Cis Peptide Bond, Abnormal C-alpha to C-alpha distances, Missing Main-Chain atoms, Missing Side-Chain atoms, Nonstandard atom names Chirality of C-alpha atom and Alternate Conformations were analyzed in detail.

4.5. VADAR 3 D profile quality index analysis

Quantitative protein structure evaluation was analyzed with VADAR(Volume Area Dihedral Angle Reporter)(Willard, 2003) available at http://redpoll.pharmacy.ualberta.ca/vadar/. PDB format of all predicted structures were given as input with default parameters in analysis.

5. Biological function with docking analysis

Biological Function Analysis of all predicted structures were compared with molecular docking studies in GOLD 3.2 (Verdonk et al., 2003) software against RIP (RNA III inhibiting peptide). Synthetic RIP was designed in its amide form as YSPWTNF-NH2 in Chemdraw and taken as Ligand. *S. aureus* virulence can be inhibited by hepta peptide RNA III inhibiting peptide (RIP). RIP competes with RAP, thus inhibiting the phosphorylation of TRAP, leading to reduced adhesion and inhibition of RNA III synthesis, which leads to the suppression of toxin synthesis(Balaban et al., 2001; Gov et al., 2004). Synthetic RIP was designed in its amide form as YSPWTNF-NH2 and docking analysis was performed with all predicted structures.

6. Result and discussion

6.1. Selection of template and model generation

Staphylococcus aureus (strain MRSA252) Q6GFM2 sequence was selected for Homology modeling study. The present study was carried out to modeled the RNA III inhibiting Peptide. The downloaded Sequence was first carried out for Identity and similarity. We had applied 6 different methods to develop homology based three dimensional model of RNA-III inhibiting Peptide. The six methods includes Discovery Studio2.1, SWISS MODEL, MODBASE, GENO 3D, and CPH models and I-TASSER. Only Discovery studio was offline software, whereas remaining were online server with automated configuration to model three dimensional model. The results (Table 1) indicate the similarity and identity ranging from 10.1 to 16.1 and 26.4 to 42.2 respectively.

6.2. Model evaluation

The important step in homology modeling is model evaluation. To strengthen this part we had applied several approach to our model, which includes evaluation with Rasmol, Rampage, Discovery Studio utility and VADAR.

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