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Structural and dynamical aspects of *Streptococcus gordonii* FabH through molecular docking and MD simulations

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ABSTRACT

β-Ketoacyl-ACP-synthase III (FabH or KAS III) has become an attractive target for the development of new antibacterial agents which can overcome the multidrug resistance. Unraveling the fatty acid biosynthesis (FAB) metabolic pathway and understanding structural coordinates of FabH will provide valuable insights to target *Streptococcus gordonii* for curing oral infection. In this study, we designed inhibitors against therapeutic target FabH, in order to block the FAB pathway. As compared to other targets, FabH has more interactions with other proteins, located on the leading strand with higher codon adaptation index value and associated with lipid metabolism category of COG. Current study aims to gain *in silico* insights into the structural and dynamical aspect of *S. gordonii* FabH via molecular docking and molecular dynamics (MD) simulations. The FabH protein is catalytically active in dimerization while it can lock in monomeric state. Current study highlights two residues Pro88 and Leu315 that are close to each other by dimerization. The active site of FabH is composed of the catalytic triad formed by residues Cys112, His249, and Asn279 in which Cys112 is involved in acetyl transfer, while His249 and Asn279 play an active role in decarboxylation. Docking analysis revealed that among the studied compounds, methyl-CoA disulfide has highest GOLD score (82.75), binding affinity (−11 kcal/mol) and exhibited consistently better interactions. During MD simulations, the FabH structure remained stable with the average RMSD value of 1.7 Å and 1.6 Å for undocked protein and docked complex, respectively. Further, crucial hydrogen bonding of the conserved catalytic triad for exhibiting high affinity between the FabH protein and ligand is observed by RDF analysis. The MD simulation results clearly demonstrated that binding of the inhibitor with *S. gordonii* FabH enhanced the structure and stabilized the dimeric FabH protein. Therefore, the inhibitor has the potential to become a lead compound.

1. Introduction

Streptococcus gordonii resistance against majority of antibiotics has necessitated the search for new therapeutic antibacterial agents with novel targets [1]. The identification of compounds with novel mode of action towards a new *S. gordonii* target enzyme would be an effective solution. *S. gordonii* belongs to the viridians group which is involved in biofilm formation [2]. Biofilm is an important component of human dental plaque by virtue of its ability to adhere to tooth surfaces [3]. Bacterial biofilms are source of chronic infections because they show resistance to antibiotics and disinfectant chemicals [4]. *S. gordonii* causes bacterial endocarditis and septic arthritis by entering into the blood stream usually after oral trauma [5]. Major surveys of septic arthritis demonstrate that its predominant causative organisms are streptococci. Anaerobic organisms rarely cause septic arthritis, but are more common when there is a history of penetrating trauma [6]. Treatment for septic arthritis was undertaken by penicillin, ampicillin, cefotaxime, erythromycin, clindamycin and vancomycin. Gentamycin (5 mg/kg/day) and rifampicin (900 mg/day) were added to the treatment of endocarditis [5]. These antibiotics are effective in early stages but multi-drug resistance (MDR) complicates the treatment and leads to high failure rate. Identification of novel drug targets is the key step to combat these infections. Highlighting the drug targets in *S. gordonii*, fatty acid biosynthesis (Fab) has proven alluring target for causing oral infection [7]. Notably, β-Ketoacyl-ACP-synthase III (FabH or KAS III) (EC 2.3.1.180) a condensing enzyme [8], plays an essential and regulatory role in bacterial fatty acid elongation cycles [7,9–11]. Moreover, it characterizes a promising target for the design of novel therapeutic drugs through various kinds of compounds [12,13].

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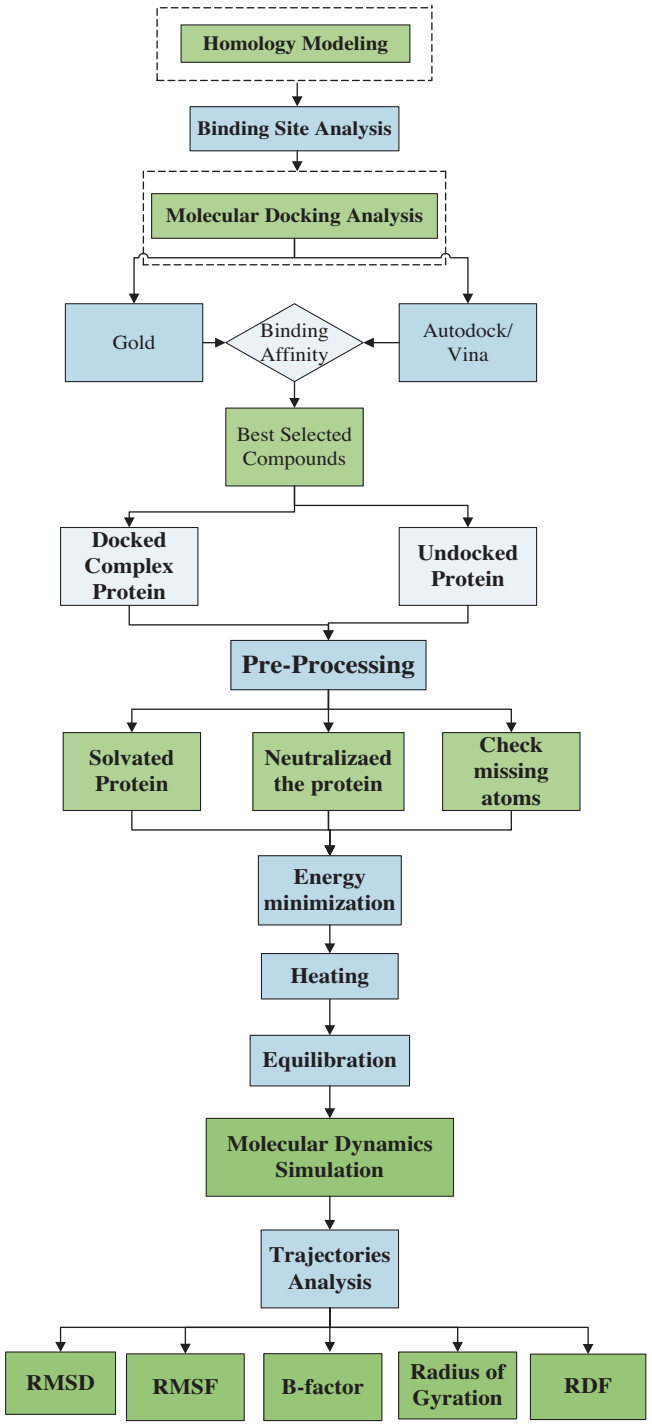

Fig. 1. The schematic workflow is illustrating the complete hierarchy of docked and undocked protein analysis.

FabH is highly conserved among these pathogens; *Escherichia coli* [8], *Plasmodium falciparum* [14], *Mycobacterium tuberculosis* [15], *Staphylococcus aureus* [16] and *Streptococcus pneumonia* [17]. In above mentioned pathogens, FabH catalyses a direct condensation reaction between the acyl coenzyme A (CoA) primers used to initiate fatty acid biosynthesis [15,18,19]. In *E. coli* FabH, the active site is consisted of a catalytic triad in which Cys112 residue is adjacent to His244 and Asn274 [20]. The residue Cys112 is required to attack the acetyl-CoA substrate to form the acetyl-FabH intermediate while His244 and Asn274 play an active role in decarboxylation [21].

Table 1
Analysis of modeller structures for prediction of *Streptococcus gordonii* FabH model.

Modeller	Most favoured regions	Additional allowed regions	Generously allowed regions	Disallowed regions	Non-glycine and non-proline residues	Total number of residues	G-factors	Molpdf score	DOPE score	GA341 score	ProSA Z-score	ERRAT (overall quality factor)
Model 1	271	19	2	0	292	324	−0.12	1908.45	−36114.66	1	−8.14	69.108
	92.80%	6.50%	0.70%	0.00%	100.00%							
Model 2	268	21	3	0	292	324	−0.11	2043	−36115.62	1	−8.11	73.548
	91.80%	7.20%	1.00%	0.00%	100.00%							
Model 3	266	23	2	1	292	324	0.36	1972.91	−36137.17	1	−8.36	72.381
	91.10%	7.90%	0.70%	0.3%*	100.00%							
Model 4	270	17	5	0	292	324	−0.15	2121.79	−35937.78	1	-8.36	79.1
	92.50%	5.80%	1.70%	0.00%	100.00%							
Model 5	269	19	3	1	292	324	−0.1	2028.01	−36170.12	1	−8.36	74.434
	92.10%	6.50%	1.00%	0.3%*	100.00%							
Minimized Model 4	238	49	3	2	292	324	−0.39	–	−36805.57	1	−8.26	79.743
	81.5%*	16.80%	1.00%	0.7%*	100.00%							
Dimer Model 4	476	98	6	4	584	648	−0.39	–	−75661.7	1	−8.26	–
	81.5%*	16.80%	1.00%	0.7%*	100.00%							

* Represents that values below −0.5 are unusual.