Pak. J. Biochem. Mol. Biol., 2023, 56(4):174-179

Research Paper

Structural Bioinformatics of Human HMG-CoA Reductase Inhibition by Statins

Fauzia Iqbal

Department of Biochemistry, Dow Medical College, Dow University of Health Sciences, Karachi, Pakistan.

ABSTRACT

Familial Hypercholesterolemia (FH) is a hereditary disorder characterized by elevated levels of low-density lipoprotein cholesterol (LDL-C), predisposing affected individuals to premature cardiovascular disease. The *HMGCR* gene, encoding 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase (HMG Co A reductase), plays a crucial role in cholesterol metabolism and is frequently implicated in FH pathogenesis. Here, we carried out an in-silico characterization of human HMG-CoA reductase using structural bioinformatics resources to elucidate the spectrum of enzyme-inhibitor interactions. By examining the 3D profiles of the substrate binding pocket of HMG-CoA reductase, insights into the structural implications of statin inhibition were gained.

KEYWORDS: Familial Hypercholesterolemia, HMGCR, HMGCoA, Cholesterol, Statins

INTRODUCTION

Familial hypercholesterolemia (FH) is an autosomal dominant disorder. It is characterized by very high levels of cholesterol in the blood. Cholesterol plays important roles in forming cell membrane structure and in the synthesis of steroid hormones, bile acids, and vitamin D (https://ghr.nlm.nih.gov/condition/familial-hypercholesterolemia; https://thefhfoundation.org/familial-hypercholesterolemia/what-is-familial-hypercholesterolemia.).

Cholesterol is transported in the circulation via lipoprotein particles. Cholesterol biosynthesis starts with the transport of acetyl CoA within the mitochondria to the cytosol. In cholesterol biosynthesis, the rate-limiting step is at the level of the 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase-catalyzed step [2,4]. Familial hypercholesterolemia resulting from pathogenic mutations in several genes including HMGCR, LDLR, APOB, LDLRAP1, and PCSK9 [7] (https://www.omim.org/entry/607786?search=PCSK9&highlight=pcsk9) affect cholesterol metabolism. These genes are located on different chromosomes in the human genome [1-3]. Generally, these genes have an autosomal dominant pattern of inheritance. Mutations in the HMGCR, APOB, LDLR, LDLRAP1, and PCSK9 genes cause familial hypercholesterolemia. For instance, pathogenic mutations in the LDLR gene are the most common cause of this condition. The LDLR gene encodes a low-density lipoprotein receptor. This receptor type binds to particles called low-density lipoproteins (LDLs), the primary carriers of cholesterol in the blood. By removing LDLs from the bloodstream, these receptors play a critical role in regulating cholesterol levels.

Familial hypercholesterolemia is also caused by APOB, LDLRAP1, and/or PCSK9 gene mutations. Proteins produced from these genes are essential for the normal function of low-density lipoprotein receptors. Mutations in any of these genes prevent cells from making functional receptors or alter the receptors' function. Hypercholesterolemia results when low-density lipoprotein receptors cannot effectively remove cholesterol from the blood. Some people with familial hypercholesterolemia do not have a mutation in one of these genes. In these cases, the cause of the condition is the defect in the

rate-limiting enzyme i.e. HMGCR in cholesterol synthesis.

The present study aimed to characterize human HMGCR enzyme using structural bioinformatics approaches.

MATERIALS AND METHODS

The protein structural coordinates of HMG CoA reductase complexed with the substrate HMG CoA and different statin inhibitors were retrieved from PDB. The PDBsum database was used to analyze the interactions of different statins with HMG CoA reductase. The ligands binding amino acid residues of HMG CoA reductase were characterized in the molecular modeling package Discovery Studio Visualizer. Protein-ligand interactions were mapped using the Ligplot program.

RESULTS AND DISCUSSION

PDB search revealed 2351 structural coordinates sets of human HMG CoA reductase (HMGCR) complexed with HMG-CoA, NADP, and an array of inhibitors including statins. The description of the 8 crystal structures of HMG CoA reductase is given in table 1.

Statin-based inhibitors of HMG-CoA reductase have transformed the management of hypercholesterolemia [8-10]. These compounds are the most efficient agents for reducing plasma cholesterol. The substrate HMG CoA and statin inhibitors bind at the substrate binding pocket of HMGCR. These ligands, i.e. substrate and inhibitors form several favorable noncovalent interactions with amino acid residues of HMGCR.

The enzyme-substrate interactions are modeled using Ligplot program [5] and PDBsum [6]. The amino acid residues present at substrate binding sites in 8 PDB structures of HMGCR are given in table 2. Understanding the 3D conformations of these residues and their interactions with substrate and statin inhibitors provided structural insight. The ligand binding of HMGCoA and different statin inhibitors with HMGCR is depicted in Figures 1-4.

Table 1: Selected crystal structures of human HMG CoA complexed with substrate HMG CoA or Statin inhibitors.

PDBID	1DQ9	1DQ8	1HWL	1HWK	1HWJ	1HWI	1HW9	1HW8
Method				X-Ray diffraction				
Ligands complexed	HMG	CoA, DTT, MAH	ADP, FBI	117, ADP	116, ADP	ADP, 115	ADP, SIM	114, ADP
Mutations	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

REFERENCES

[1] The molecular genetic basis and diagnosis of familial hypercholesterolemia in Denmark. Jensen HK. Dan Med Bull. 2002 49(4):318-345.

[2] Ye, H., Zhao, Q., Huang, Y., Wang, L., Liu, H., Wang, C., Dai, D., Xu, L., Ye, M., & Duan, S. (2014). Meta-analysis of low density lipoprotein receptor (LDLR) rs2228671 polymorphism and coronary heart disease. BioMed research international, 2014, 564940.

[3] Südhof, T. C., Goldstein, J. L., Brown, M. S., & Russell, D. W. The LDL receptor gene: a mosaic of exons shared with different proteins. Science, 1985, 228(4701), 815–822.

[4] Istvan, E. S., Palnitkar, M., Buchanan, S. K., & Deisenhofer, J. Crystal structure of the catalytic portion of human HMG-CoA reductase: insights into regulation of activity and catalysis. The EMBO journal, 2000, 19(5), 819–830.

[5] Wallace, A. C., Laskowski, R. A., & Thornton, J. M. LIGPLOT: a program to generate schematic diagrams of protein-ligand interactions. Protein engineering, 1995, 8(2), 127–134.

Table 2: Amino acids residues forming substrate binding pocket in 8 crystal structures of human HMG CoA reductase.

PDBID	1DQ9	1DQ8	1HWL	1HWK	1HWJ	1HWI	1HW9	1HW8
Amino Acid residue								
Arg571	✓				✓		✓	
Arg568		✓		✓	✓		✓	
Lys722	✓	✓			✓		✓	
Ser855								
Ser565	✓	✓						
Arg590	✓					✓		✓
Asp690	✓					✓		✓
Lys735	✓					✓		✓
Lys692	✓					✓		✓
Ser852	✓	✓						
Trp479		✓	✓	✓	✓		✓	
Asn567			✓	✓	✓		✓	
Ala564			✓	✓	✓		✓	
Glu528			✓	✓	✓		✓	
Asn529			✓	✓	✓		✓	
Ser684						✓		
Lys691						✓		

[6] Laskowski, R. A., & Thornton, J. M. PDBsum extras: SARS-CoV-2 and AlphaFold models. Protein science, 2022, 31(1), 283–289.

[7] Han Y, Willis M S. The Role of PCSK9 in Lipid Metabolism and its Relationship to New Therapies for Lowering Cholesterol and Reducing Cardiac Disease. Journal of Cardiology and Therapy. 2015, 2(5):393-399.

[8] Istvan, E. S., & Deisenhofer, J. Structural mechanism for statin inhibition of HMG-CoA reductase. Science, 2002, 292(5519), 1160–1164.

[9] Stancu C, Sima A. Statins: mechanism of action and effects. J Cell Mol Med., 2001, 5(4):378-87.

[10] Istvan, E. S., Palnitkar, M., Buchanan, S. K., & Deisenhofer, J. Crystal structure of the catalytic portion of human HMG-CoA reductase: insights into regulation of activity and catalysis. The EMBO journal, 2000, 19(5), 819–830.

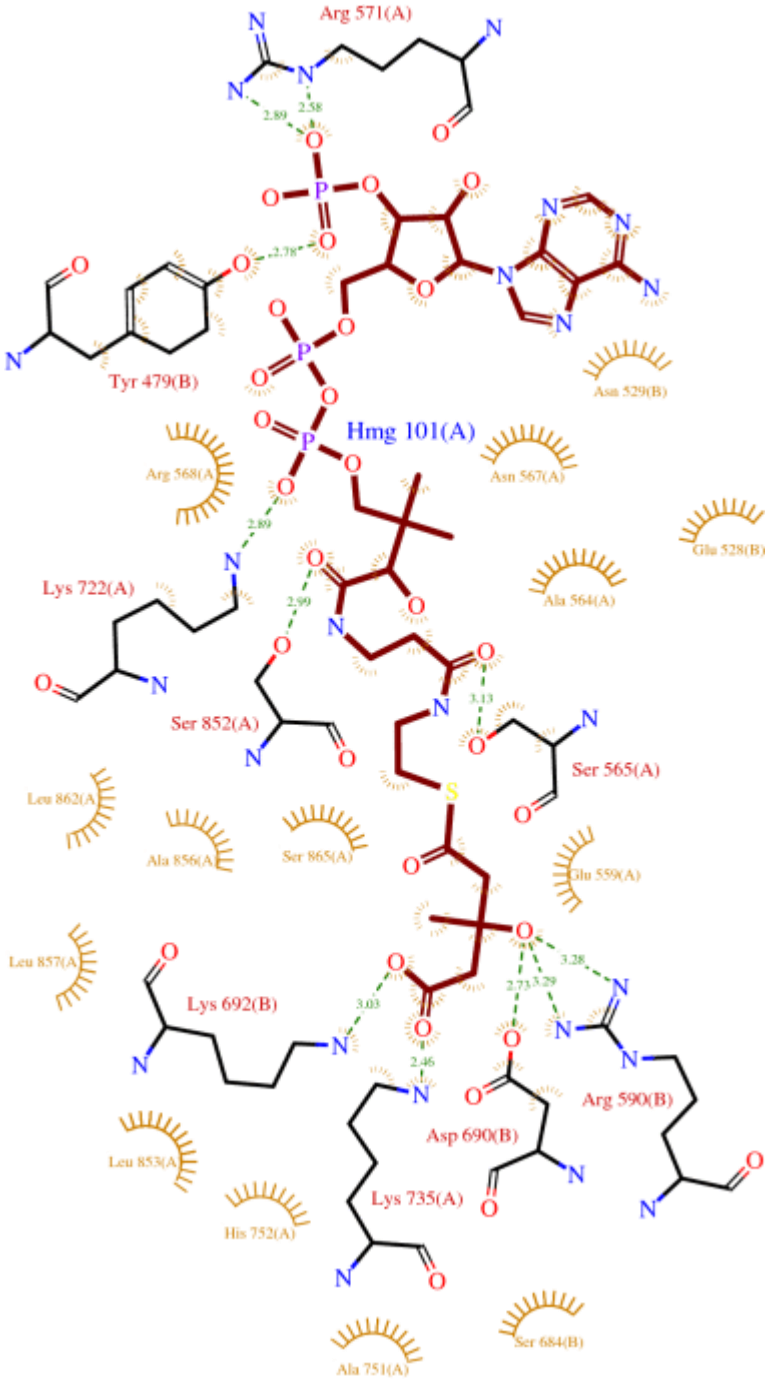

Figure 1: Ligplot image [5] depicting substrate binding pocket of HMG CoA Reductase complexed with HMG CoA [Hmg101(A)] PDBID:1DQ9.

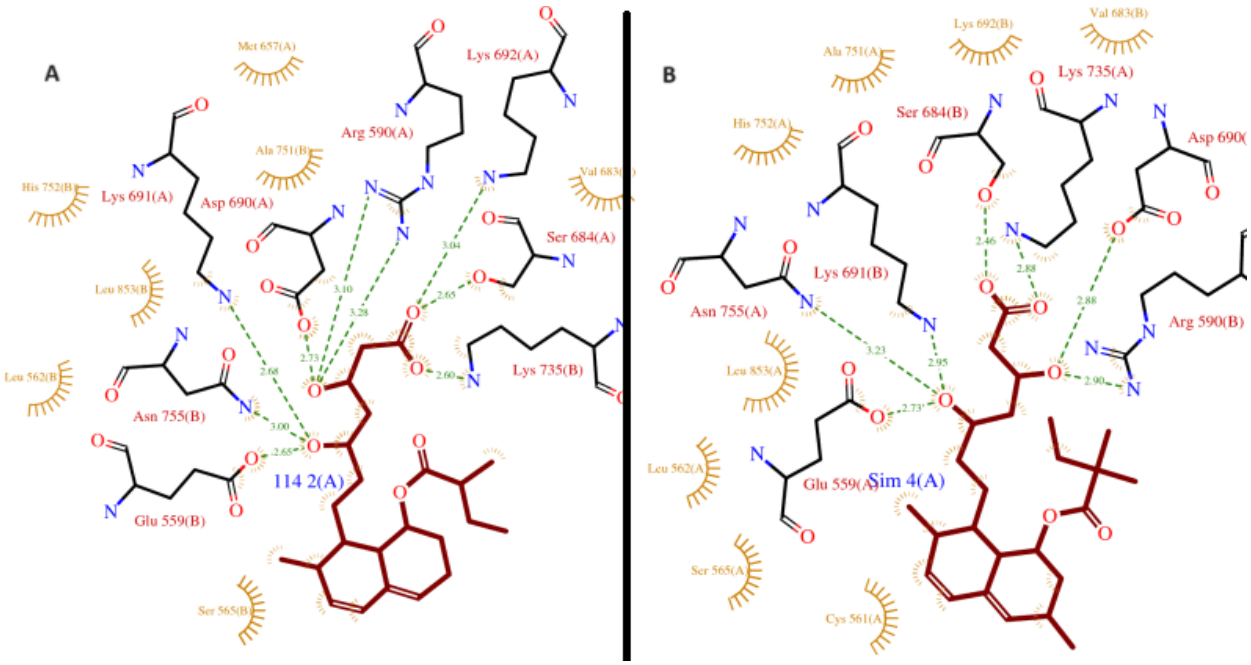

Figure 2: Ligplots depicting the active site of HMG CoA Reductase HMGCR complexed with (A) Mevastatin (PDBID:1HW8) (B) Simvastatin (PDBID:1HW9).

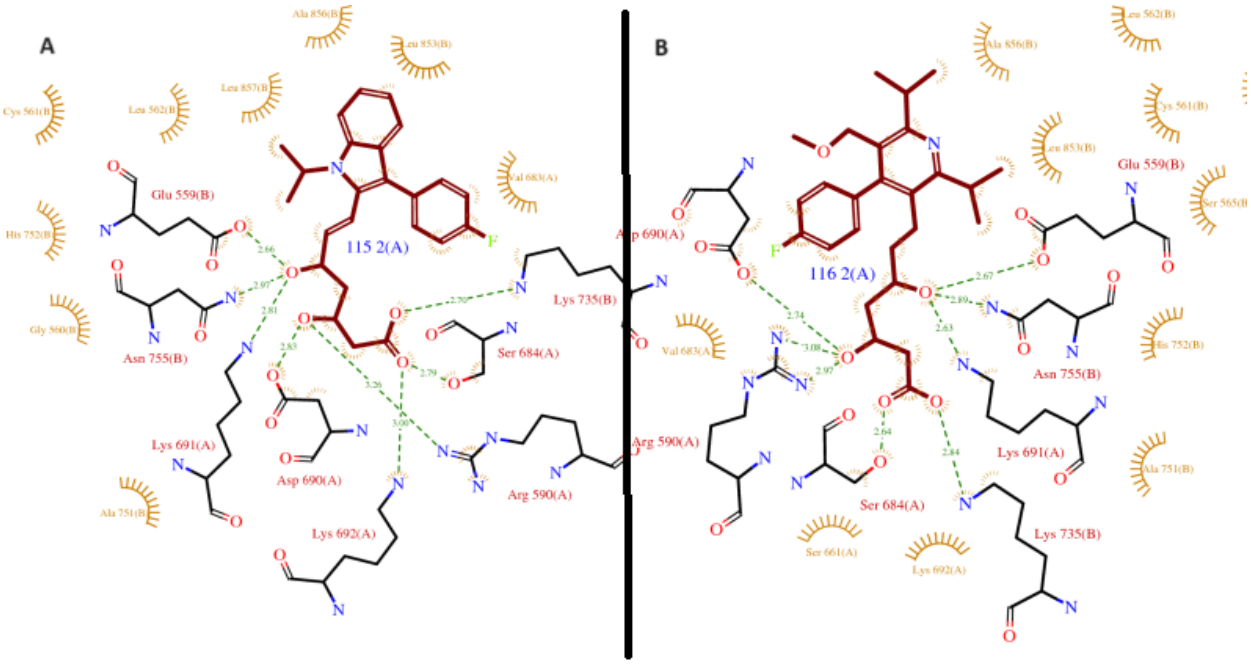

Figure 3: Ligplots depicting the active site of HMG CoA Reductase HMGCR complexed with (A) Fluvastatin (PDBID:1HWI) (B) Cerivastatin (PDBID:1HWJ).

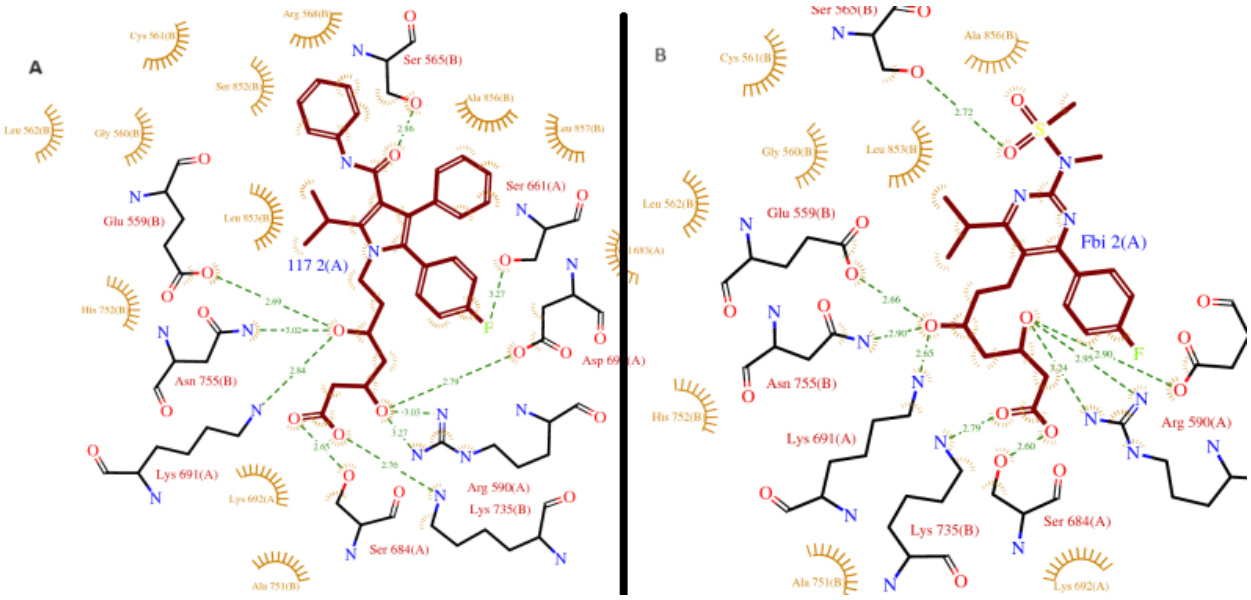

Figure 4: Ligplots depicting the active site of HMG CoA Reductase HMGCR complexed with (A) Atrovinstatin (PDBID:1HWK) (B) Rovastatin (PDBID:1HWL).