

# Molecular Modeling and Interaction Studies of HCV Core Protein

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## Abstract

HCV is a leading cause of liver disease and can lead to hepatocellular carcinoma and liver damage which in turn can cause death of patients. HCV is closely related to immune response especially inflammation suggesting that the immune response-related genes can serve as molecular targets for chemo-prevention and treatment of C-type HCC. This study was conducted to determine the 3D structures of immune responsive gene (CXCL6) that are up-regulated during Hepatitis C Virus (HCV) Infection and Hepatocellular Carcinoma (HCC) and HCV core protein. Furthermore, docking and interactions analysis of immune responsive gene with HCV core protein was performed to understand pathogenesis of HCV infection. Reliable 3D structures of both proteins were determined using comparative modeling approach. Docking of both proteins revealed functionally important residues i.e. Arg149, Arg39, Arg74 and Gln78 in HCV core protein and Leu44, Ala71, Ser76 and Pro97 in CXCL6. It can be concluded from the study that CXCL6 had potentially interacting residues with HCV core protein that can be helpful in finding clues to understand HCV pathogenesis and develop better therapeutic regimens.

**Keywords:** Hepatitis C Virus; Hepatocellular Carcinoma; Immune response; Comparative modeling; Molecular docking

## Introduction

The Hepatitis C Virus (HCV) is the leading cause of chronic liver disease worldwide [1,2]. It is estimated that 3-4 million people are infected with HCV every year. HCV causes acute and chronic hepatitis, which can eventually lead to permanent liver damage and hepatocellular carcinoma [3,4]. Chronic hepatitis C is a major cause of cirrhosis and hepatocellular carcinoma and HCV-related end-stage liver disease is, in many countries, the first cause of liver transplantation [1]. About 85% of patients with acute HCV infection can develop chronic infection and about 70% patients with chronic infection can have chronic liver disease, 10-20% of which develop liver cirrhosis. Each year hundreds of thousands people die from liver failure and liver cancer caused by this disease [5]. HCV infection is characterized by its propensity to chronicity. Because of its high genetic variability, HCV has the capability to escape the immune response of the host. Recent studies have shown that the combination therapy with alpha interferon and ribavirin induces a sustained virological response in about 40% of patients with chronic hepatitis C. Considerable progress has been made in the field of HCV since its discovery 10 years ago but a major effort needs to be made in the next decade to control HCV-related disease. HCV is closely related to immune response especially inflammation suggesting that the immune response-related genes can serve as molecular targets for chemoprevention and treatment of C-type HCC [6].

Computational analysis of biological sequences has become an extremely rich field of modern science and a highly interdisciplinary area, where statistical and algorithmic methods play a key role [7]. Comparative modeling is a computational technique for 3D structure prediction of proteins using known structures as templates [8]. *In-silico* models have potential use in the discovery and optimization of novel molecules, with affinity to the target, clarification of absorption, distribution, metabolism, excretion and toxicity properties as well as physiochemical characterization [9]. Using *in-silico* approaches to predict a structure takes less time and provides a basis for understanding protein structure and function. Moreover, structural studies can reveal many protein active sites that can lead to develop new drugs for diseases. Therefore, the immune responsive gene was selected on the basis of biological function and involvement in Hepatitis C Virus induced hepatocellular carcinoma. Viral core protein directly interacts with a number of cellular proteins and pathways involved in the viral life cycle

[10]. Therefore, this gene was subjected to docking to find potential interactions with immune responsive gene. Analysis of this immune responsive gene with HCV core protein can help investigating their role in HCV. This information might provide clues to understanding HCV pathogenesis and develop better therapeutic regimens.

## Methodology

### Gene selection and sequence retrieval

Literature survey was performed to find important immune responsive gene that is up-regulated during HCV infection. CXCL6 gene was selected on the basis of its involvement in HCV and HCC. Protein sequence of CXCL6 and HCV core gene was retrieved from NCBI protein database using accession #AAH13744 and Q1XCF0, respectively.

### Comparative modeling

After analyzing the available information of selected proteins, it was found that the crystal structure of proteins were not available. Therefore, the comparative modeling approach was used to determine the 3D model of both proteins. Comparative modeling is a computational technique for 3D structure prediction of proteins using known structures as templates [8]. 3D models were predicted using Modeller v9.10, a python based protein modeling software that models 3D structures of proteins and their assemblies by satisfaction of spatial restraints [11].

After generating 3D models, Psi/Phi Ramachandran plot was determined using PROCHECK [12] which helped in evaluating backbone conformation.

### Molecular docking

Hydrogens were added and 3D protonation of both proteins was

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carried out using MOE tool. Protein structures were minimized using an energy minimization algorithm of MOE tool using AMBER99 Forcefield. GRAMM-X [13] was employed for protein-protein docking where the HCV core was provided as receptor protein. After protein docking, docked complexes were subjected to hydrogen bonding/ $\pi$ - $\pi$  interactions analysis. UCSF chimera software was used to visualize interactions among docked proteins.

## Results

HCV is a major cause of hepatocellular carcinoma and because of its diverse genotypes, there is no vaccine developed to date. HCV can escape immune response of the host and thus it is important to study immune response genes that are involved in HCV infection and HCV induced HCC. Immune response genes can be important target for chemoprevention and treatment of HCV induced HCC [6]. This study was designed to perform structural analysis and interaction studies on important immune responsive gene i.e., CXCL6. CXCL6 is chemotactic for neutrophil granulocytes and is up-regulated during HCV and HCV induced HCC [14].

## Comparative modeling and model evaluation

Sequences of selected proteins were retrieved from the Uniprot database and were subjected to PSI blast against a PDB database. Structures with maximum identity were selected and were used to predict the 3D structure of target proteins using Modeller v9.10 software which is a python based software used to predict 3D structures of proteins using homology modeling approach. The predicted structures are shown in Figure 1.

After that, generated 3D structures were validated by Ramachandran plot. PROCHECK [12] was used to find Psi/Phi Ramachandran plot which helped in evaluating backbone conformation (Table 1).

Ramachandran plot of CXCL6 showed 78.3% residues in the most favorable regions and Ramachandran plot of HCV core protein showed 81% of residues in the most favorable regions. These 3D structures can be helpful in understanding interactions between proteins and can also be important in drug designing.

## Molecular docking and interaction analysis

Molecular docking of HCV core with CXCL6 was carried out using GRAMM-X server. After docking, docked complex was analyzed to find interacting residues (Table 2). UCSF chimera was utilized for the visualization of interactions shown in Figure 2.

After analyzing docked complex of CXCL6 and HCV core protein, it was found core protein was having 5 interacting atoms. N of Arg149 was interacting with O of Leu 44 in CXCL6 with a bond distance of 3.72. Core protein atom NH2 of Arg39 interacted with O of Ala 71 with a bond distance of 3.36. NH1 of Arg74 interacted with O of Ser76 and lastly, NE2 of Gln 78 interacted with O of Pro97 with a bond distance of 3.34. Thus, it can be inferred that these interactions can be important in understanding HCV infections and Hepatocellular Carcinoma.

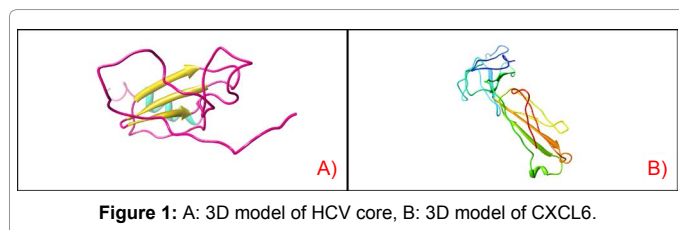


Figure 1: A: 3D model of HCV core, B: 3D model of CXCL6.

Target Protein	Template	Identity	Ramachandran plot
HCV core	1XCQ_P	98%	81%
CXCL6	1MI2_A	54%	78.3%

Table 1: Comparative modeling of HCV core protein and CXCL6.

HCV Core	Hydrogen bond [Å]	CXCL6
ARG 149 [N]	3.72	LEU 44 [O]
ARG 39 [NH2]	3.36	ALA 71 [O]
ARG 74 [NH1]	3.89	SER 76 [OG]
ARG 74 [NH1]	2.61	SER 76 [O]
GLN 78 [NE2]	3.34	PRO 97 [O]

Table 2: Binding interactions of HCV core protein with immune responsive protein CXCL6.

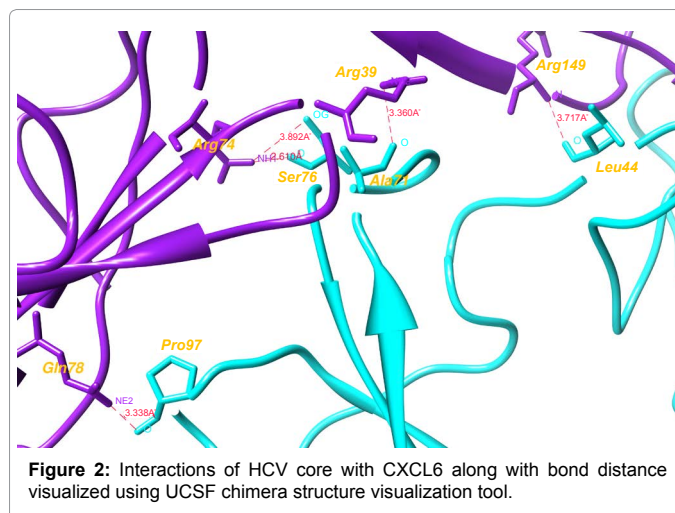


Figure 2: Interactions of HCV core with CXCL6 along with bond distance visualized using UCSF chimera structure visualization tool.

## Conclusion

This study was conducted to predict the 3D structure of an important immune responsive protein that is up-regulated during HCV and HCV induced HCC and HCV core protein. The predicted structure was subjected to interaction analysis with HCV core protein. It was found that both proteins had potentially interacting residues that can be helpful in finding clues to understand HCV pathogenesis and develop better therapeutic regimens.

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