Advanced Studies in Biology, Vol. 16, 2024, no. 1, 187 - 192
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https://doi.org/10.12988/asb.2024.91965

Role of Hepatitis C Viral Proteins Influencing Functional Efficiency of Tumor Suppressor Protein

Nuzhat Maqbool Peer [1], Vinod Joshi [1,*], Irfan Gul [2,3], Bennet Angel [1], Ambreen Shafaat Khan [1], Khushbu Kumari [1] and Aarya Chitransh [1]

[1] Centre of Excellence in Virology & Immunology, Sharda University
Greater Noida, UP, India-201310

[2] Faculty of Veterinary Sciences and Animal Husbandry, Sher-e-Kashmir University of Agricultural Sciences and Technology of Kashmir, Srinagar, India

[3] Department of Biotechnology, University of Kashmir, Srinagar, India

[*] *Corresponding author*

Abstract

Hepatitis C virus is one of the leading cause of serious complications, cirrhosis and cancer of the liver. The RNA of the virus encodes for 10 proteins each playing an important role either as structural or non-structural component. Hepatitis C virus which is a member of the Flavivirus family, is considered to be the only RNA virus which is associated with progression to Cancer, and which still remains a question for many researchers. Studies are ongoing in looking into how the various viral protein interacts in subduing the normal function of the liver cells, but the transformation events also remain to be fully proved. In the present study, we have undertaken in-silico studies of important viral proteins and studied their interaction with the Tumor Suppressor protein. It was observed that the confidence score above 0.9 indicated higher binding affinity which was found to occur between viral NS5 protein and p53 protein. This suggest that the non-structural protein NS5 may interact with the p53 protein during the course of its synthesis and may thus inhibit the functionality of the Tumor Suppressor protein leading to progression of cancer after some time.

Keywords: Hepatitis C virus, Hepatocellular Carcinoma, viral protein, p53

1 Introduction

The long-term infection caused by Hepatitis C virus has led to serious health problems, infecting around 180 million people worldwide. The prominent liver manifestations range from Chronic liver hepatitis to Cirrhosis and finally Hepato-Cellular-Carcinoma. It has been reported that interaction of viral proteins with host proteins/cells results in oxidative stress, dysregulation of signaling pathways and liver inflammation (Ivanov et al., 2017). This leads to the activation of oncogenes and causes metabolic disturbances in cells, liver fibrosis and process of angiogenesis. During the presence of Hepatitis C virus in the liver cells, it has been found that the Core and E2 protein of HCV stimulates the cellular growth and causes heteroplastic degeneration (Nevola at al., 2018; Suhail et al., 2022;). Core protein also leads to the overproduction of reactive oxygen species thereby damaging the host cell, accumulation of genetic variations and leads to the development of cancer. It has been found that HCV core protein leads to the inhibition of host Tumor Suppressor genes i.e. TP53, TP73, Retinoblastoma protein (RB1) and CDKN1A (Cyclin-dependent kinase inhibitor-1) (Lu et al., 1999). HCV NS3 which is a serine protease plays a crucial role in the neoplastic transformation that induces the acquisition of liver hepatocyte clones in a proliferative condition (Zemel et al., 2001). HCV NS5A appears to alleviate PTEN's (phosphatase and tensin homolog) inhibitory effect on the PI3K-Akt signaling pathway by down-regulating it, which may indirectly lead to inhibition of apoptosis process by stimulating the PI3K-Akt survival pathway (Cheng et al., 2015). Though studies have been done, but the physical interactions of these proteins with the host proteins have not been understood well. The present study is an in-silico approach to understand the protein-protein physical interactions between host Tumor Suppressor Protein and various Hepatitis C virus proteins and understand crucial points between them for drug and vaccine targets.

2 Materials and Methods

The protein-protein docking analysis was conducted between the human Tumor Suppressor Protein (TP53) with five distinct HCV proteins (Core, Envelope protein, NS3, NS5A and NS5B). The Protein Data Bank (PDB) was explored and following structures were used: 1TUP for Tumor suppressor P53; 1CWX for HCV Core protein, 4MWF for HCV Envelope protein, 3M5L for HCV Protease Protein (NS3), 3FQM for HCV RDRP Protein (NS5A) and 4TLR HCV Methyltransferase (NS5B). The interactions between amino acid chains of TP53 with different HCV-proteins were explored using PyMOL, HDock and PDBsum. The docking scores were calculated based on iterative scoring function ITScorePP or ITScorePR. A more negative docking score means a more possible binding model.

3 Results

The protein preparation phase was conducted utilizing the Chimera software suite, focusing on the structure named 1TUP (Tumor Suppressor protein, P53). During this preparatory stage, the protocol was refined to include only chain A of protein structure and taken for docking, accompanied by the addition of the requisite hydrogen atoms to ensure structural completeness and computational accuracy. Following the preparation of the proteins, the subsequent phase involved protein-protein docking experiments. These were executed by interfacing with the Cluspro online webserver, where each of the five Hepatitis C Virus (HCV) proteins (Core, E2, NS3, NS5A and NS5B) were docked individually against the prepared protein structures (Figure 1 to 5). The docking scores are given in the Table 1**.** It was observed that the docking scores of all interactions were above -200 and the confidence score was above -0.8 which means the affinity between two molecules to bind was more. However, the highest docking score was found between p53 and NS5A (-270.60) and that of confidence score was (0.9177). Using HDock server for assessing the amino acid interactions between p53 and HCV proteins we found that a greater number of HCV NS5A amino acids were interfacing p53 with shorter bond length indicating more strong bond formation and stability between these two proteins.

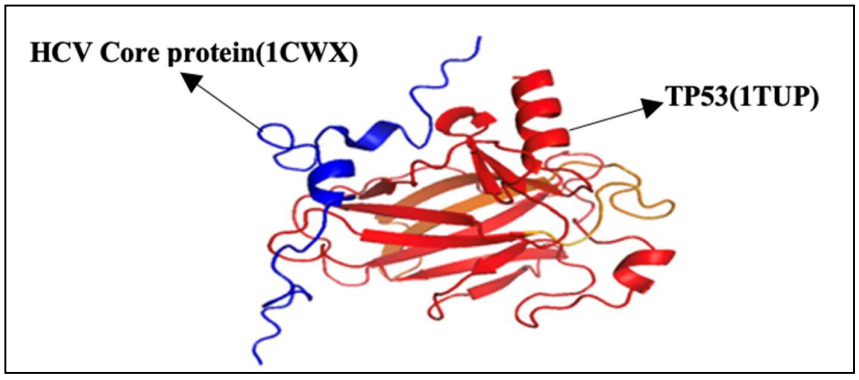

Figure 1. 3D interaction between human tumor suppressor protein p53 (Red) and Core HCV protein (Blue)

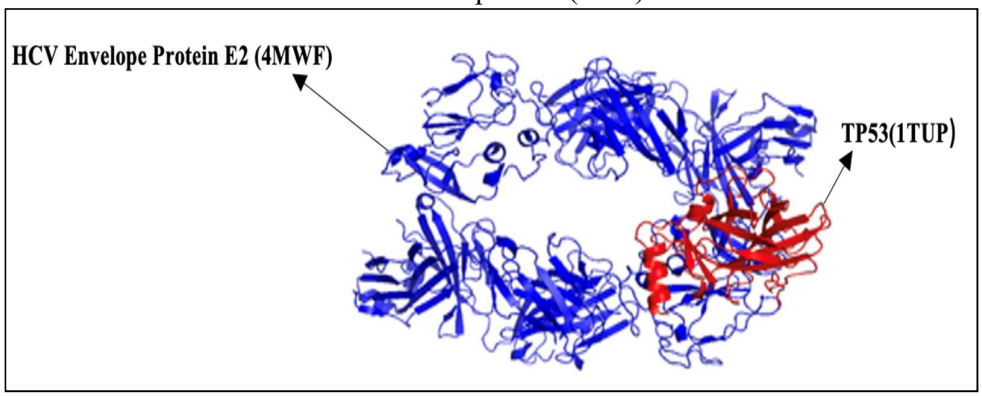

Figure 2. 3D interaction between human tumor suppressor protein p53 (Red) and E2 HCV protein (Blue)

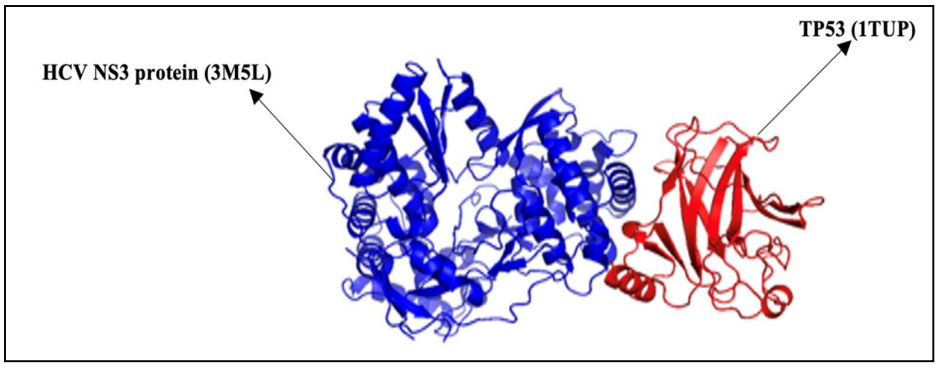

Figure 3. 3D interaction between human tumor suppressor protein p53 (Red) and NS3 HCV protein (Blue)

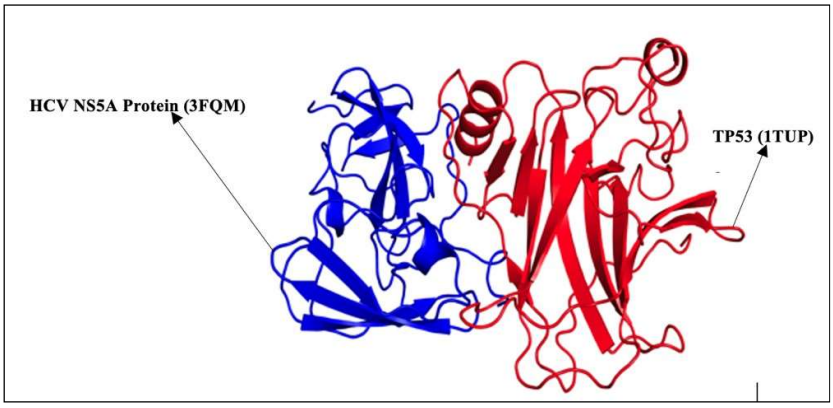

Figure 4. 3D interaction between human tumor suppressor protein p53 (Red) and NS5A HCV protein (Blue)

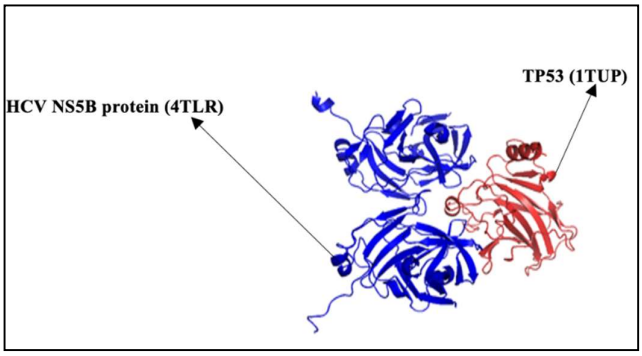

Figure 5. 3D interaction between human tumor suppressor protein p53 (Red) and NS5B HCV protein (Blue)

Table. 1. Docking scores of TP53 protein with HCV proteins

Protein –protein interaction	**Docking score**	**Confidence score**
TP53-Core Protein	-252.49	0.8859
TP53-E2	-256.97	0.8947
TP53-NS3	-232.45	0.8388
TP53-NS5A	-270.60	0.9177
TP53-NS5B	-248.95	0.8786

4 Discussion

Several research studies have established multiple approaches to determine the correlation of Hepatitis C virus proteins and their interaction with human Tumor Suppressor Protein (McGivern & Lemon, 2009; Mahmoudvand et al., 2019; Park et al., 2022). However, knowledge on the exact cause & effect relationship between these two is still incomplete. Efforts to unravel the inter-genotype clinical and serological variations, functional differences in viral proteins and their effect on host immune system is yet to be studied. Researchers have found that the amino acid variability in HCV genotypes and its impact on host protein synthesis and modifications create hindrance in the current understanding of the virus-host interaction. In current study we focused on In-silico approach to assess the similarities between sequences of TP53 and HCV proteins. Of the amino acid interactions amongst all the HCV proteins, HCV NS5B showed the greater interactions with TP53 protein. Additionally, when amino acid interface residues were explored, we found more number amino acid residues of p53 were interacting with amino acid residues of NS5A HCV protein with shorter bond lengths, indicating stronger bond and stability. The confidence scores above 0.9 shows the higher binding affinity between the two proteins.

5 Conclusion

The present study provides an in-depth analysis of TP53 with HCV genes specifically NS5B. The study also further enhances in investigating whether the same interaction exists between inter-HCV genotypes. If so, then precise antiviral treatment regimen or new protein candidate can be formulated to target this interaction.

Acknowledgements. The authors would like to thank Indian Council of Medical Research, New Delhi, India for providing us funds (Grant id: 2020-2521) to conduct this study.

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Received: November 27, 2024; Published: December 9, 2024