Abstract Template for 1st International Conference of Rehabilitation & Allied Health Sciences

Title: An *in-silico* approach to analyze HCV genotype-specific binding-site variation and its effect on drug-protein interaction

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ABSTRACT

Introduction

Genetic variation is a crucial feature of virus that greatly contributes in viral evolution, persistence, epidemiology, immune escape and development of antiviral drug resistance. However; a systematic approach that can provide in-depth analysis of the genetic variations and insights on the effect of these respective variations on drug-protein interactions remains unraveled. Therefore, we present an in-silico approach to explore genotype specific amino acid variations and its substantial effect on drug-protein interaction. In these regards, we used NS3 helicase of Hepatitis C Virus (HCV) and fluoroquinolone as potential helicase inhibitors. Herein, we have investigated the genotype specific amino acid variations in NS3 HCV in genotype and subsequently, the effect of amino acid variations in genotype 1a, 1b, 2b and 3a in NS3 HCV on NS3-fluoroquinolone interaction.

Method

We imported 687, 667, 101 and 248 nucleotide sequences of NS3 HCV genotypes 1a, 1b, 2b and 3a, respectively from Los Alamos database. 3D protein models for each genotype were constructed using the consensus sequences. To explore the amino acid variations, sequence and structural comparison of genotype-specific NS3 were performed followed by molecular docking of a batch of 8 fluoroquinolones on individual genotype-specific models of NS3.

Results

HCV NS3 genotype shows substantial sequence divergence with the identity score ranging from 80-93%. We found a total of 90 variable sites were determined via Multiple Sequence Alignment. The structures of the four HCV genotypes exhibit 98% structural similarity. Docking interactions varied significantly across the genotypes where genotype 3a exhibited maximum variations. In the light of the docking results, substitution of serine at positions 297 in genotype 1b, 500 and 558 in genotype 3a drastically increased the interactions.

Conclusion

Therefore, we believe our approach can be easily extrapolated to include other viruses to study the clinical significance of genotype specific variations in drug-protein interactions.

Funding Sources:

N/A

Keywords

Hepatitis C Virus, HCV Genotypes, HCV Non-Structural Protein 3, Fluoroquinolones.

References

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