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Communication

Cholesterol modulating the orientation of His17 in hepatitis C virus p7 (5a) viroporin – A molecular dynamic simulation study

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Graphical abstract

The cholesterol molecules interact with p7 channel between the adjoint H3 helixes, resulting in prominent conformational changes of these helical segments, which further exerts influence on the His17 residues of i+2 monomer, leading to the residues facing towards to the lumen of the pore. Such side chain orientations of His17 are considered to be essential for the channel's ionic selectivity and gating.

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ABSTRACT

Protein p7 of HCV is a 63 amino acid channel forming membrane protein essential for the progression of viral infection and the sensitivity of this channel to small-molecule inhibitors renders p7 a potential target for novel therapies against HCV infection. Previous biochemical experiments suggested that the His17 of p7 is a pore-lining residue and solvated-exposed to participate in channel gating. However, a recent NMR structural identification of the p7 hexamer in dodecylphosphocholine (DPC) micelles indicated that the His17 is embedded into the protein matrix. In this work, we performed molecular dynamic simulations to bridge the controversial observations. Our results illustrated that by incorporating the cholesterol into DOPC membranes to mimic an actual membrane-like composition, the orientation of His17 in the hexameric bundles spontaneously access to the central pore region, indicating a versatile property of the p7 viroporin conformation that could be voluntarily influenced by its surrounding environments.

Hepatitis C is the infection of the liver that causes from the Hepatitis C virus (HCV), a small, enveloped, positive-sense single-stranded RNA virus of the family *Flaviviridae* with the size of 55–65 nm.

Acute infection of HCV can range in severity from a very mild illness with few or no symptoms of a critical condition. Individuals who get acute infected and could not be able to clear the Hepatitis C virus may develop a chronic infection, which would cause serious health problems. Globally, the morbidity and mortality attributable to hepatitis C virus (HCV) infection continue to increase, and ~130–150 million people are detected with a chronic infection of HCV. Each year, an estimated 700,000 people die from HCV-related complications including fatty liver (cirrhosis), cancer (hepatocellular carcinoma) and liver failure [1].

Unlike the other two type hepatitis A and B, there is currently no vaccine to prevent hepatitis C infection. Thus, at present, the optimal treatment for chronic HCV infection is the pegylated interferon (IFN) combined with ribavirin [2], although the combination is inefficient in 50% patients [3]. Despite progress in the treatment of HCV, there is still considerable room for improvement and expansion of antiviral drugs.

For example, the ion-channel function of the p7 viroporin in lipid membranes is essential for viral assembly and replication. Therefore, the p7 may constitute an attractive potential drug target [4]. The small molecules, such as amantadine [5], rimantadine and

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