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Site-directed fragment-based design of databases of virtual sialic acid analogues against influenza A hemagglutinin

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Abstract

Inhibition of influenza A virus to avoid morbidity and mortality is of main concern during epidemics and of major concern during pandemics. Three influenza A pandemics have been occurred in 20th century; in 1918 by H1N1, 1957 by H2N2, and in 1968 by H3N2. Recently in early 2009, H1N1 has re-emerged after being genetically reassorted in swine. Two types of surface glycoprotein form the main antigenic determinants of influenza A virus namely; hemagglutinin (HA) and neuraminidase (NA). HA is responsible for viral attachment to the infected cell through surface-bound sialic acid (SA) moieties, while NA is responsible for hydrolysing the glycosidic bond that connects SA with the cell membrane resulting in viral detachment. Structure-based drug design approach has been successfully used in designing clinically available NA inhibitors such as Zanamivir and Oseltamivir. However, there is no effective low molecular weight inhibitor that have been developed which target HA and prevent the initial viral attachment. In this study molecular modeling tools were used to design databases of virtual SA analogues by a single substitution at either C2, C5 or C6 positions of SA scaffold. A commercially available molecular fragment was used for the substitution candidate. By using a structure-based molecular docking approach, the molecular fragments were placed at sites within and around HA binding pocket where crystallographic functional groups of C2, C5 and C6 of SA and other SA analogues are located. Then, the aligned fragments were connected to the SA scaffold with or without incorporation of molecular linkers using an in-house developed programming script. Thus, three databases of SA analogues with single substituted fragments at C2, C5 or C6 were obtained. The three databases were then docked to the whole natural SA binding site of HA using AutoDock3.05 and screened for their binding energies. Our results showed that C6-derived SA analogues have higher affinity toward HA (up to 30,000 fold of SA) compared to C5-derived (up to 3,500 fold of SA) and C2-derived analogues (up to 1,500 fold of SA). Therefore the designed SA analogues have the potential to block the HA binding site and consequently inhibit viral attachment to host cell.

Keywords: Influenza A Hemagglutinin, Sialic acid analogues, Fragment-based molecular design, Molecular docking.
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