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In-Depth Analysis on Sequence Evolution and Molecular Interaction of Influenza Receptors (Hemagglutinin and Neuraminidase)

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Abstract : Hemagglutinin (HA) and Neuraminidase (NA) play an important role in host immune evasion across influenza virus evolution process. The correlation between HA and NA evolution in respect to epitopic evolution and drug interaction has yet to be investigated. In this study, combining of sequence to structure evolution and statistical analysis on epitopic/binding site specificity, we identified potential therapeutic features of HA and NA that show specific antibody binding site of HA and specific binding distribution within NA active site of current inhibitors. Our approach introduces the use of sequence variation and molecular interaction to provide an effective strategy in establishing experimental based distributed representations of protein-protein/ligand complexes. The most important advantage of our method is that it does not require complete dataset of complexes but rather directly inferring feature interaction from sequence variation and molecular interaction. Using correlated sequence analysis, we additionally identified co-evolved mutations associated with maintaining HA/NA structural and functional variability toward immunity and therapeutic treatment. Our investigation on the HA binding specificity revealed unique conserved stalk domain interacts with unique loop domain of universal antibodies (CR9114, CT149, CR8043, CR8020, F16v3, CR6261, F10). On the other hand, NA inhibitors (Oseltamivir, Zaninamivir, Laninamivir) showed specific conserved residue contribution and similar to that of NA substrate (sialic acid) which can be exploited for drug design. Our study provides an important insight into rational design and identification of novel therapeutics targeting universally recognized feature of influenza HA/NA.

Keywords : influenza virus, hemagglutinin (HA), neuraminidase (NA), sequence evolution
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