Dynamic residue interaction network analysis of the neuraminidase H274Y mutant conferring drug resistance in influenza virus

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Influenza is a highly contagious respiratory disease caused by influenza virus, resulting in mild to severe illness and sometimes even death. Influenza virus glycoproteins, hemagglutinin (HA) and neuraminidase (NA), play essential roles in its replication process. HA mediates virus entry into the host cell by binding to the terminal sialic acid (SA) of sugar chains on the host cell surface. NA plays a role in the virus release, by cleaving the bond between SA and the sugar chain in the last stage of infection, which allows the progeny viruses to liberate to begin infecting the surrounding host cells.

Oseltamivir (OTV) is a leading NA inhibitor used in the treatment and prevention of influenza. However, the OTV resistant influenza virus strains are emerging rapidly. One of the major OTV resistant influenza virus strain exhibits His-to-Tyr mutation at residue 274 in N1 NA. However, the molecular mechanism of the reduction in H274Y mutant N1 NA binding affinity to OTV have not been fully elucidated. Hence, in this study, we theoretically investigated the changes in residue-residue and residue-ligand interactions associated with the H274Y mutation in N1 NA bound to OTV using dynamic residue interaction network (dRIN) analysis based on molecular dynamics (MD) simulation.[1]

dRIN analysis revealed that the OTV binding site of N1 NA and its H274Y mutation site interact via the three interface residues, S246, E276, and R292, connecting them. Due to H274Y mutation in N1 NA, the interaction between residue 274 and the three interface residues, S246, E276, and R292, significantly increased, thereby significantly decreasing the interaction between OTV and its surrounding 150-loop residues, D151, and R152. Such changes in residue interactions could reduce the binding affinity of N1 NA to OTV, resulting in OTV resistance in influenza viruses. In conclusion, using dRIN analysis, we succeeded in understanding the characteristic changes in residue interactions due to H274Y mutation in N1 NA, which can elucidate the molecular mechanism of reduction in OTV binding affinity to N1 NA. Finally, the dRIN analysis used in this study can be widely applied to various systems such as individual proteins, protein-protein complexes, and protein-ligand complexes to characterize the dynamic aspects of the interactions.

[1] Yadav, M.; Igarashi, M.; Yamamoto, N. Dynamic residue interaction network analysis of the oseltamivir binding site of N1 neuraminidase and its H274Y mutation site conferring drug resistance in influenza A virus, *PeerJ*, **2021**, e11552.