Remarkable Loop Flexibility in Avian Influenza Neuraminidase and its Implications for Antiviral Drug Design

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Abstract

Avian influenza virus type A, subtype H5N1, is becoming the world's largest pandemic threat due to its high virulence and lethality in birds, quickly expanding host reservoir, and high rate of mutations. Antigenic drift has given rise to new strains that are resistant to existing drugs and antigenic shift is resulting in new virulent subtypes of the flu virus, underscoring the need to design novel therapeutics. The first crystal structures of a group-1 NA in apo form and in complex with currently available drugs revealed that although the binding pose of Tamiflu was similar to that seen in previous crystallographic complexes, the 150-loop adopted a distinct conformation, opening a new cavity adjacent to the active site. These structures also suggested a slow conformational change may occur upon inhibitor binding. Despite this detailed structural information, the interpretation of the loop dynamics based on crystal structures alone is a difficult task. As a complement to the crystallographic structures, all-atom explicit solvent and generalized Born molecular dynamics (MD) simulations of the apo and Tamiflu-bound systems were performed. These extensive simulations suggested that the 150- and 430-loops, which are important due to their proximity to the sialic-acid binding site, may be even more flexible than observed in the crystal structures. Ensemble-based virtual screens and end point free energy calculations have revealed provocative insights into the binding and recognition of known and novel antiviral compounds.