Impact of Tetramerization on Neuraminidase Dynamics and Binding Site Conformations

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Influenza neuraminidase (NA) is a tetrameric surface protein of the influenza virus and the target for antiviral drugs e.g. oseltamivir and zanamivir. The conformational diversity of the 150-loop was revealed by crystal structures of the group 1 neuraminidases [1] and investigated by molecular dynamics (MD) simulations [2, 3]. The open state conformation shows an additional subpocket (150-cavity) exploitable for drug design [4, 5].

We present a systematic analysis of three neuraminidases (avian 2005, pandemic 1918, pandemic 2009) with all-atom, explicit solvent MD simulations applying the Amber forcefield ff99SB [6]. Comparative simulations of monomeric, dimeric and tetrameric systems reveal that the sampled conformational phase space for the tetramer is distinctable from the monomer simulations. These findings point to a stabilization of the active conformations by the protein-protein-interface. In contrast to Amaro et al. [2, 3], we show, that backbone dynamics of the flexible 150-loop and the 430-loop are limited by interaction with adjacent neuraminidase subunits.

These results underline the importance of protein-protein-interactions in the neuraminidase tetramer for the examination of molecular flexibility. In consequence, considering these interactions is crucial for drug development and elucidating the mechanism of drug resistance.

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