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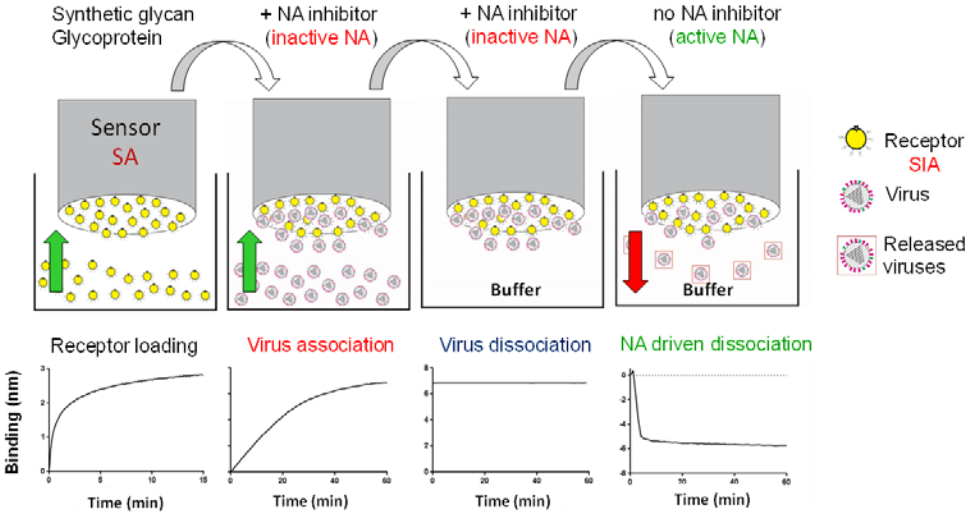
Grant Title: Dissecting the complexity of influenza A virus binding kinetics

Abstract

Influenza A virus (IAV) neuraminidase (NA) receptor-destroying activity and hemagglutinin (HA) receptor-binding affinity need to be balanced with the host receptor glycan repertoire for optimal viral fitness. Using our recently developed biolayer interferometry assays (Guo et al., PLoS Pathogens, 2018), we analyzed the importance of the 2nd sialic acid-binding site (2SBS) for the HA-NA-receptor balance of avian and human IAVs. The 2SBS, which is located adjacent to the active site is conserved in avian, but not in human (pandemic) IAVs. NAs of H2N2/1957 pandemic virus with or without a functional 2SBS and viruses containing this NA were analysed. Avian-like N2, with a functional 2SBS, cleaved multivalent receptors more efficiently than human N2, in agreement with the enhanced binding properties of this avian-like N2. The absence or presence of a functional 2SBS also affected the replication properties of IAVs, in an HA- and cell-type dependent manner. Bio-layer interferometry assays revealed a clear effect of the 2SBS on the dynamic interaction of virus particles with receptors. The absence or presence of a functional 2SBS affected virion-receptor binding and receptor cleavage required for particle movement on a receptor-coated surface and subsequent NA-dependent self-elution. The contribution of the 2SBS to virus-receptor interactions depended on the receptor-binding properties of HA and the identity of the receptors used. We conclude that the 2SBS is an important and underappreciated determinant of the HA-NA-receptor balance. The rapid loss of a functional 2SBS in pandemic viruses may have served to balance the novel host receptor-repertoire and altered receptor-binding properties of the corresponding HA protein. The results of this study have been accepted for publication in PLoS Pathogens, in May 2019.



Biolayer interferometry analysis of virion-receptor interactions. Biolayer interferometry can be used to perform kinetic analysis of virus association and dissociation from a glycan receptor- containing sensor. The kinetics of virus dissociation, for which NA activity is strictly required, reflect the HA-NA-receptor balance (Guo et al., PLoS Pathogen, 2018). We used this assay to analyze the importance of the 2nd sialic acid binding site in NA for this balance.