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The 2nd sialic acid-binding site of influenza A virus neuraminidase contributes to the hemagglutinin-neuraminidase-receptor balance

Content

It is generally accepted that the catalytic activity of influenza A virus (IAV) neuraminidase (NA) needs to match the receptor-binding activity of the corresponding hemagglutinin (HA) and the sialic acid (SIA)-receptor repertoire of the host. What this HA-NA-receptor balance entails at the molecular level is, however, not known. NA of avian, but not human viruses contain a 2nd SIA-binding site (2SBS), adjacent to the catalytic site, which contributes to sialidase activity against multivalent substrates. It is not known to what extent the 2SBS contributes to the HA-NA-receptor balance of virus particles. Here, we analysed the NA of 1957 H2N2 pandemic virus with and without a functional 2SBS (referred to as human and avian-like N2, respectively). Recombinant avian-like N2 was much more active than human N2, but only when multivalent substrates containing α2,3-linked SIAs were used, in agreement with the increased binding of this N2 to these receptors. When introduced in human H3N2 viruses, avian-like N2 resulted in altered plaque morphology and decreased replication when compared to human N2. The importance of the 2SBS for receptor binding of and cleavage by virus particles was analysed by kinetic bio-layer interferometry assays. A functional 2SBS contributed to virion-receptor binding and NA-dependent self-elution in a HA- and receptor-dependent manner. In conclusion, the 2SBS is an important determinant of the HA-NA-receptor balance. The rapid loss of a functional 2SBS in pandemic viruses probably served to balance the altered receptor-binding properties of the corresponding HA and host receptor-repertoire.

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