# Influenza A viruses use multivalent sialic acid clusters for cell binding and receptor activation

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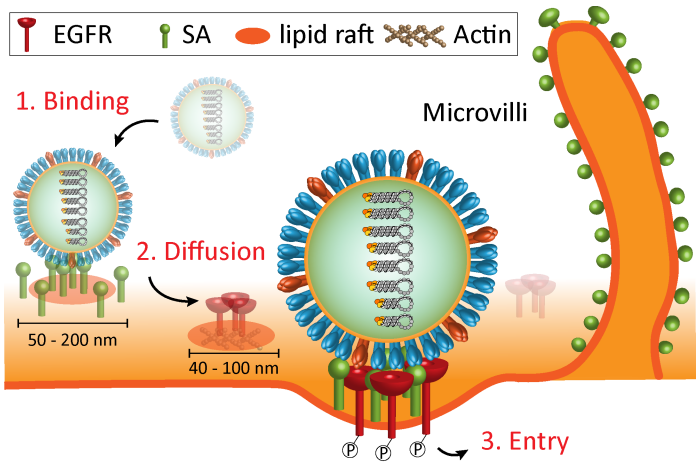
Influenza A virus (IAV) binds its host cell using the major viral surface protein hemagglutinin recognizing sialic acid (SA), a plasma membrane glycan that functions as the specific primary attachment factor. Since SA alone cannot fulfil a signalling function, the virus needs to activate downstream factors in order to trigger endocytotic uptake. Recently, the epidermal growth factor receptor (EGFR) was shown to be activated by and transmit IAV entry signals. However, how IAV engages and activates EGFR remained largely unknown. We used quantitative super-resolution microscopy to study the lateral organization of both, IAV attachment factors as well as its functional receptor at the scale of the virus-cell interface (<100 nm). We show that SA and EGFR are organized in partially overlapping submicrometer clusters in the apical plasma membrane of permissive A549 cells. Within SA domains, that are distinct of microvilli, the local SA concentration, a parameter that directly influences virus-cell binding, strongly increases towards the cluster center, thereby representing a multivalent virus-binding platform. Our quantitative cluster analysis allowed us to simulate virus membrane movement revealing that IAVs distinct membrane motility is dominated by the local SA concentration, which could be confirmed by live cell single- virus tracking. In contrast to SA, for EGFR we find clusters of rather low molecule abundance. Virus binding activates EGFR but interestingly this process occurs without a major lateral EGFR redistribution, suggesting the activation of preformed long-lived clusters. Taken together, our results provide a first step towards understanding the nanophysiology of influenza virus infection. We are able to relate the structural organization of the cell surface with its functional role during virus-cell binding and receptor activation[1].




[1] Sieben et al., *bioRxiv*, 10.1101/26471

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