NANOPHYSIOLOGY OF INFLUENZA A VIRUS INFECTION

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Influenza A viruses (IAV) bind cells using the viral protein hemagglutinin recognizing sialylated plasma membrane glycans, IAVs primary attachment factors (AF). Since AFs cannot fulfill a signaling function, the virus needs to activate downstream factors in order to trigger endocytic uptake. The epidermal growth factor receptor (EGFR) was shown to be activated and transmit IAV entry signals [1] but how IAV engages and activates EGFR remains unclear. We used quantitative super-resolution microscopy to study the lateral organization of 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 nanoclusters in the apical plasma membrane of permissive A549 cells [2]. Within AF clusters, that are distinct of microvilli, the local AF concentration, a parameter that directly influences virus-cell binding, strongly increases towards the cluster center, thereby representing a multivalent virus-binding platform. Our quantitative analysis allowed us to simulate virus-membrane interaction suggesting that IAVs perform an explorative movement dominated by the local SA concentration, which could be confirmed by live-cell single-virus tracking. 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. 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.

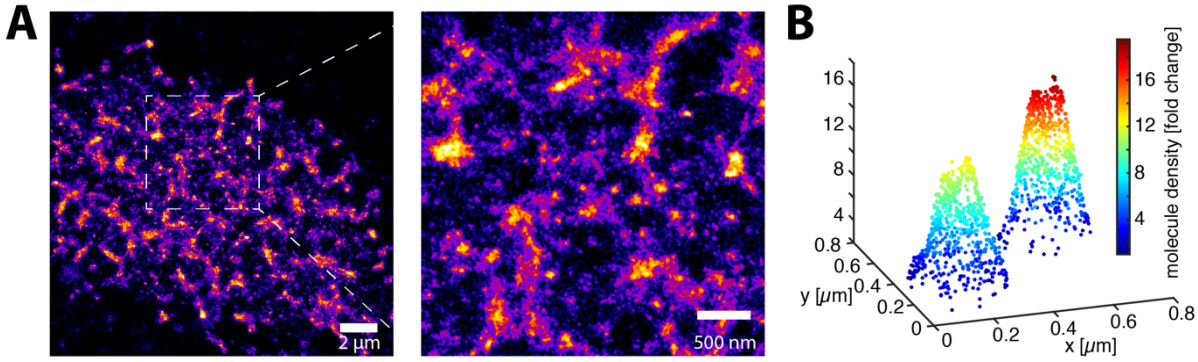

Figure 1: Influenza A virus attachment factors are organized in sub-micrometer clusters with varying densities on permissive epithelial cells.

[1] Eierhoff *et al.*, *PLoS Pathogens* **2010** 6(9), [2] Sieben *et al.*, *PLoS Pathogens* **2020** 16(7)