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Meeting abstract

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The epidermal growth factor receptor (EGFR) contributes to efficient entry of influenza A viruses into host cells

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Previous observations suggested that the entry process of influenza A viruses (IAV) is at least in part a signaling-regulated event. Although it is well known that sialic acids on the cell surface serve as direct receptors for IAV by binding to the viral HA, the requirement of early signaling events for viral entry suggests the involvement of signal transmitting receptors. However, the nature of these receptors that could transmit entry relevant signals across the membrane, are so far unknown. Our recent observation that the phosphatidylinositol-3 kinase (PI3K), that is an effector enzyme of growth factor receptors, is involved in IAV entry [1] lead to the hypothesis that receptor tyrosine kinases may play a role as cellular signaling receptors upon virus binding to cells. In this study we introduce the EGFR, a prominent member of the receptor tyrosine kinase family as a novel player to be involved in IAV entry processes.

Inhibition of tyrosine kinases in general by small molecule inhibitors as well as specific inhibition of the EGFR by inhibitors, siRNA mediated knock-down or treatment of cells with EGFR blocking antibodies results in reduced viral uptake and subsequently to reduced progeny virus titers. In contrary, overexpression of the EGFR or treatment with EGF during infection leads to enhanced uptake and increased virus titers. Furthermore, infection results in a redistribution of the EGFR similar to that observed upon stimulation with the ligand EGF. IAV at least in part co-localizes with the EGFR and both, viral particles on the surface and the receptor are localized in lipid rafts. According to our data we propose, that influenza virus is a multivalent agent that induces a clustering of EGFR and other signaling receptors into lipid rafts, by binding to sialic acid coupled proteins. This may lead to a low level induction of the receptor-induced signaling cascades, such as PI3K/Akt that facilitates viral entry. Thus, we could identify for the first time the EGFR as an indirect viral receptor to form a lipid raft-based signaling platform required for efficient IAV uptake.

References

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