

MHC-II functions as pH-dependent membrane fusion switch for bat influenza A virus

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Influenza A virus hemagglutinin is a prototypical class I viral fusion protein that binds sialylated glycans and is activated by low pH in endosomes. In contrast, bat-derived IAV subtypes H17N10 and H18N11 use major histocompatibility complex class II (MHC-II) as an entry receptor, but how this receptor contributes to membrane fusion remains unknown. We find that MHC-II-dependent hemagglutinin subtypes H17, H18, and H19 possess an increased negative net charge relative to canonical HAs. Using cryo-electron tomography, we demonstrate that H18N11 morphology remains stable and H18 is in prefusion conformation at strongly acidic pH. Remarkably, H18 undergoes fusion-relevant conformational changes only when both MHC-II binding and low pH are present. By reconstitution of H18N11 fusion with liposomes and purified MHC-II, we show that receptor engagement is required to trigger the fusion activity of H18. These findings identify MHC-II as a receptor that directly triggers membrane fusion and reveal a previously unrecognized receptor-dependent mechanism of influenza virus entry.

Keywords

Bat influenza A virus, H18N11, Hemagglutinin, MHC-II, membrane fusion, cryo-electron tomography

Professional status of the speaker

Professor

Junior scientist status

No, I am not a junior scientist.

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Author: CHLANDA, Petr (Heidelberg University Hospital)

Co-authors: PETERL, Sarah; ROBERT, Jonathan; OSMAN, Maria; HAINES, Rebecca; FISCHER, Konstantin; LANGI, Richard; CIMINSKI, Kevin; SCHWEMMLE, Martin; REUTHER, Peter

Presenter: CHLANDA, Petr (Heidelberg University Hospital)

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