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Interplay between H1N1 influenza a virus infection, extracellular and intracellular respiratory tract pH, and host responses in a mouse model

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Abstract:

During influenza A virus (IAV) entry, the hemagglutinin (HA) protein is triggered by endosomal low pH to undergo irreversible structural changes that mediate membrane fusion. HA proteins from different isolates vary in the pH at which they become activated in endosomes or become irreversible inactivated if exposed to extracellular acid. Little is known about extracellular pH in the upper respiratory tracts of mammals, how pH may shift during IAV infection, and its impact on replication of viruses that vary in HA activation pH. Here, we inoculated DBA/2J mice intranasally with A/TN/1-560/2009 (H1N1) (activation pH 5.5) or a mutant containing the destabilizing mutation HA1-Y17H (pH 6.0). We measured the kinetics of extracellular pH during infection using an optical pH-sensitive microsensor probe placed in the naris, nasal sinus, soft palate, and trachea. We also measured intracellular pH of single-cell suspension of live, primary lung epithelial cells with various wavelength pH-sensitive dyes localized to cell membranes, cytosol, endosomes, secretory vesicles, microtubules, and lysosomes. Infection with either virus decreased extracellular pH and increased intracellular pH. Peak host immune responses were observed at 2 days post infection (DPI) and peak pH changes at 5 DPI. Extracellular and intracellular pH returned to baseline by 7 DPI in mice infected with HA1-Y17H and was restored later in wildtype-infected. Overall, IAV infection altered respiratory tract pH, which in turn modulated replication efficiency. This suggests a virus-host pH feedback loop that may select for IAV strains containing HA proteins of optimal pH stability, which may be approximately pH 5.5 in mice but may differ in other species.

Keywords: Influenza A virus, hemagglutinin protein, respiratory tract pH, endosomes, cell membranes, immune response