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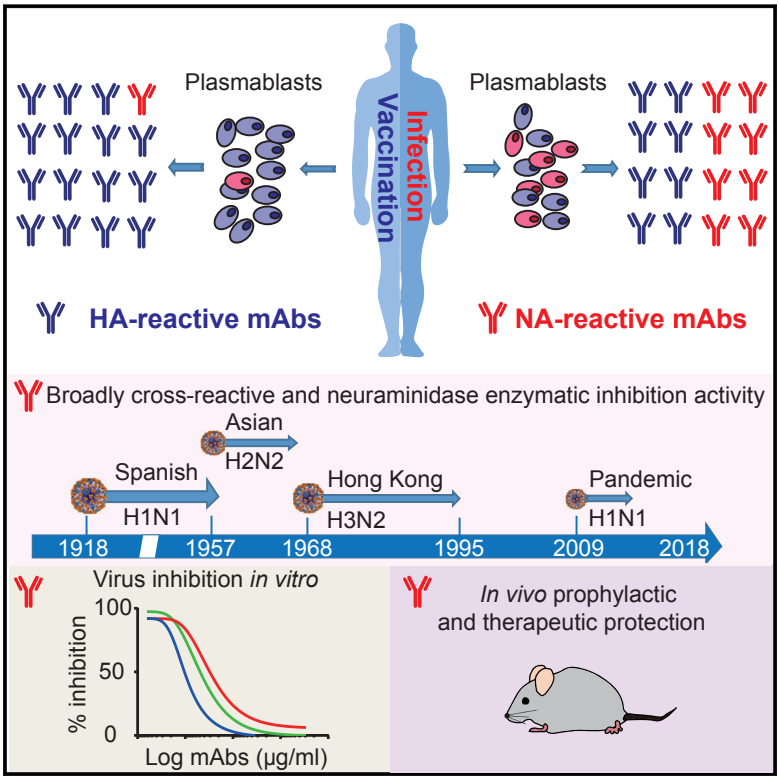
Influenza Infection in Humans Induces Broadly Cross-Reactive and Protective Neuraminidase-Reactive Antibodies

Graphical Abstract



Highlights

- Flu virus infection induces many neuraminidase (NA)-reactive B cells and antibodies
- NA antibodies have broad cross-reactivity and inhibit neuraminidase enzyme activity
- Current flu vaccines poorly display key NA epitopes and do not produce NA antibodies
- NA-reactive antibodies offer protection against lethal flu virus infection

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In Brief

Current influenza vaccines predominantly produce antibodies targeting the viral hemagglutinin (HA). However, during natural infection, the body also produces antibodies targeting the viral neuraminidase (NA). These NA antibodies can provide robust and broad protection and could potentially be elicited prophylactically or via new vaccine strategies or used therapeutically.

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Influenza Infection in Humans Induces Broadly Cross-Reactive and Protective Neuraminidase-Reactive Antibodies

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SUMMARY

Antibodies to the hemagglutinin (HA) and neuraminidase (NA) glycoproteins are the major mediators of protection against influenza virus infection. Here, we report that current influenza vaccines poorly display key NA epitopes and rarely induce NA-reactive B cells. Conversely, influenza virus infection induces NA-reactive B cells at a frequency that approaches (H1N1) or exceeds (H3N2) that of HA-reactive B cells. NA-reactive antibodies display broad binding activity spanning the entire history of influenza A virus circulation in humans, including the original pandemic strains of both H1N1 and H3N2 subtypes. The antibodies robustly inhibit the enzymatic activity of NA, including oseltamivir-resistant variants, and provide robust prophylactic protection, including against avian H5N1 viruses, *in vivo*. When used therapeutically, NA-reactive antibodies protected mice from lethal influenza virus challenge even 48 hr post infection. These findings strongly suggest that influenza vaccines should be optimized to improve targeting of NA for durable and broad protection against divergent influenza strains.

INTRODUCTION

Influenza is an acute respiratory illness that causes up to 5 million cases of influenza virus infection and 250,000–640,000 deaths annually around the world (Iuliano et al., 2017). The influenza virus has two main surface glycoproteins, hemagglutinin (HA) and neuraminidase (NA). HA, the more abundant protein, mediates binding to sialic acid receptors and subsequent fusion between the virus and host cell membranes. The less-abundant tetrameric NA protein is essential for cleaving terminal sialic acid residues present on host cell surfaces, allowing the release of the newly formed viral particles (Matrosovich et al., 2004; Palese and Compans, 1976).

Currently, the seasonal influenza virus vaccine is the most widely available method to reduce the annual impact of influenza infection (Nichol, 2008). HA-reactive antibodies are typically considered the *de facto* mediators of protection from influenza infection; indeed, inhibition of HA activity has been the primary measure of influenza vaccine efficacy for decades. Therefore, most of the current approaches for vaccine design focus on inducing an antibody response to influenza virus HA. Influenza vaccine effectiveness can vary widely from season to season such that protection is always limited. For example, vaccine effectiveness ranged from only 19%–48% during the past three influenza seasons (Flannery et al., 2017). Studies have shown that HA antigenic drift (viral genome point mutations) is the primary reason for the limited effectiveness of the seasonal influenza vaccine (Karron and Collins, 2013). Due to viral mutations, preexisting antibodies often show limited neutralization against currently circulating viruses (Wohlbold and Krammer, 2014). Although point mutations also occur in the NA protein, the rate of antigenic drift around the active site of NA in the head domain is slower than that for HA among influenza A viruses (Abed et al., 2002; Air, 2012).

Historically, NA has served as an important target for antivirals or therapeutics due to its critical role in the influenza virus replication cycle (Wohlbold and Krammer, 2014). Inhibition of NA