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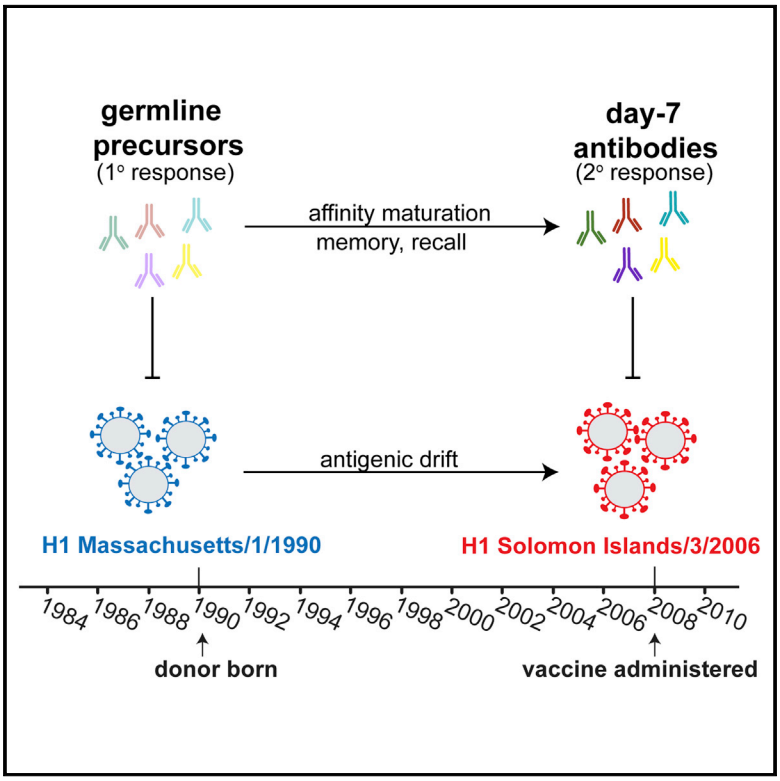
Immunogenic Stimulus for Germline Precursors of Antibodies that Engage the Influenza Hemagglutinin Receptor-Binding Site

Graphical Abstract



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In Brief

Schmidt et al. use an approach they call "immuno-viral archaeology" to probe the history of influenza exposure and antibody response in a single individual. They find that viruses, circulating during a donor's infancy, bind tightly to the germline precursors of six distinct lineages of antibodies targeting the hemagglutinin receptor binding site.

Highlights

- UCAs of RBS-directed lineages bind viruses circulating during a donor's infancy
- H1 viruses circulating after 1995 have escaped binding by lineage UCAs
- Vaccination recalled lineages, with further maturation and increased breadth
- Imprinting by H1 influenza early in life may direct later B cell responses

Schmidt et al., 2015, Cell Reports *13*, 2842–2850
December 29, 2015
http://dx.doi.org/10.1016/j.celrep.2015.11.063

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Cell Reports
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Immunogenic Stimulus for Germline Precursors of Antibodies that Engage the Influenza Hemagglutinin Receptor-Binding Site

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SUMMARY

Influenza-virus antigenicity evolves to escape host immune protection. Antibody lineages within individuals evolve in turn to increase affinity and hence potency. Strategies for a "universal" influenza vaccine to elicit lineages that escape this evolutionary arms race and protect against seasonal variation and novel, pandemic viruses will require directing B cell ontogeny to focus the humoral response on conserved epitopes on the viral hemagglutinin (HA). The unmutated common ancestors (UCAs) of six distinct, broadly neutralizing antibody lineages from one individual bind the HA of a virus circulating at the time the participant was born. HAs of viruses circulating more than 5 years later no longer bind the UCAs, but mature antibodies in the lineages bind strains from the entire 18-year lifetime of the participant. The analysis shows how immunological memory shaped the response to subsequent influenza exposures and suggests that early imprinting by a suitable influenza antigen may enhance likelihood of later breadth.

INTRODUCTION

Influenza virus in humans evolves in response to pressure from immunity in the susceptible population, leading to progressive variation of viral antigenicity. Introduction of a new strain of influenza A from birds or swine ("antigenic shift") initiates a cycle of antibody generation and viral escape ("antigenic drift"), the latter largely through mutation of surface residues on the viral hemagglutinin (HA) but secondarily through variation of antigenic determinants on the neuraminidase (NA). Detailed antigenic analysis of annual HA variation in H1 and H3 subtypes shows a punctuated evolutionary trajectory, with a shift in "antigenic cluster" (defined by reactivity with standard panels of ferret immune sera) every few years (Smith et al., 2004; Fonville et al., 2014). Strong selective pressure from widespread immunity in the human population thus appears to require more than one seasonal cycle.

The humoral response within individuals also evolves, through immune memory and B cell affinity maturation. When stimulated by a new exposure (infection or vaccination), memory cells can re-enter germinal centers and undergo new rounds of somatic hypermutation and selection (Victora and Nussenzweig, 2012; De Silva and Klein, 2015). The net effect of this on-going selection across the entire population exposed to the virus is a virus-immunity "arms race." Mutated HA with reduced affinity for a particular antibody can, in principle, select for mutations in the latter that restore strong binding. We can study this evolutionary process by detecting B cells descended from the same common ancestor and determining the sequences of their rearranged variable-domain genes (Moody et al., 2011).

Antigenic variation requires an annual revision of vaccine components. A more effective vaccine strategy would protect against many rounds of this seasonal variation and ideally against introduction of new serotypes from viruses circulating in animal reservoirs (a so-called "universal" influenza vaccine; Burton et al., 2012; Krammer and Palese, 2015). Broad protection will probably come from a humoral response to conserved sites on the viral HA. The two relatively invariant epitopes so far recognized are the receptor binding site (RBS) on the HA "head" and a surface along the HA "stem" (Knossow et al., 2002; Ekiert et al., 2009; Sui et al., 2009; Corti et al., 2011; Whittle et al., 2011; Corti and Lanzavecchia, 2013). Study of over 100 influenza (subtype H1) RBS-directed antibodies from three individuals, all of whom received the trivalent influenza vaccine in 2008 (Moody et al., 2011), has shown that antibodies engage the RBS through contacts that recapitulate many of those made by the viral receptor, sialic acid (Weis et al., 1988; Whittle et al., 2011; Schmidt et al., 2015). The key interactions come from a critical dipeptide (valine-aspartic acid or a related