LONGITUDINAL LANDSCAPES OF SERUM ANTIBODY REPERTOIRES AFTER INFLUENZA INFECTION AND VACCINATION

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Vaccination is the most effective means of infectious disease prevention. Despite its success, however, we still lack a clear understanding of vaccine responses in humans. For example, influenza vaccines still leave a large fraction of population vulnerable. Over the past decade, single B-cell analysis and next-generation sequencing (NGS) technologies have become invaluable tools for studying the antibody repertoire to influenza. Such studies have led to discoveries of broadly-neutralizing antibodies (bNAbs), which can neutralize across multiple strains of influenza virus, promoting the notion of designing a universal vaccine that will elicit such antibodies. One of such isolated bNAbs, called FI6, showed remarkable ability to neutralize all of the influenza A virus strains through targeting the conserved epitope in the stem of hemagglutinin (HA). However, it remains unclear whether such bNAbs actually play a role in conferring protection against influenza since antibody proteins (not B-cells) need to circulate at physiologically relevant concentrations in serum to have implications in protection. Using high-resolution proteomics coupled with NGS, we quantitatively determined the serological antibody repertoire to CA09 HA (H1) at the individual clonotype-level in a donor (whom FI6 was isolated from) following influenza infection (in 2010 with pandemic CA09) and vaccination across five years (2010-2014 with seasonal flu vaccine). We analyzed the temporal changes of head-targeting and stem-binding antibodies, illustrating the gradual increase of stem-targeting antibodies following repeated exposures to CA09 HA. Following vaccination in 2014, >60% of the repertoire consisted of one single clonotype of stem-binding antibody that was present at very low abundance in 2010. Our data demonstrate that the repetitive exposure to influenza skews the serological repertoire toward antibodies that target conserved epitopes, and these antibodies continue to be boosted every time the same epitopes are encountered. Once elicited, stem-binding antibodies displayed a tendency to persist in serum across multiple years while head-specific antibodies decayed quicker. The differential longevity of stem-binding and head-specific antibodies presented here has direct implications for the design of the future universal vaccine.