PERSISTENT ANTIBODY CLONOTYPES DOMINATE THE SERUM RESPONSE TO INFLUENZA FOLLOWING REPEATED VACCINATION OVER MULTIPLE YEARS

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Key Words: Antibody repertoire, longitudinal vaccine response, proteomics, serological imprinting

We used Ig-Seq, a liquid chromatography tandem mass spectrometry (LC-MS/MS)–based serum antibody proteomics methodology, to determine the clonal composition and dynamics of the H1N1 California/7/2009 (CA09) hemagglutinin (HA)-reactive antibody repertoire over 5 years in a well-characterized donor from whom a large number of homosubtypic and heterosubtypic neutralizing monoclonal antibodies had been previously isolated by B cell analysis. The donor was infected with the CA09 strain in 2009 and immunized annually for the next five years with seasonal influenza vaccine which contained the CA09 strain. We find that the serological repertoire in this donor was highly static, with a modest number (24) of persistent antibody clonotypes, detected in serum for at least 4 out of 5 years, accounting on average for 72.6 ± 10.0% of the repertoire to the CA09 HA. These persistent antibodies: (i) displayed a higher degree of somatic hypermutation relative to antibodies that could be detected in the serum transiently (i.e. lasted less than 1 year in serum); (ii) comprised a significant fraction that also bound to HA from a phylogenetically distant H5N1 A/Vietnam/1203/2004 (VT04) strain, a hallmark of stem-binding antibodies due to the lack of homology between CA09 and VT04 in the head region of HA and (iii) perhaps most strikingly, but consistent with the wealth of heterosubtypic neutralizing antibodies that had previously been identified from this donor, some of the most abundant persistent antibody clonotypes, including the dominant clone that accounted on average for 18.6 ± 12.3% of the serum titer across 5 years, neutralized both the CA09 and VT04 influenza strains. Our analysis highlights the magnitude of ‘serological imprinting’ in the donor’s serum response to CA09, indicates that seasonal vaccination can further reinforce a stable serological memory and finally suggests that once elicited, antibodies cross-reactive between CA09 and VT04 with heterosubtypic neutralization activity, thus likely to bind to HA-stem, can persist for many years, which is a fundamental goal of universal influenza vaccines.