# MOLECULAR UNDERSTANDING OF THE SERUM ANTIBODY REPERTOIRES AFTER SEASONAL INFLUENZA VACCINATION AMONG DIFFERENT AGE COHORTS

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Numerous influenza vaccination studies based on bulk serology have indicated that the antibody responses to the vaccine markedly decrease in the elderly. However, whether such decline results from the changes in the overall quantity or the quality of the circulating antibodies in serum remains unknown. Utilizing novel antibody repertoire profiling technologies, combining tandem mass spectrometry (LC-MS/MS) and high-throughput sequencing, we investigated the influenza-specific serological repertoires of 10 donors ranging from 26 to 70 years old vaccinated with Fluzone® 2013-2014 and/or 2014-2015. In particular, we determined the serum antibodies that are specific to the H1 or H3 component of the vaccine or cross-reactive between the two (H1+H3) and examined their relative quantitative distributions. Our data indicate that the proportion of H1+H3 antibodies significantly increases in the elderly and that the somatic hypermutation rates of the influenza-specific antibodies are higher in the elderly. These results suggest that the repeated exposure to the different virus subtypes could have led to the prolonged selection of H1+H3 antibodies targeting highly conserved epitopes. To evaluate the potency of the antibodies circulating in different age groups, we recombinantly expressed a number of representative monoclonal antibodies isolated from the donors in different age groups for further characterizations. Overall, our analysis suggests that the influenza-specific repertoire in the elderly may converge toward shared epitopes but the quality of the antibodies can be superior in terms of cross-reactivity. However, because the antibody repertoire “shrinks” as we age while targeting more conserved epitopes across different influenza subtypes, it is possible that the elderly is particularly susceptible to significantly altered strains. Collectively, profiling vaccine induced serological repertoires among different age cohorts can provide unprecedented insights regarding humoral immunity associated with age and a potential explanation for the vulnerability of the elderly.