Clonal structure, stability and dynamics of human memory B cells and circulating plasmablasts

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Abstract

Memory B cells are known to persist for a lifetime and rapidly differentiate into antibody-producing plasma cells upon antigen rencounter. However, the clonal structure of memory B cells and their relationship with recently generated plasma cells is far from being understood. Using single cell sequencing of multi-year serial blood samples from two healthy donors, combined with the isolation of specific monoclonal antibodies, we found that the memory B cell repertoire was dominated by large clonal families producing IgM, IgA and IgG2, while IgG1 families, including those encoding antibodies to recall antigens, were of small size. Remarkably, 0.2% of primarily IgM families shared highly similar VH/VL sequences in the two donors delineating multiple convergent antibodies. The comparative analysis of serial samples demonstrated the stability of the memory B cell pool in all its subsets over several years. Surprisingly, recurrent plasma cell clonotypes related to memory B cells were found among recently generated circulating plasmablasts and contained mainly IgA, IgG2 and, at lower frequency, IgG1 specific for recall antigens. We also demonstrate the continuous generation of plasmablasts specific for recall antigens such as measles virus or tetanus toxoid in the absence of recent exposure. Taken together, these findings support a model where polyclonal bystander activation of memory B cells continuously generates plasmablast at low rate, thus contributing to the maintenance of bone marrow plasma cells and serum antibody levels. Collectively, this study provides a global view of the structure, stability and dynamics of the human memory B cell and plasma cell pools and shows that a large fraction of memory B cell families is active at any time point in the generation of plasma cells.