6. Abstract

Human peripheral B cells that co-express the surface B cell antigen receptor (BCR) and pre-BCR (V-preB$^+$L$^+$ B cells) represent about 0,5-1% of the peripheral B cell pool in healthy individuals but are significantly enriched in the joints of patients with rheumatoid arthritis (RA). To address the possible causal role of V-preB$^+$L$^+$ B cells in the pathogenesis of RA, a new method was established that allowed the analysis of the repertoire and the antigen specificity of the antibodies produced by individual V-preB$^+$L$^+$ B cells. In brief, the immunoglobulin heavy and light chain genes derived from the single cell-sorted V-preB$^+$L$^+$ B cells were sequenced and expressed in A293 fibroblasts in quantities that allowed the serological analysis of their specificity. The immunoglobulin gene repertoire of individual V-preB$^+$L$^+$ B cells suggested their ability to produce poly-/autoreactive antibodies. Using this novel approach, 68% of antibodies expressed by V-pre$^+$L$^+$ B cells were found to be self-reactive. These antibodies recognized nuclear antigens as well as various other self-antigens such as DNA, cytoskeletal proteins, LPS, and insulin. Most importantly, a significant fraction of these antibodies bound to GPI, the antigen that is recognized by arthritogenic antibodies in the serum of RA patients. To prove the self-reactive nature of V-preB$^+$L$^+$ B cell derived antibodies, transgenic mice were generated that expressed one of the most characteristic V-preB$^+$L$^+$ B cell IgH gene (ED45H-tg). Expression of this transgenic BCR in the absence of the pre-BCR resulted in clonal deletion of developing B cells. Collectively, these data revealed the potential contribution of V-preB$^+$L$^+$ B cells to the pathogenesis of autoantibody-induced RA and suggests a novel mechanism of tolerance evasion through ectopic expression of pre-BCR on peripheral autoreactive B cells.