How are B cells displaying arthritogenic antibodies tolerized?

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K/BxN mice are made by crossing a T cell receptor transgenic line (KRN) with the NOD strain. These mice spontaneously develop a joint disease highly reminiscent of human rheumatoid arthritis. Both T and B cells are required for disease development. B cells from the arthritic mice produce arthritogenic antibodies that provoke arthritis when transferred into healthy, lymphocyte-deficient recipients. The autoantigen for both T and B cells is glucose-6-phosphate isomerase (GPI), a glycolytic enzyme that resides in the cytoplasm of all cells and is also found in the blood. The goal of this project is to determine why B cells with potentially arthritogenic antibody specificities are unreactive in normal mice and are activated in K/BxN mice. In order to track these B cells, we generated knock-in mice of rearranged anti-GPI immunoglobulin sequences. GPI-autoreactive cells are arrested during their maturation in the spleen and are out-competed in the periphery. Some of these autoreactive cells undergo receptor editing and some of them express an endogenous kappa allele in addition to the knock-in allele. So multiple strategies are employed to maintain the tolerance of arthritogenic B cells.

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