How B cell-autonomous functions of Bach2 regulate the susceptibility to systemic lupus erythematosus

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Systemic lupus erythematosus (SLE or lupus) is a systemic autoimmune disease characterized by an abundance of antibodies against nuclear self-antigens. Although its etio-pathogenesis is poorly understood, it is generally accepted that class-switched IgG, but not IgM, autoantibodies play a crucial role in the development of SLE. Bach2 is a bZip-family transcription repressor which is well-known to be required for class switch recombination of Ig genes in B cells. Therefore, Bach2-deficient mice exhibit reduced titers of IgG at steady and activated states. However, we found that, surprisingly, Bach2-deficient B cells produce more IgG autoantibodies than WT B cells, sufficient to induce SLE in mice. To resolve this mystery, we have carried out mechanistic studies using Bach2-deficient mice, including transcriptome analysis, mixed BM chimerism, and metabolic profiling. Our results suggest that Bach2-deficient autoreactive B cells preferentially react at extrafollicular sites to give rise to IgG class-switched plasma cells and that this effect requires the help of $Bach2^{-}Icos^{hi}$ helper T cells. Thus, the cell-autonomous roles of Bach2 in B cells and in their cognate $CD4^{+}$ T cells are required to maintain self-tolerance against SLE. Moreover, we found that Bach2 deficiency perturbs the lipid metabolic program of naive B cells, which presumably promotes their premature turnover to cells with proinflammatory phenotypes. Here, I would like to present the results and discuss with you how Bach2 regulates self-tolerance and auto-reactivity.