A key role for Fas ligand expressed on B cells in initiation of autoimmune diabetes

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Type-1 diabetes (T1D) is an organ specific autoimmune disease that affects young children. T cells, dendritic cells, and B cells infiltrate the islets in the early stage of the disease leading to insulitis followed by islet destruction and hyperglycemia. Studies in non-obese diabetic (NOD) mouse show that development of T1D is completely inhibited by gld or lpr mutations of Fas and FasL, respectively, even though the Fas pathway is not essential for T cell activation and that mutant mouse develop T cell lymphoproliferation. Recently, we have shown heterozygous gld mutation provides complete protection without causing lymphoproliferation in NOD-gld/+ mice. Using NOD-gld/+ mouse as a model, we found that the protection is not due to deletion of autoreactive T cells or switching of T helper polarization. Furthermore, islet-reactive BDC2.5 TCR transgenic CD4 T cells transferred into NOD-gld/+ mice were efficiently primed in the pancreatic lymph nodes but failed to accumulate in the pancreas. FasL deficiency selectively affects B cells resulting in reduced expression of CD40 and B cell frequency in the pancreas. Transfer of wild type B cells into NOD-gld/+ mice results in mobilization of endogenous T cells particularly of CD8 T cells and of co-transferred BDC2.5 T cells resulting in severe insulitis. These results provide the first evidence that B cells play an essential role in gld-mediated protection from T1D and that expression of functional FasL on B cells is key for the initiation insulitis.