

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 insulinitis 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 insulinitis. 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 insulinitis.