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Survival of diabetogenic T cells in pancreatic islets is mediated by Fas ligand

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Type 1 diabetes (T1D) is an important autoimmune disease that is becoming an increasing health problem. Diabetogenic T cells primed by islet derived autoantigens in pancreatic lymph nodes (PLN) migrate into pancreatic islets where they expand and cause destruction of insulin-producing beta cells. However, molecular mechanisms that regulate survival of autoreactive T cells in pancreas are poorly understood. Our previous data show that pharmacological blockade of FasL prevents diabetes in non-obese diabetic (NOD) mice, a widely used model for T1D. Here we show that intact Fas pathway is essential for survival and accumulation of diabetogenic T cells in pancreas of diabetes in NOD mice. This is demonstrated using adoptive transfer of islet-reactive BDC2.5 TCR transgenic T cells and analysis of endogenous diabetogenic T cells in NOD mice bearing *gld* mutation of Fas ligand (FasL). Proliferation and differentiation of diabetogenic T cells in PLN is not affected by the *gld* mutation. However, unlike in wild type mice, diabetogenic T cells that enter the pancreas of *gld* mice fail to express CD44, CD40L and undergo apoptosis. Our data point to deficient CD40 expression on B cells in the pancreas but not PLN as an important factor in aborting the diabetogenic process in *gld* mice. Immunization of *gld* mice with agonist CD40 antibody restores CD40L and CD44 expression on T cells and inhibits their apoptosis. These data reveal that full expression of FasL is essential for survival of effector T cells in pancreas and promotion of autoimmune diabetes development by CD40/CD40L dependent pathway.