Constitutive Expression of the NKG2D Ligand RAE1ε Within Pancreatic Islets Ameliorates Autoimmune Diabetes Development in Non-Obese Diabetic Mice

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Type 1, or autoimmune, diabetes is driven by T cell-mediated destruction of the insulin-producing β cells in pancreatic islets. The natural killer cell activating receptor NKG2D and its ligands are implicated in this process. However, the mechanism by which NKG2D-NKG2D ligand interaction affects diabetes development is poorly understood. Transgenic expression of the NKG2D ligand retinoic acid early transcript 1ε (RAE1ε) in β-islet cells of the pancreas induces the recruitment of cytotoxic T lymphocytes (CTLs) to the islets in mice. Surprisingly, however, we report here that the severity of spontaneous autoimmune diabetes is decreased in non-obese diabetic (NOD) mice expressing RAE1ε in islets (RIP-RAE1ε NOD). Despite similar infiltration of lymphocytes to the pancreas, NKG2D expression is reduced on the surface of T cells within the pancreas of RIP-RAE1ε NOD mice compared with control NOD mice. This suggests that transgenic expression of RAE1ε in pancreatic islets leads to the down-regulation of NKG2D surface expression on T cells, decreasing the ability of the cells to respond to NKG2D engagement by ligands naturally expressed in the pancreas. We further demonstrate that the NKG2D ligand H60a is expressed on T cells within the pancreas of wild-type NOD mice. Together, these data suggest that interaction between NKG2D and H60a expressed on T cells within the pancreas plays a critical role in the development of NOD diabetes and that blocking this interaction may be therapeutically useful in type 1 diabetes.