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**“How inactivation of Fas-pathway prevents autoimmune diabetes?”**

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**Background:** Fas-mediated apoptosis plays a critical role in deleting autoreactive T cells and maintaining T cell homeostasis. Yet disrupting the Fas pathway prevents rather than exacerbates T cell-mediated autoimmunity. The underlying mechanism(s) of this paradox has not been fully understood.

**Design:** In this study we used NOD model to investigate the impact of defects of the Fas pathway on T cell tolerance. We analyzed the effect of inactivating the Fas pathway on CD25+CD4+ regulatory T cell homeostasis. Using adoptive scid transfer model and bone marrow chimera, we investigated the role of gld mutation on lymphoid or non-lymphoid tissue on the protection mechanism.

**Results and Conclusion:** Here we show that resistance of NOD mice carrying heterozygous gld mutation (gld/+) to diabetes is due to protective mechanisms that involve expansion of regulatory T cells ( $T_{reg}$ ) with potent suppressor capacity. In vivo neutralization of  $T_{reg}$  function with anti-GITR, anti-CTLA-4 or anti-IL-2 antibodies abrogated the protection and led to diabetes in NOD-gld/+ mice. In addition, CD25-depleted splenocytes from diabetes resistant NOD-gld/+ mice induced diabetes in NOD-scid mice showing that diabetes resistant NOD-gld/+ mice contain potent diabetogenic cells but are actively suppressed by regulatory T cells. Bone marrow chimera experiments show the requirement of gld mutation on non-lymphoid tissue in the protection mechanism and expansion of CD25+CD4+  $T_{reg}$  cells. These results have important implications in understanding the mechanisms that regulate homeostasis of CD25+CD4+  $T_{reg}$  cells and will help in designing new therapeutic strategies for autoimmune diseases.