Deletion of Vβ3+ CD4+ T-cells by endogenous mouse mammary tumor virus 3 prevents type 1 diabetes induction by autoreactive CD8+ T-cells

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In both humans and NOD mice, type 1 diabetes (T1D) develops from the autoimmune destruction of pancreatic beta cells by T-cells. Interactions between both helper CD4+ and cytotoxic CD8+ T-cells are essential for T1D development in NOD mice. Previous work has indicated that pathogenic T-cells arise from deleterious interactions between relatively common genes which regulate aspects of T-cell activation/effector function (Ctla-4, Tnfrsf9, Il2/Ii21), peptide presentation (H2-Ag7, B2m), and T-cell receptor signaling (Ptpn22). In this study, we used a combination of subcongenic mapping and a CRISPR/Cas9 screen to identify the NOD-encoded Mtv3 provirus as a genetic element affecting CD4+/CD8+ T-cell interactions through an additional mechanism, altering the T-cell receptor (TCR) repertoire. Mtv3 encodes a superantigen that deletes the majority of Vβ3+ thymocytes in NOD mice. Ablating Mtv3 and restoring Vβ3+ T-cells has no effect on spontaneous T1D development in NOD mice. However, transferring Mtv3 to C57BL/6 (B6) mice congenic for the NOD H2g7 MHC haplotype (B6.H2g7) completely blocks their normal susceptibility to T1D mediated by transferred CD8+ T-cells transgenically expressing AI4 or NY8.3 TCRs. The entire genetic effect is manifest by Vβ3+ CD4+ T-cells, which unless deleted by Mtv3, accumulate in insulitic lesions and trigger in B6 background mice the pathogenic activation of diabetogenic CD8+ T-cells. Our findings provide evidence that endogenous Mtv superantigens can influence autoimmune responses. Furthermore, since most common mouse strains have gaps in their TCR Vβ repertoire due to MtvS, it raises questions about the role of MtvS in other mouse models designed to reflect human disorders.