ST2 gene-deletion reveals a role of Foxp3$^+$ regulatory T cells in diabetes modulation in BALB/c mice

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BALB/c mice are resistant to diabetes induced by multiple low doses of streptozotocin (MLD-STZ; 5 × 40 mg/kg body weight (b.w.)) regimen in contrast to C57/BL6 mice. The deletion of ST2 gene renders BALB/c mice susceptible to diabetes induction. Cyclophosphamide (CY) in the dose of 175 mg/kg b.w. eliminated CD4$^+$Foxp3$^+$ regulatory T cells (Tregs) and enhanced disease severity in C57/BL6 mice, but it did not overcome resistance to diabetes in BALB/c mice and did not affect diabetes progression in ST2 knock-out (ST2KO) mice. We argued that a lower dose of CY may selectively eliminate Tregs while sparing effector T cells in BALB/c mice. Indeed, only a very low dose of CY (50 mg/kg b.w.) enhanced diabetes severity in ST2KO mice. This treatment eliminated Tregs in pancreatic lymph nodes in ST2KO mice, while markedly increasing the influx of CD8$^+$, CD4$^+$TNF-α^+, and CD4$^+$IFN-γ^+ effector T cells (Teffs) in pancreata. Also, the aggravation of diabetes was accompanied with increased serum levels of TNF-α, IFN-γ, and IL-17. Taken together, our data suggest that the prevailing Th2 immune response in BALB/c mice may be responsible for the resistance to MLD-STZ diabetes and that ST2 gene deletion reveals the role of highly cyclophosphamide sensitive CD4$^+$Foxp3$^+$ regulatory T cells in the pancreatic lymph nodes in diabetes modulation. (Translational Research 2013;161:118–129)

Abbreviations: b.w. = body weight; CY = cyclophosphamide; MLD-STZ = multiple low doses of streptozotocin; pLNs = pancreatic lymph nodes; ST2KO = ST2 knockout BALB/c mice; T1D = type 1 diabetes mellitus; Teffs = effector T cells; Tregs = CD4$^+$Foxp3$^+$ regulatory T cells

Type 1 diabetes mellitus (T1D) is a chronic inflammatory autoimmune disease in which autoreactive T cells infiltrate islets of Langerhans and induce progressive destruction of β-cells.[1,2] Multiple low-dose streptozotocin (MLD-STZ) administration induced beta-cell apoptosis which precedes islet infiltration of T cells. Activated T cells are responsible for the further loss of beta-cells and the initiation of insulitis.[3] The dominant role of T cells in the development of insulitis has been supported by the experiment in which the administration of T cell-depleting antibodies (anti-CD4, anti-CD8) prevents induction of MLD-STZ diabetes.[4]

Tregs are a unique subpopulation of CD4$^+$ cells that maintain immunologic homeostasis[5] and mediate an active suppression of diabetes, which has been documented in nonobese diabetic (NOD) mice and C57/BL6 mice.[6,7] Tregs appear to play a prominent role in limiting disease progression in the diabetes induced

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