

ABSTRACT

Type 1 diabetes (T1D) is an autoimmune disease resulting from the destruction of insulin-producing β cells by autoreactive lymphocytes. CD4+FOXP3+ T regulatory cells (Tregs) are essential for immune tolerance, and murine studies suggest that their dysfunction can lead to T1D. Tregs require the cytokine interleukin-2 (IL-2) for maintenance of their suppressive function, and polymorphic variants in IL-2/IL-2R pathway genes are associated with T1D. Tregs can display plasticity by converting into Th17 cells, and intermediate FOXP3+IL-17+ cells have been identified. We hypothesized that pancreatic β cell destruction in T1D is driven by conversion of autoreactive Treg cells into a Th17 phenotype due to defective Treg IL-2 signaling in T1D subjects, who have polymorphic variants in the *IL2RA* gene.

We assessed by flow cytometry the proportion of Treg and Th17 subsets in peripheral blood mononuclear cells from T1D subjects. The subjects were genotyped to determine whether they had the T1D-associated IL2RAs3118470 CC risk haplotype. Samples from T1D subjects were also obtained before the onset of disease.

We found that Tregs are potentially transitioning towards a Th17 phenotype in recent-onset T1D subjects as they have an elevated proportion of FOXP3+IL-17+ cells and Th17 cells in their peripheral blood. We went on to show that T1D subjects with the T1D-associated IL2RAs3118470 CC risk haplotype have Treg cells with IL-2 signaling deficits and an increase in the proportion of IL-17+FOXP3+ cells in their peripheral blood at diagnosis. We did not find changes in the overall proportions of Tregs and Th17 cells in T1D subjects sampled before the onset of diagnosis. However, we observed a subset of CD39-expressing Treg cells were reduced in proportion before disease onset and could act as a biomarker of T1D.

We show that defective IL-17-secreting Tregs are involved with T1D pathogenesis in a genetically identifiable subset of subjects, and provide a rationale for the treatment of T1D with therapeutics that target the IL-17 pathway.