Concentration and activity of the soluble form of the interleukin-7 receptor \( \alpha \) in type 1 diabetes identifies an interplay between hyperglycemia and immune function.

Abstract: Soluble interleukin-7 (IL-7) receptor \( \alpha \) (sCD127) is implicated in the pathogenesis of autoimmune diseases. We show that serum sCD127 concentrations are increased at the onset of type 1 diabetes (T1D; \( n = 390 \)) as compared with concentrations in age-matched islet autoantibody-negative first-degree relatives of patients (\( n = 392; P = 0.00001 \)). sCD127 concentration in patients was influenced by islet autoantibody status (\( P = 0.003 \)) and genotype of the rs6897932 single nucleotide polymorphism within the IL-7RA gene (\( P = 0.006 \)). Release of sCD127 in vitro was strongly upregulated by activation of T lymphocytes and affected by exposure to cytokines. sCD127 bound IL-7 and was antagonistic to IL-7 signaling and IL-7-mediated T-cell proliferation, suggesting a regulatory feedback mechanism on T-cell expansion. Remarkably, high glucose led to a glycated form of sCD127 that was ineffective as an IL-7 antagonist. The finding of glycated sCD127 in the circulation of patients at onset of T1D suggested that physiological regulation of IL-7-mediated T-cell survival and expansion by sCD127 may be compromised in T1D. The findings indicate that genetic, immunologic, and metabolic factors contribute to a dysregulation of the IL-7/IL-7 receptor pathway in T1D and identify a novel
hyperglycemia-mediated interference of immune regulatory networks.