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.

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