Reinstalling immune regulatory tryptophan catabolism in juvenile diabetes via interleukin 6 receptor blockade

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Indoleamine 2,3-dioxygenase 1 (IDO1) is a potent immunoregulatory enzyme that catalyses the degradation of the essential amino acid tryptophan (Trp) along the kynurenines pathway. Significant changes in systemic Trp catabolism have been reported in many diseases, including cancer and autoimmunity. In female nonobese (NOD) mice, a prototypic model for human type 1 diabetes (T1D), IDO1 expression and hence immune tolerance to pancreatic b-cell autoantigens are defective in conventional dendritic cells stimulated with IFN-γ, the main IDO1 inducer. Although the evidences in NOD mice suggest that IDO1 function is impaired, the existence of the IDO1 defect in human T1D has not been proven yet. Here we monitored the IDO1 expression and activity in peripheral blood mononuclear cells (PBMCs) of children with T1D as compare to age-matched control subject, in response to IFN- γ. Results from kynurenines assay and Western blot analysis demonstrate that the majority of patients with T1D is characterized by defective Trp catabolism. Moreover, our data indicated that this defect is mainly imputable to a SOCS3-mediated, dysregulated IL-6 signaling that would favor IDO1 proteasomal degradation in inflammatory environments, i.e. dominated by IFN-γ. To confirm this, we measured IDO1 expression and activity in PBMCs co-incubated with IFN-γ and Tocilizumab (TCZ), a licensed IL-6 receptor blocker. Results showed that TCZ is able to restore normal levels of IDO1 catalytic activity in response to IFN-γ in approximately 30% of the examined T1D population. Besides further confirming the heterogeneity of the disease, our data indicate the existence of a subset of individuals with T1D who may gain clinical benefit in restoring immunoregulatory mechanisms by treatment with tocilizumab.