REINSTALLING IMMUNE REGULATORY TRYPTOPHAN CATABOLISM IN JUVENILE DIABETES VIA TOCILIZUMAB, A LICENSED 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 □-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 IDO1 activity in peripheral blood mononuclear cells (PBMCs) of children with T1D as compared to age-matched control subject, in response to IFN-γ. T1D in children was characterized by a remarkable defect in IDO1 function. 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. In paediatric patients with dysfunctional IDO1, in vitro incubation of PBMCs with tocilizumab (TCZ), a licensed interleukin 6 receptor blockade, rescues IDO1 activity in approximately 30% of the examined T1D population. In the experimental setting with NOD mice, TCZ restored normoglycemia via IDO1-dependent mechanisms. Our data indicate the existence of a subset of paediatric T1D patients who may gain clinical benefit in restoring immunoregulatory mechanisms by treatment with TCZ and suggest the screening of IDO1 activity as a biomarker for selecting TCZ-responsive T1D patients.