

PTPN2, a potential therapeutic target for type 1 diabetes?

PTPN2 é um alvo terapêutico potencial no diabetes tipo 1?

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We read with great interest the article by Rheinheimer and cols. (1), showing that four hundred and eighty six patients with type 1 diabetes (T1D) and 484 non-diabetic subjects were conducted to discuss the rs1893217 (T/C) polymorphism in protein tyrosine phosphatase, non-receptor type 2 gene (PTPN2) gene for T1D from Southern Brazil, by which the C allele was observed in 14.5% of the T1D patients and 12.2% of the non-diabetic subjects ($P = 0.152$). Moreover, the frequencies of this variant did not differ markedly between T1D patients and non-diabetic subjects when assuming recessive (T/C + T/T *versus* C/C), dominant (T/T *versus* T/C + C/C), or additive (C/C *versus* T/T) model. The clinical and laboratory characteristics of T1D patients did not differ markedly among the three genotypes of the rs1893217 polymorphism. These findings suggest that PTPN2 gene polymorphism may not correlate with T1D. However, Espino-Paisan and cols. (2) genotyped 439 T1D Spanish subjects and 861 controls for PTPN2 rs2542151 and rs478582, showing that the frequency of rs2542151 G carriers was significantly higher in the early-onset patients compared with late-onset patients ($P = 0.023$) and with controls ($P = 0.005$), while the analysis of rs478582 did not reach statistical significance.

Type 1 diabetes is an inflammatory disease of the pancreatic islet, where insulin producing β -cells are preferentially destroyed to varying degrees by the concerted action of autoreactive T-cells and monocytic cells. Single nucleotide polymorphism in PTPN2 encodes T cell protein tyrosine phosphatase (TCPTP). TCPTP can attenuate T cell activation and proliferation *in vitro* and blunt antigen-induced responses *in vivo*, where T cell-specific TCPTP-deficient mice lowered the *in vivo* threshold for TCR-dependent CD8(+) T cell proliferation (3). Consistently, TCPTP-deficient mice developed widespread inflammation and autoimmunity that was transferable to wild-type recipient mice by CD8(+) T cells alone. This autoimmunity was related to increased serum levels of pro-inflammatory cytokines and anti-nuclear antibodies, T cell infiltrates in non-lymphoid tissues, and liver disease (3). PTPN2 mRNA and protein are expressed in human islets and rat beta-cells and increased by cytokines (4). Transfection with PTPN2 siRNAs inhibited basal- and cytokine-induced PTPN2 expression in rat beta-cells and dispersed human islets cells. Decreased PTPN2 expression exacerbated interleukin (IL)-1 β + interferon (IFN)- γ -induced beta-cell apoptosis and turned IFN- γ alone into a proapoptotic signal (4). Similarly, PTPN2 knockdown exacerbated type I IFN-induced apoptosis in INS-1E, primary rat, and human beta cells. PTPN2 silencing and exposure to type I and II IFNs induced BAX translocation to the mitochondria, cytochrome c release, and caspase 3 activation (5).

Collectively, available evidence suggests that PTPN2 may play a potential role in the pathogenesis of T1D, and may give therapeutic potential for T1D. However, further studies are still needed to clarify the role of PTPN2 in T1D, either the genetic susceptibility of PTPN2 in different populations, or the immunologic mechanisms played in T1D. Therefore, with more studies about PTPN2 in T1D, the clear mechanisms of PTPN2 played in T1D may be addressed in the future.

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