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Review

T-cell protein tyrosine phosphatase: A role in inflammation and autoimmunity

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ABSTRACT

A cDNA of *PTPN2* encoding for T-cell protein tyrosine phosphate (TC-PTP) was isolated and characterized as long as 20 years ago. However, findings suggesting a potentially exciting role of this enzyme in general autoimmunity have only recently been obtained. Genome-wide association scans of the human genome revealed the involvement of *PTPN2* in susceptibility to a several autoimmune disorders such as Crohn's disease, type 1 diabetes, and Graves' disease. Functional studies in immune cells revealed a key role of this enzyme in down-regulation of cytokine expression and inflammatory response, which provides an essential background to explaining the pathophysiological role of TC-PTP in autoimmunity. Thus, in addition to *PTPN22*, *PTPN2* is likely to represent a second member of the broad family of non-receptor PTPs contributing to general autoimmunity.

1. Introduction

Many genes identified as causing or predisposing to autoimmunity encode proteins that are involved in lymphocyte, macrophage, or dendritic cell signal transduction. Among those, intracellular protein tyrosine phosphatases (PTPs) play a unique role as the key regulators of signal transduction. To date, around 110 PTP-encoding genes are found in the human genome [1]. All cells of the immune system exhibit high levels of tyrosine phosphorylation and express more PTP genes (up to 70) than any other tissue, with the possible exception of neurons [2]. Acute phenotypes in many PTP-knockout mice associated with deficient or hyperactive immune states and severe hematopoietic abnormalities suggest a crucial role of PTPs in maintaining immune balance [3].

In mice, deficient for T-cell protein tyrosine phosphate (TC-PTP; EC 3.1.3.48), a product of the *ptpn2* gene, multiple defects in the lymphoid lineage were reported [4]. Analysis of T-cell populations derived from the spleen of TC-PTP$^{-/-}$ mice revealed a 2- to 3-fold lower proliferation rate compared with TC-PTP$^{+/+}$ lymphocytes [5]. The numbers of CD4^{+}CD8^{+} T cells and pre-B-cells were decreased. B lymphocytes exhibited impaired T-cell dependent responses thereby suggesting for alterations in immune regulation. In contrast, a dramatic increase in number of colony-forming macrophage units was observed [4]. TC-PTP$^{-/-}$ mice developed an inflammatory disorder characterized by chronic myocarditis, gastritis, and nephritis due to the widespread tissue mononuclear cell infiltration. The mouse also exhibited a drastic increase in levels of nitric oxide and inflammatory cytokines such as interferon-γ (IFN-γ), tumor necrosis factor-α (TNF-α), and interleukin-2 (IL-2) that resulted in massive myocyte and hepatic necrosis [6]. These findings therefore suggest for marked anti-inflammatory properties of TC-PTP in the immune response.

Previously, a solid support was obtained for a role of two PTPs in autoimmunity. There are lymphoid tyrosine phosphate (LYP), which is encoded by the *PTPN22* gene and implicated in a broad spectrum of autoimmune disorders, and CD45, whose genetic alterations are linked to multiple sclerosis and likely to be linked to autoimmune hepatitis [7]. Due to the recent advances in genome-wide association (GWA) studies, a new member could be added to the list of PTPs involved in autoimmunity. There is TC-PTP, a product of the human *PTPN2* gene. In this review, we summarize current knowledge suggesting the implementation of TC-PTP in inflammatory and autoimmune diseases.

2. TC-PTP expression results in two isoforms

The *PTPN2* gene maps to chromosome 18p11.3-p11.2 [8]. The 100-kb gene comprises 10 exons, with exons 1–7 encoding a conservative PTP catalytic domain [9]. The promoter of *PTPN2* is shown to contain multiple regulatory sites, including two putative responsive elements each for c-myc and PEA3, recognition sequences for the Sp1 and AP2 transcription factors and putative NFκB- and APF-binding sites [10]. The *PTPN2* promoter also has a suppressor element that inhibits expression of TC-PTP, while switching from G1 to S phase of the cell cycle. This therefore suggests that the

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transcription of *PTPN2* is regulated by cell-cycle progression reaching a maximal level at G1. TC-PTP is ubiquitously expressed, with the highest expression levels in hematopoietic tissues [11]. Expression of TC-PTP could be stimulated by various agents including mitogen concanavalin A [12] and anti-inflammatory cytokine IL-10 [13].

Alternative splicing results in two forms of TC-PTP that share a highly conservative PTP catalytic domain consisted of 272 amino acids (a.a.) but differ in the C termini [14,15]. The catalytic domain of TC-PTP shares a higher homology (74% amino acid identity) with the catalytic domain of PTP1B, the first protein tyrosine phosphatase ever being identified and characterized [16]. The less abundant 48-kDa isoform of the enzyme comprises 415 amino acid (a.a.) residues and is present in the endoplasmic reticulum (ER) and also in the nuclear membrane [17]. This isoform has a hydrophobic C-terminal tail that is necessary for binding two proteins, p23 and p25, targeting the enzyme to the endoplasmic reticulum [18]. Interestingly, the C-terminal part of TC-PTP negatively influences the enzyme activity. The removal of the hydrophobic C terminus of TC-PTP resulted in a 30-fold increase in activity [19]. In addition, limited proteolysis of TC-PTP released a highly active 33-kDa fragment, which again could be inhibited by the addition of the non-catalytic C-terminal segment of the 45-kDa TC-PTP [20]. The autoinhibition is a likely consequence of intramolecular interactions.

The major 45-kDa form of TC-PTP consists of 387 a.a. The C-terminal region of the 45-kDa isoform has a specific bipartite nuclear localization sequence that targets the enzyme to the nucleus [21]. This C-terminal region of TC45 is also involved in binding to DNA [15]. The nuclear form is able to shuttle between the nucleus and the cytoplasm in response to extracellular stimuli, thereby providing access for the nuclear enzyme to a larger variety of substrates, compared to the cytoplasmic TC-PTP isoform [22,23].

3. Regulation of TC-PTP activity

Activity of PTPs is regulated *in vivo* through oxidation and reduction reactions involving an invariant cysteine in an active site sequence motif [I/V]HCxxGxxR[S/T] [24]. In the catalytic domain of TC-PTP, the invariant cysteine is located at position 216 [9]. Oxidation of the Cys216 is likely to be attributable to the inactivation of TC45 by reactive oxygen species in response to insulin [25]. Since TC-PTP is involved in negative regulation of insulin-mediated signaling, the reversible oxidation of the Cys216 could be crucial in regulating TC-PTP activity in peripheral tissues such as the muscles and liver, which are major targets for the insulin action [26]. However, whether this mechanism plays a pivotal role in the regulation of TC-PTP activity in immune cells needs to be elucidated.

Phosphorylation/dephosphorylation is a common mechanism for regulating PTPs activity. Cyclin-dependent protein kinases (CDKs) preferably CDK1/cyclin-B1 were found to phosphorylate the Ser304 in TC45 not in TC48 [27]. The phosphorylation was cell cycle-dependent, increasing as cells progressed from G_2 into mitosis. However, the physiological relevance of this phosphorylation remains unclear since, the Ser304 resides outside the catalytic domain of TC-PTP, and modification of this amino acid residue does not have any apparent effect on the activity or intracellular localization of the enzyme [27]. The role of phosphorylation in the modulation of TC-PTP activity needs further clarification. In the enzyme, other steady-state phosphorylation sites may exist. Otherwise, in addition to the Ser340, other sites may be phosphorylated in response to specific stimuli, and then, together with Ser-304 phosphorylation, these may regulate TC45.

4. Role of TC-PTP in myeloid cells

A range of stimulatory signals and intracellular protein substrates of TC-PTP varies depending on the tissue where this enzyme is expressed. For example, in the muscles and liver, TC-PTP functions as a negative regulator of insulin receptor-mediated signaling [28]. In hematopoietic tissues, TC-PTP regulates cellular proliferation *via* several pathways, including the dephosphorylation of growth factor receptors such as the epidermal growth factor [29] and the platelet-derived growth factor [30]. In myeloid cell lines, the enzyme downregulates colony-stimulating factor 1 (CSF-1)-mediated signaling [31]. CSF-1 binding to the CSF-1 receptor causes the autophosphorylation of the receptor molecule that leads to the recruitment of Src family kinases and other signaling molecules including Erk kinase, a key regulator of differentiation in a number of cell systems [32]. Erk activation then stimulates the proliferation of macrophage progenitor cells and their differentiation to mature macrophages [33]. TC-PTP dephosphorylates Tyr807 of the CSF-1 receptor, whose phosphorylation is shown to be crucial in the activation of Erk [34].

The treatment of human monocytes with CSF-1 was found to result in the tyrosine phosphorylation of $p52^{Shc}$ adaptor protein and its association with Grb2, which is required in GSF-1-mediated macrophage differentiation [35]. 45-kDa form of TC-PTP is able to specifically recognize and then dephosphorylate $p52^{Shc}$ phosphorylated on Tyr239 thereby preventing association of $p52^{Shc}$ with Grb2 [23]. Thus, TC-PTP could suppress CSF-1-dependent stimulation of the macrophage lineage through two mechanisms, i.e. *via* dephosphorylation of the CSF-1 receptor and the dephosphorylation of $p52^{Shc}$. In addition, TC-PTP could also inhibit the development of macrophages through direct dephosphorylation and down-regulation of Srk kinases [33].

5. Role of TC-PTP in lymphoid cells

In lymphoid cells, TC-PTP possesses anti-inflammatory activity through the suppression of inflammatory response induced by a variety of proinflammatory cytokines. The enzyme downregulates IL-2 and IFN-γ-mediated signaling (that leads to the activation of macrophages and induction of the inflammatory response) through dephosphorylation of JAK1 and JAK3 tyrosine kinases that participate in the activation of receptors for these cytokines (Fig. 1) [37]. In addition, both cytoplasmic and nuclear TC-PTP could suppress IFN-γ-mediated gene expression, causing the dephosphorylation of the signal transducer and activator of transcription 1 (STAT-1) [38,39].

TC-PTP downregulates the expression of TNF-α and TNF-α-mediated signaling in immune cells. TC-PTP suppresses TNF-α-mediated activation of immune cells *via* binding to TRAF2, a component of the TNF-α-signaling pathway, which targets TC-PTP to Src kinase and then leads to the subsequent inhibition of Erk-dependent signaling (Fig. 1) [36].

The nuclear 45-kDa TC-PTP isoform implies in the dephosphorylation of the downstream JAK effectors, the STATs that regulate transcription of many genes. In addition to STAT1, STAT3, STAT5a, and STAT5b are found to be substrates for TC-PTP [40,41]. Dephosphorylation of STAT5a/b by TC-PTP is associated with blocking prolactin signaling [40]. Dephosphorylation of STAT3 by TC-PTP suppresses the signaling pathway mediated by IL-6, a pleiotropic cytokine, which plays a role in hematopoiesis, immune system and inflammatory reactions [41].

6. Genetic analyses reveal a role of *PTPN2* as a putative susceptibility gene for general autoimmunity

In two recent GWA scans performed in Europeans, a highly significant evidence for association with type 1 diabetes (T1D) was obtained for the chromosome region 18p11 containing the *PTPN2* gene [42,43]. Two T1D-associated single nucleotide polymor-

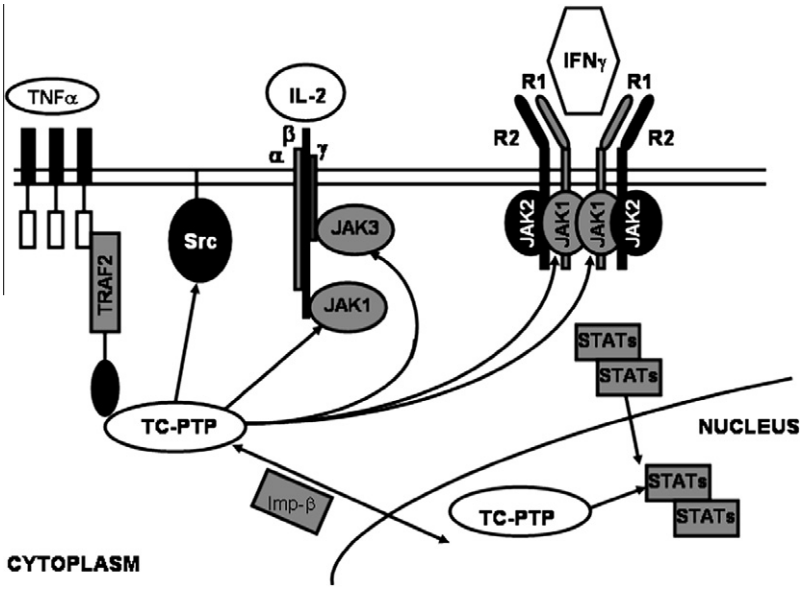

Fig. 1. Substrates targeted by T-cell protein tyrosine phosphatase (TC-PTP). TC-PTP negatively regulates JAK/STAT signaling that leads to the induction of the inflammatory reaction. TC-PTP downregulates signaling mediated by proinflammatory cytokines (IFN-γ, TNF-α, and IL-2) through the dephosphorylation of JAK1, JAK3 and Src kinases, which activate downstream signaling pathways induced by binding of the cytokines to their receptors. As a part of the complex with Importin-β (Imp-β), TC-PTP is able to shuttle from the cytoplasm to the nucleus, where the enzyme can dephosphorylate STATs, the molecules involved in signal transduction and activation of the transcription of a number of genes.

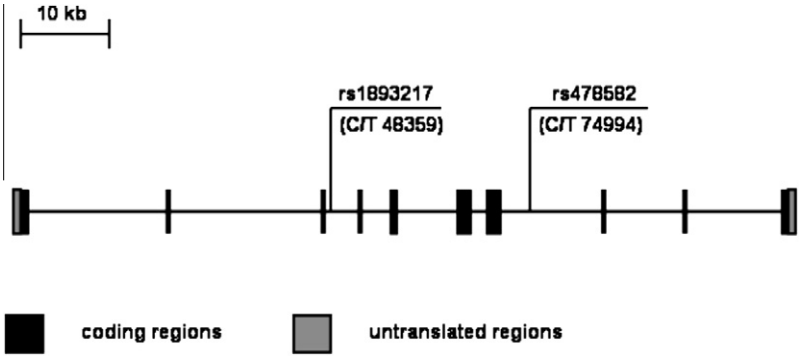

Fig. 2. Structure of the protein tyrosine phosphatase, non-receptor 2 (*PTPN2*) gene encoding T-cell protein tyrosine phosphatase. The *PTPN2* gene encompasses nearly 100 kb on chromosome 18p11 and includes 10 exons. The location of two SNPs associated with type 1 diabetes is shown.

phisms (SNPs) of *PTPN2* are situated in intronic portions of the gene (e.g., rs478582 (*C/T*) and rs1893217 (*C/T*) in intron 3 and 7, respectively) (Fig. 2). Both SNPs are located within a 114-kb-long linkage disequilibrium block that includes the entire *PTPN2* gene [44]. The association between *PTPN2* and T1D was then confirmed by GWA analysis of the independent cohort of US Caucasians and the subsequent meta-analysis of the joint (American + European) population sample (Odds Ratio (OR) = 1.14; $p = 8.73 \times 10^{-8}$ for marker rs2542151 (*A/C*) located near the *PTPN2* gene) [45].

Both markers within *PTPN2* (rs1893217 and rs478582) that showed association with T1D were found to be associated with Graves' disease (OR = 1.13 ($p = 0.0251$) for rs1893217 and OR = 0.91 ($p = 0.0239$) for rs478582) [42]. The marker rs2542151 (*A/C*) located near the *PTPN2* gene also showed a strong association with Crohn's disease (OR = 1.15; $p = 3.16 \times 10^{-8}$) in a GWA-based search analysis of 1182 affected and 2024 control individuals from UK [46]. The association between *PTPN2* and Crohn's disease was then replicated by several large-scale population studies in Caucasians [47–50].

These findings suggest that the *PTPN2* gene could represent a general autoimmunity locus implicated in susceptibility to several autoimmune diseases. Although additional studies are required to replicate this association, as well as to analyze the functionality of the disease-associated markers, recent genetic analyses provide intriguing evidence for the presence of a genetic locus, with a likely involvement of *PTPN2*, that controls predisposition to autoimmunity on chromosome 18p11.

7. Conclusion

In summary, strong evidence in support of the implication of *PTPN2* in organ-specific autoimmunity is obtained for Crohn's disease and T1D. Findings about the role of this gene in susceptibility to Graves' disease require further confirmation. Disease-associated markers at *PTPN2* are located in non-coding regions, and their function is unclear. To date, the etiological variant(s) in *PTPN2* is

unknown, and therefore should be revealed through resequencing and other robust genetic approaches.

Generally, a role of the predisposing variants of *PTPN2* in autoimmunity might be attributed to less efficient suppression of the inflammatory response. The hypothesis can be supported by deleterious outcomes observed in the murine models deficient for *ptpn2* [4–6]. The major protective role of TC-PTP in autoimmunity is likely to be referred to the anti-inflammatory activity of this enzyme in the immune system and its inhibitory effects against macrophage hyperactivity. TC-PTP suppresses expression of major proinflammatory cytokines such as TNF-α and IL-6 whose overproduction accomplishes acute phase response in the pathogenesis of Crohn's disease, rheumatoid arthritis and other autoimmune inflammatory disorders [51]. Etiological variants of the PTPN2 gene that are needed to be discovered and functionally characterized could alter the function of TC-PTP as an anti-inflammatory trigger and hence predispose to impaired immune response, a prerequisite of many autoimmune-related inflammatory diseases.

A role of the *PTPN22* gene encoding for lymphoid tyrosine phosphatase in a broad spectrum of autoimmune disorders was recently established [52]. Therefore, *PTPN2* is a likely candidate to extend the list of members of the large family of non-receptor PTPs involved in general autoimmunity.

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