

PTPN22 and islet-specific autoimmunity: What have the mouse models taught us?

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Abstract

An allelic variant of the protein tyrosin phosphatase non-receptor 22 (*PTPN22*) gene, PTPN22 R620W, constitutes the strongest non-HLA genetic risk factor for the development of type 1 diabetes (T1D). A number

studies using mouse models have addressed how PTPN22 predisposes to T1D. PTPN22 downmodulation, overexpression or expression of the variant gene in genetically manipulated mice has generated controversial results. These discrepancies probably derive from the fact that PTPN22 has differential effects on innate and adaptive immune responses. Moreover, the effects of PTPN22 are dependent on other genetic variables. Here we discuss these findings and try to explain the discrepancies. Exploring the mechanism by which PTPN22 contributes to islet-specific autoimmunity could help us understand its role in T1D pathogenesis and exploit it as a potential therapeutic target to prevent the disease.

Key words: Protein tyrosin phosphatase non-receptor 22; Type 1 diabetes; Genetic susceptibility; Mouse model; Autoimmunity; Islet-specific autoimmunity

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Core tip: Protein tyrosin phosphatase non-receptor 22 (*PTPN22*) is the strongest non-HLA gene associated with type 1 diabetes (T1D) and many other autoimmune diseases. Several studies using mouse models have generated controversial results on how PTPN22 predisposes to T1D. In our manuscript we summarize these results and try to explain the discrepancies. Our analysis reveals that PTPN22 assumes different roles in innate and adaptive immunity and its effect is strongly dependent on other genetic variables. Hence, additional studies are required to better understand the mechanism by which PTPN22 predisposes to T1D and to exploit it as a potential therapeutic target in T1D and other autoimmune diseases.

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INTRODUCTION

Autoimmune diseases are a type of disorders characterized by abnormal immune responses against self tissues and organs that are subjected to continuous inflammation leading to their demise. Both genetic predisposition and environmental factors are implicated in autoimmune disease pathogenesis^[1]. Great amount of research has led to the identification of several disease susceptibility genes; however, the immunological malfunctions that these genes introduce are often poorly understood. In this review we focus on the autoimmune predisposing gene protein tyrosin phosphatase non-receptor 22 (*PTPN22*), which is associated with multiple autoimmune diseases and among them type 1 diabetes (T1D)^[2-6]. *PTPN22* encodes a protein tyrosine phosphatase, which plays key roles in innate and adaptive immunity. *PTPN22* is involved in T cell receptor (TCR), B cell receptor (BCR) and innate immune signaling and controls the threshold of immune activation and consequently the outcome of an immune response^[7,8]. Here, we discuss recent research on the role of *PTPN22* in islet-specific autoimmunity experimentally addressed by mouse models. Our aim is to summarize the current knowledge on *PTPN22*, as raising from mouse model studies, and to highlight the unmet research needs on its role in autoimmunity.

T1D

T1D is an autoimmune disease mediated by autoreactive CD4⁺ and CD8⁺ T cells that infiltrate the pancreas and destroy insulin-secreting beta cells^[9]. Beta-cell loss results in the reduced production of insulin, which is essential for the glucose metabolism. This condition is life-threatening unless patients undergo substitution therapy, which is based on self-administration of insulin for the rest of their lives. However, insulin replacement is not a cure and despite tight glycemic control, a number of secondary complications can emerge such as heart and kidney disease^[9,10]. T1D is a multifactorial disease where genetic and environmental factors contribute to the loss of immunological tolerance to beta-cell antigens^[11-13]. Several years elapse between the initial stages of the autoreactive response and the onset of clinical diabetes. During this preclinical phase, autoantibodies (AABs) against beta-cell antigens emerge, which are currently the most reliable predictive biomarker of the disease. The presence of multiple islet-specific AABs together with metabolic parameters and particularly dysglycemia can predict with approximately 90% accuracy the development of T1D^[14,15]. However, we still lack biomarkers that will reliably indicate the dynamic loss beta cells and predict the emergence of the disease^[16].

Islet-specific T cells play central role in the pathogenesis of T1D. They kill beta cells and promote the development of AABs through their B-cell helper

activity^[17,18]. As such, they have become the focus of extensive research with the aim to be used as targets for immunotherapy and as biomarkers in prediction and therapeutic studies^[19-21]. Important but less recognized is the role of B cells and AABs in the autoimmune process. Autoreactive B cells are thought to play key role in the development of islet-specific autoimmunity by promoting the presentation of beta-cell antigens to autoreactive T cells, which in turn by providing B-cell help signals, promote the production of AABs^[22]. This autoreactive process has been postulated to take place predominantly within germinal centers (GCs), specialized structures in secondary lymphoid organs where the maturation of B cells into long-lived plasma cells and memory B cells takes place^[23,24].

T follicular helper (TFH) cells, a subset of CD4 T cells, are essential for the formation of GCs and the development of optimal antibody responses by guaranteeing the survival of B cells presenting high affinity antigens^[25]. The exact mechanism by which autoreactive B cells are eliminated during the GC response is not fully understood, but TFH cells and a subset of FOXP3 regulatory T cells [follicular regulatory T (TFR) cells] are thought to play central role^[26]. Interestingly, recent reports documented that diabetic patients have cellular and molecular indicators of increased presence of circulating TFH cells^[27,28]. We (unpublished data) and others^[29] also found that these indicators are present in the peripheral blood prior to disease onset in AAB-positive (AAB⁺) non-diabetic individuals, suggesting that TFH cells might contribute to AAB pathogenesis and T1D development.

Genetic susceptibility to T1D is defined by more than 10 genetic loci^[30-32]. The most important genetic regions are: The *HLA* region, a critical susceptibility locus for many human autoimmune diseases^[33,34], the *Insulin* gene, whose susceptibility resides in a variable number of tandem repeat polymorphisms in the promoter region of the gene^[35-37], the *CTLA-4* gene, involved in negative regulation of immune responses^[38,39], and importantly, the *PTPN22* gene, which encodes the lymphoid protein tyrosine phosphatase (LYP) an important negative regulator of TCR signaling, that is also involved in BCR and innate immune signaling^[40-43]. The most convincing evidence that environmental factors play a major role in influencing T1D development derives from studies in monozygotic (MZ) twins where disease concordance is approximately 50%^[44]. Viruses, vaccines, toxins and dietary factors (e.g., breast feeding vs cow's milk) have been suspected for the increase of T1D incidence in developed countries^[45-49]. However, the mechanism by which they activate the autoimmune process is unknown and they are thought to modify susceptibility by affecting the T cells' epigenome^[50,51].

PTPN22

PTPN22 is the strongest non-HLA gene associated with the onset of T1D and other autoimmune diseases^[7]. *PTPN22* encodes a non receptor protein tyrosine

phosphatase (PTP) which is expressed in hematopoietic cells. The PTP encoded protein, named LYP, consists of three domains: An N-terminal catalytic domain, an interdomain region and a C-terminal domain, characterized by the presence of a proline-rich region (P1-P4), that is important for the interaction with other proteins (reviewed in^[7,81]).

PTPN22 plays a key role in regulating innate and adaptive immune responses. PTPN22 by enhancing pattern recognition receptors (PRRs) signaling, drives the activation of myeloid cells and promotes type 1 interferon (IFN) production. Specifically, PTPN22 associates with the TLR signaling molecule TRAF3 to promote its ubiquitination and thus the activation of IRF3 and IRF7 and the production of type 1 IFN^[52]. PTPN22 dampens T-cell activation by restricting signalling downstream of the TCR. It dephosphorylates positive regulatory tyrosine residues in Src family kinases including ZAP-70 and Lck interacting with the C-terminal Src kinase (CSK) through its P1 motif^[53-55] (reviewed also in^[56]).

An allelic variant of *PTPN22* confers susceptibility to T1D^[2-4] and other autoimmune diseases, like rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE)^[57-59]. This polymorphism is characterized by a single aminoacid substitution: An Arg (R) is replaced by a Trp (W) at position 620. This is a nonconservative variation of a residue within the P1 motif, which as we mentioned above, is critical for interacting with CSK. As a consequence, the predisposing autoimmunity variant R620W exhibits reduced interaction with CSK that leads to a further reduction of TCR signaling rendering T cells hyporeactive^[60,61].

The PTPN22 autoimmune predisposing allelic variant influences B cells leading to reduced BCR signaling and increased resistance to apoptosis. Furthermore, the allelic variant R620W induces an up-regulation of various genes belonging to the BCR, CD40 and Toll-like receptor (TLR) signaling pathways that converge on nuclear factor- κ B (NF- κ B)^[62,63]. As a consequence, increased survival of transitional and naïve B cells was observed^[64]. PTPN22 R620W carriers contained increased frequencies of circulating transitional and anergic autoreactive B cells^[63,65]. These alterations in the composition of the B cell pool were also characteristic of T1D patients, who also displayed higher frequencies of autoreactive clones^[62].

The murine homologue of PTPN22 has a structure similar to the human protein and plays important roles in immune responses. Several mouse models were generated in order to understand the mechanism by which PTPN22 contributes to autoimmunity^[56,66]. In mice, the allelic variant R619W is the equivalent of R620W in humans. The possibility to study PTPN22 R619W-expressing mouse models has allowed us to make direct comparisons between the human PTPN22 R620W allelic variant and the murine orthologue. For example, PTPN22 R619W knock-in mice reproduce many aspects of the human predisposing allelic variant

including the increase of peripheral T effector/memory cells and autoreactive B cells^[67-69], the reduction of circulating mature B cells^[67,69] and the increase of transitional B cells^[63,67] (also reviewed in^[66]). These findings strongly suggest that the mouse orthologue could significantly reproduce the autoimmune risk effect of the human PTPN22 susceptibility allele. Below we discuss the role of PTPN22 in islet-specific autoimmunity as addressed by mouse studies.

PTPN22 IN ANIMAL MODELS OF T1D

The use of T1D animal models like the non-obese diabetic (NOD) mouse model, have helped us understand a lot about the pathogenesis of autoimmune diabetes^[70,71]. These models serve to address how autoimmune predisposing genes like PTPN22 alter the immune system leading to T1D. Several mouse models including PTPN22 knock-out^[72-75], PTPN22 R619W knock-in^[67,68,76], PTPN22 R619W transgenic^[77], PTPN22 knock-down^[78] and PTPN22 WT transgenic^[79] have been created on autoimmune-prone (like the NOD) or resistant genetic backgrounds to address the role of PTPN22 in autoimmunity. Whereas many of these studies showed a clear association between PTPN22 and autoimmunity, others supported the opposite. These controversial results indicated that the effect of PTPN22 on peripheral tolerance highly depends on the genetic background of the animal model employed, suggesting that other genes relevant for autoimmune predisposition play important role. These results also highlighted the complex role that PTPN22 plays in immune tolerance.

In the study where PTPN22 knock-out mice were described for the first time, lymphoproliferation, enlarged GCs and expansion of memory-phenotype cells were found^[72]. However, no AABs were produced nor spontaneous autoimmunity developed^[72]. Aged PTPN22 knock-out mice exhibited increased numbers of TFH cells that support spontaneous GC formation and activity^[75]. Interestingly, in a study where PTPN22 R619W knock-in mice were generated, anomalies comparable to those described in PTPN22-deficient mice were seen^[68]. Also in this model no signs of spontaneous autoimmunity were observed^[68]. This suggested that the autoimmune predisposing allele of PTPN22 represents a loss-of-function mutation. Interestingly, in a different report where a different PTPN22 R619W knock-in mouse strain was generated, spontaneous autoimmunity characterized by production of AABs and cell infiltrates in multiple tissues (but not in pancreas) were seen^[67]. In contrast to the first PTPN22 R619W knock-in mice however, which were generated on C57BL/6 (B6) autoimmune-resistant background, the PTPN22 R619W knock-in mice were placed on a mixed (B6x129) genetic background. Thus, these two studies suggest that the effect which PTPN22 has on the immune system is strongly dependent on the presence of other “modifier genes” present in the genetic background.

Table 1 Summary of mouse models where the role of protein tyrosin phosphatase non-receptor 22 in type 1 diabetes incidence has been directly or indirectly addressed

	Genetic background	Spontaneous autoimmunity ¹	AAbs	T1D	B cells	T cells	Ref.
PTPN22 knock-out	C57BL/6	No	No	No	intact	↑Memory/effector number ↑Treg number and function ↑TFH number and function ↑Tr1 number and function	[72-75,84]
PTPN22 knock-out	RIP-LCMV (B6)	No	No	Exacerbated	Not examined	↑Effector function	[81]
PTPN22 R619W knock-in	C57BL/6	No	No	No	Not examined	↑Memory/effector number	[68]
PTPN22 R619W knock-in	C57BL/6 x 129	Lupus-like disease	Yes	No	↑Transitional and Self-reactive	↑Memory/effector number	[67]
PTPN22 R619W transgenic	C57BL/6	No	No	No	Not examined	No differences	[77]
PTPN22 knock-down	NOD	No	No	Protected	Activation	↑Treg number and function	[78]
PTPN22 transgenic	NOD	No	No	Protected	Not examined	↓Memory/effector number	[79]
PTPN22 R619W knock-in	NOD	No	↑↑	Exacerbated	Not examined	Not examined	[76]

¹Other than T1D. T1D: Type 1 diabetes; AAbs: Autoantibodies; Treg: T regulatory cell; PTPN22: Protein tyrosin phosphatase non-receptor 22; TFH: T follicular helper.

The role of PTPN22 in T1D was directly addressed by employing the NOD mouse model. Unexpectedly, NOD mice where PTPN22 expression was targeted by a knock-down genetic approach were protected from autoimmune diabetes^[78]. Surprisingly, PTPN22 transgenic NOD mice that overexpressed PTPN22 were also protected from T1D^[79]. Thus, either downregulation or overexpression of PTPN22 had a protective effect from T1D in NOD mice. PTPN22 knock-down in NOD mice resulted in T1D prevention possibly because of a dominant effect of PTPN22 on the T regulatory cell (Treg) compartment. As it was shown in several mouse models of diverse genetic background, the number and functionality of Treg cells increase when PTPN22 levels reduce^[73,74,78]. On the other hand, transgenic NOD mice over-expressing PTPN22 were protected from T1D due to effects of PTPN22 on the effector T cell compartment, which showed reduced activation^[79]. Instead, Treg development, differentiation and suppressive activity in PTPN22 overexpressing mice were similar to control^[79]. These data suggest that whereas reduction in PTPN22 levels affects the Treg compartment, PTPN22 overexpression modifies the effector T cell compartment. In both cases the end result is protection from T1D. Additional experiments with conditional overexpression or downmodulation of PTPN22 and its variant, murine cell transfers and bone marrow chimeras could clarify these discrepancies. Nevertheless, these studies underline that if PTPN22 is selected as therapeutic target, caution should be taken in directing the drug to the correct cellular compartment.

More recently, PTPN22 R619W mutant NOD mice were generated in order to directly address the effect of the murine ortholog of R620W allele on T1D incidence. In contrast to PTPN22-knocked down mice, PTPN22 R619W NOD mice showed accelerated T1D and increased prevalence and elevated titer of insulin AAbs, suggesting an early loss of tolerance to insulin^[76]. Thus, these findings suggest that the R619W variant possibly is not a loss-of-function variant.

To further understand the role of PTPN22 in T1D pathogenesis, our group employed a mouse model of virally-induced autoimmune diabetes (RIP-LCMV), which also served to address the role of PTPN22 on antiviral immunity^[80]. RIP-LCMV PTPN22-deficient mice were more susceptible to diabetes compared to control mice^[81]. Lack of PTPN22 altered the generation and function of effector-memory viral-specific T cells in an antigen-specific manner^[81]. Our follow-up studies showed that PTPN22 plays central role in T-cell clonal expansion and effector function during acute infection; it promotes antigen-driven responses by positively regulating interferon signaling in T cells^[82]. Thus, we identified a novel role of PTPN22 in T1D triggered by an acute viral infection and determined the role of PTPN22 in antiviral immunity.

We also explored the role of PTPN22 in pancreatic islet transplantation, which is one of the most promising approaches to cure T1D^[83]. By employing a mouse model of acute allograft rejection, we found that PTPN22-deficient mice generate higher number of alloreactive T cells compared to control mice, but reject grafts with similar kinetics^[84]. This was due to an increase of Treg and also T regulatory type 1 (Tr1) cells. In addition, a tolerogenic treatment known to induce transplant tolerance in C57BL/6 mice *via* Tr1 cell generation was more effective in PTPN22-deficient mice because it augmented the number and functions of both Tr1 and Treg cells^[84]. Thus, lack of PTPN22 strengthened transplant tolerance to pancreatic islets, suggesting it could serve as therapeutic target to boost transplant tolerance.

Our group also investigated how PTPN22 affects the generation of Foxp3 Treg and T helper type 1 (Th1) cells. From *in vivo* and *in vitro* studies using PTPN22 knock-out mice we found that PTPN22 plays a key role in Treg induction and acts mainly through modulating the threshold of T cell activation. CD4 T cells from PTPN22 knock-out mice showed increased sensitivity to TCR activation and subsequently increased FOXP3

expression at low levels of stimulation^[85]. However, FOXP3 expression was reduced at optimal-to-high levels of activation. Furthermore, we found that the absence of PTPN22 altered Th1 cell differentiation only at low levels of T-cell activation. These results underline the dual role PTPN22 has on determining Treg vs Th1 cell induction^[85].

Taken together, several animal studies have examined the role PTPN22 on predisposing to autoimmunity and particularly T1D. Results so far corroborate with the notion that the immunomodulatory effects of PTPN22 are complex and suggest that PTPN22 may promote or inhibit autoimmunity depending on the genetic background and experimental setting.

CONCLUSION

The PTPN22 R620W allelic variant is associated with T1D and is considered the most important non-HLA predisposing gene. As detailed above and summarized in Table 1, using a number of murine models, investigators have started to decipher the role of PTPN22 in immune tolerance to pancreatic antigens. Because PTPN22 impacts multiple cells lineages it will be difficult to find the key cell subset or molecular mechanism by which PTPN22 breaks self tolerance unless advanced lineage-specific knock-in or deletion systems are employed. Importantly, the effect PTPN22 imparts on the immune system is strongly influenced by other genetic variants. In this review we focused on PTPN22 and its role on islet-specific autoimmunity highlighting that targeting this protein may serve as possible future strategy to prevent T1D and perhaps other autoimmune diseases.

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