

World Journal of *Diabetes*

World J Diabetes 2017 July 15; 8(7): 311-389



**EDITORIAL**

- 311 PCSK9 and carbohydrate metabolism: A double-edged sword
Filippatos TD, Filippas-Ntekouan S, Pappa E, Panagiotopoulou T, Tsimihodimos V, Elisaf MS

REVIEW

- 317 Obesity, metabolic syndrome and diabetic retinopathy: Beyond hyperglycemia
Mbata O, Abo El-Magd NF, El-Remessy AB

MINIREVIEWS

- 330 PTPN22 and islet-specific autoimmunity: What have the mouse models taught us?
Galvani G, Fousteri G
- 337 Saponins as adipokines modulator: A possible therapeutic intervention for type 2 diabetes
Elekofehinti OO, Ejelonu OC, Kamdem JP, Akinlosotu OB, Adanlawo IG

ORIGINAL ARTICLE**Retrospective Cohort Study**

- 346 Vitamin D levels in subjects with or without chronic kidney disease among Veterans with diabetes in North East United States
Yaturu S, Youngberg B, Zdunek S

Observational Study

- 351 Type 2 diabetes in a Senegalese rural area
Duboz P, Boëtsch G, Gueye L, Macia E
- 358 Quality of sleep and its determinants among people with type 2 diabetes mellitus in Northwest of Iran
Shamshirgaran SM, Ataei J, Malek A, Iranparvar-Alamdari M, Aminisani N

Prospective Study

- 365 Are body mass index and waist circumference significant predictors of diabetes and prediabetes risk: Results from a population based cohort study
Haghighatdoost F, Amini M, Feizi A, Iraj B
- 374 Effect of bariatric surgery on adiposity and metabolic profiles: A prospective cohort study in Middle-Eastern patients
Mazidi M, Rezaie P, Jangjoo A, Tavassoli A, Rajabi MT, Kengne AP, Nematy M

Randomized Controlled Trial

- 381** Autologous bone marrow derived stem cell therapy in patients with type 2 diabetes mellitus - defining adequate administration methods

Sood V, Bhansali A, Mittal BR, Singh B, Marwaha N, Jain A, Khandelwal N

Contents

World Journal of Diabetes
Volume 8 Number 7 July 15, 2017

ABOUT COVER

Editorial Board Member of *World Journal of Diabetes*, Wei-Chung V Yang, PhD, Director, Professor, Center for Translational Medicine, College of Medical Science and Technology, Taipei Medical University, Taipei 110, Taiwan

AIM AND SCOPE

World Journal of Diabetes (*World J Diabetes*, *WJD*, online ISSN 1948-9358, DOI: 10.4239), is a peer-reviewed open access academic journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

WJD covers topics concerning α , β , δ and PP cells of the pancreatic islet, the effect of insulin and insulinresistance, pancreatic islet transplantation, adipose cells and obesity.

We encourage authors to submit their manuscripts to *WJD*. We will give priority to manuscripts that are supported by major national and international foundations and those that are of great clinical significance.

INDEXING/ABSTRACTING

World Journal of Diabetes is now indexed in Emerging Sources Citation Index (Web of Science), PubMed, PubMed Central, and Scopus.

FLYLEAF

I-VI Editorial Board

EDITORS FOR THIS ISSUE

Responsible Assistant Editor: *Xiang Li*
Responsible Electronic Editor: *Ya-Jing Lu*
Proofing Editor-in-Chief: *Lian-Sheng Ma*

Responsible Science Editor: *Fung-Fung Ji*
Proofing Editorial Office Director: *Jin-Lai Wang*

NAME OF JOURNAL

World Journal of Diabetes

ISSN

ISSN 1948-9358 (online)

LAUNCH DATE

June 15, 2010

FREQUENCY

Monthly

EDITORS-IN-CHIEF

Lu Qi, MD, PhD, Assistant Professor, Department of Nutrition, Harvard School of Public Health, Boston, MA 02115, United States

Jingbo Zhao, PhD, Associate Professor, Aalborg Hospital Science and Innovation Centre, Aalborg Hospital, Aarhus University Hospital, Aalborg 9000, Denmark

EDITORIAL BOARD MEMBERS

All editorial board members resources online at <http://www.wjgnet.com/1948-9358/editorialboard.htm>

EDITORIAL OFFICE

Xiu-Xia Song, Director
World Journal of Diabetes
Baishideng Publishing Group Inc
7901 Stoneridge Drive, Suite 501,
Pleasanton, CA 94588, USA
Telephone: +1-925-2238242
Fax: +1-925-2238243
E-mail: editorialoffice@wjgnet.com
Help Desk: <http://www.f6publishing.com/helpdesk>
<http://www.wjgnet.com>

PUBLISHER

Baishideng Publishing Group Inc
7901 Stoneridge Drive, Suite 501,
Pleasanton, CA 94588, USA
Telephone: +1-925-2238242
Fax: +1-925-2238243
E-mail: bpgoffice@wjgnet.com
Help Desk: <http://www.f6publishing.com/helpdesk>
<http://www.wjgnet.com>

PUBLICATION DATE

July 15, 2017

COPYRIGHT

© 2017 Baishideng Publishing Group Inc. Articles published by this Open-Access journal are distributed under the terms of the Creative Commons Attribution Non-commercial License, which permits use, distribution, and reproduction in any medium, provided the original work is properly cited, the use is non-commercial and is otherwise in compliance with the license.

SPECIAL STATEMENT

All articles published in journals owned by the Baishideng Publishing Group (BPG) represent the views and opinions of their authors, and not the views, opinions or policies of the BPG, except where otherwise explicitly indicated.

INSTRUCTIONS TO AUTHORS

<http://www.wjgnet.com/bpg/gerinfo/204>

ONLINE SUBMISSION

<http://www.f6publishing.com>

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

Giuseppe Galvani, Georgia Foustieri

Giuseppe Galvani, Georgia Foustieri, Diabetes Research Institute, IRCCS San Raffaele Scientific Institute, 20132 Milan, Italy

Author contributions: Galvani G conducted the literature search, drafted, edited, and approved the final version of the paper; Foustieri G conceived the manuscript, helped with the writing, revised critically, and approved the final version of the manuscript.

Conflict-of-interest statement: The authors declare no conflict-of-interest.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Manuscript source: Invited manuscript

Correspondence to: Georgia Foustieri, MSc, PhD, Diabetes Research Institute, IRCCS San Raffaele Scientific Institute, via Olgettina 60, 20132 Milan, Italy. foustieri.georgia@hsr.it
Telephone: +39-02-26433184
Fax: +39-02-26437759

Received: December 18, 2016

Peer-review started: December 22, 2016

First decision: March 28, 2017

Revised: April 11, 2017

Accepted: May 12, 2017

Article in press: May 15, 2017

Published online: July 15, 2017

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

© The Author(s) 2017. Published by Baishideng Publishing Group Inc. All rights reserved.

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.

Galvani G, Foustieri G. PTPN22 and islet-specific autoimmunity: What have the mouse models taught us? *World J Diabetes* 2017; 8(7): 330-336 Available from: URL: <http://www.wjnet.com/1948-9358/full/v8/i7/330.htm> DOI: <http://dx.doi.org/10.4239/wjd.v8.i7.330>

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.

ACKNOWLEDGMENTS

We thank all the members of our lab.

REFERENCES

- 1 Wang L, Wang FS, Gershwin ME. Human autoimmune diseases: a comprehensive update. *J Intern Med* 2015; **278**: 369-395 [PMID: 26212387 DOI: 10.1111/joim.12395]
- 2 Bottini N, Musumeci L, Alonso A, Rahmouni S, Nika K, Rostamkhani M, MacMurray J, Meloni GF, Lucarelli P, Pellicchia M, Eisenbarth GS, Comings D, Mustelin T. A functional variant of lymphoid tyrosine phosphatase is associated with type I diabetes. *Nat Genet* 2004; **36**: 337-338 [PMID: 15004560 DOI: 10.1038/ng1323]
- 3 Ladner MB, Bottini N, Valdes AM, Noble JA. Association of the single nucleotide polymorphism C1858T of the PTPN22 gene with type 1 diabetes. *Hum Immunol* 2005; **66**: 60-64 [PMID: 15620463 DOI: 10.1016/j.humimm.2004.09.016]
- 4 Zoledziwska M, Perra C, Orrù V, Moi L, Frongia P, Congia M, Bottini N, Cucca F. Further evidence of a primary, causal association of the PTPN22 620W variant with type 1 diabetes. *Diabetes* 2008; **57**: 229-234 [PMID: 17934143 DOI: 10.2337/db07-0289]
- 5 Bottini N, Vang T, Cucca F, Mustelin T. Role of PTPN22 in type 1 diabetes and other autoimmune diseases. *Semin Immunol* 2006; **18**: 207-213 [PMID: 16697661 DOI: 10.1016/j.smim.2006.03.008]
- 6 Foustier G, Liossis SN, Battaglia M. Roles of the protein tyrosine phosphatase PTPN22 in immunity and autoimmunity. *Clin Immunol* 2013; **149**: 556-565 [PMID: 24269925 DOI: 10.1016/j.clim.2013.10.006]
- 7 Stanford SM, Bottini N. PTPN22: the archetypal non-HLA autoimmunity gene. *Nat Rev Rheumatol* 2014; **10**: 602-611 [PMID: 25003765 DOI: 10.1038/nrheum.2014.109]
- 8 Bottini N, Peterson EJ. Tyrosine phosphatase PTPN22: multi-functional regulator of immune signaling, development, and disease. *Annu Rev Immunol* 2014; **32**: 83-119 [PMID: 24364806 DOI: 10.1146/annurev-immunol-032713-120249]
- 9 Atkinson MA, Eisenbarth GS, Michels AW. Type 1 diabetes. *Lancet* 2014; **383**: 69-82 [PMID: 23890997 DOI: 10.1016/S0140-6736(13)60591-7]
- 10 Eisenbarth GS. Type I diabetes mellitus. A chronic autoimmune disease. *N Engl J Med* 1986; **314**: 1360-1368 [PMID: 3517648 DOI: 10.1056/NEJM198605223142106]
- 11 Boitard C. Pancreatic islet autoimmunity. *Presse Med* 2012; **41**: e636-e650 [PMID: 23182678 DOI: 10.1016/j.lpm.2012.10.003]
- 12 Knip M, Veijola R, Virtanen SM, Hyöty H, Vaarala O, Akerblom HK. Environmental triggers and determinants of type 1 diabetes. *Diabetes* 2005; **54** Suppl 2: S125-S136 [PMID: 16306330]
- 13 Jeker LT, Bour-Jordan H, Bluestone JA. Breakdown in peripheral tolerance in type 1 diabetes in mice and humans. *Cold Spring Harb Perspect Med* 2012; **2**: a007807 [PMID: 22393537 DOI: 10.1101/cshperspect.a007807]
- 14 Ziegler AG, Rewers M, Simell O, Simell T, Lempainen J, Steck A, Winkler C, Ilonen J, Veijola R, Knip M, Bonifacio E, Eisenbarth GS. Seroconversion to multiple islet autoantibodies and risk of progression to diabetes in children. *JAMA* 2013; **309**: 2473-2479 [PMID: 23780460 DOI: 10.1001/jama.2013.6285]
- 15 Insel RA, Dunne JL, Atkinson MA, Chiang JL, Dabelea D, Gottlieb PA, Greenbaum CJ, Herold KC, Krischer JP, Lernmark Å, Ratner RE, Rewers MJ, Schatz DA, Skyler JS, Sosenko JM, Ziegler AG. Staging presymptomatic type 1 diabetes: a scientific statement of JDRF, the Endocrine Society, and the American Diabetes Association. *Diabetes Care* 2015; **38**: 1964-1974 [PMID: 26404926 DOI: 10.2337/dc15-1419]
- 16 Simmons KM, Michels AW. Type 1 diabetes: A predictable disease. *World J Diabetes* 2015; **6**: 380-390 [PMID: 25897349 DOI: 10.4239/wjcd.v6.i3.380]
- 17 Roep BO. The role of T-cells in the pathogenesis of Type 1 diabetes: from cause to cure. *Diabetologia* 2003; **46**: 305-321 [PMID: 12687328 DOI: 10.1007/s00125-003-1089-5]
- 18 Walker LS, von Herrath M. CD4 T cell differentiation in type 1 diabetes. *Clin Exp Immunol* 2016; **183**: 16-29 [PMID: 26102289 DOI: 10.1111/cei.12672]
- 19 Rekers NV, von Herrath MG, Wesley JD. Immunotherapies and immune biomarkers in Type 1 diabetes: A partnership for success. *Clin Immunol* 2015; **161**: 37-43 [PMID: 26122172 DOI: 10.1016/j.clim.2015.05.021]
- 20 Mallone R, Roep BO. Biomarkers for immune intervention trials in type 1 diabetes. *Clin Immunol* 2013; **149**: 286-296 [PMID: 23510725 DOI: 10.1016/j.clim.2013.02.009]
- 21 Culina S, Mallone R. Immune biomarkers in immunotherapeutic trials for type 1 diabetes: cui prodest? *Diabetes Metab* 2012; **38**: 379-385 [PMID: 22858113 DOI: 10.1016/j.diabet.2012.05.005]
- 22 Marrack P, Kappler JW. Do MHCII-presented neoantigens drive type 1 diabetes and other autoimmune diseases? *Cold Spring Harb Perspect Med* 2012; **2**: a007765 [PMID: 22951444 DOI: 10.1101/cshperspect.a007765]
- 23 Mesin L, Ersching J, Victora GD. Germinal Center B Cell Dynamics. *Immunity* 2016; **45**: 471-482 [PMID: 27653600 DOI: 10.1016/j.immuni.2016.09.001]
- 24 DeFranco AL. The germinal center antibody response in health and disease. *F1000Res* 2016; **5**: pii: F1000 [PMID: 27303636 DOI: 10.12688/f1000research.7717.1]
- 25 Sage PT, Sharpe AH. T follicular regulatory cells in the regulation of B cell responses. *Trends Immunol* 2015; **36**: 410-418 [PMID: 26091728 DOI: 10.1016/j.it.2015.05.005]
- 26 Zhang Y, Garcia-Ibanez L, Toellner KM. Regulation of germinal center B-cell differentiation. *Immunol Rev* 2016; **270**: 8-19 [PMID: 26864101 DOI: 10.1111/imr.12396]
- 27 Ferreira RC, Simons HZ, Thompson WS, Cutler AJ, Dopico XC, Smyth DJ, Mashar M, Schuilenburg H, Walker NM, Dunger DB,

- Wallace C, Todd JA, Wicker LS, Pekalski ML. IL-21 production by CD4⁺ effector T cells and frequency of circulating follicular helper T cells are increased in type 1 diabetes patients. *Diabetologia* 2015; **58**: 781-790 [PMID: 25652388 DOI: 10.1007/s00125-015-3509-8]
- 28 **Keneflick R**, Wang CJ, Kapadi T, Wardzinski L, Attridge K, Clough LE, Heuts F, Kogimtzis A, Patel S, Rosenthal M, Ono M, Sansom DM, Narendran P, Walker LS. Follicular helper T cell signature in type 1 diabetes. *J Clin Invest* 2015; **125**: 292-303 [PMID: 25485678 DOI: 10.1172/JCI76238]
- 29 **Viisanen T**, Ihantola EL, Nääntö-Salonen K, Hyöty H, Nurminen N, Selvenius J, Juutilainen A, Moilanen L, Pihlajamäki J, Veijola R, Toppari J, Knip M, Ilonen J, Kinnunen T. Circulating CXCR5+PD-1+ICOS⁺ Follicular T Helper Cells Are Increased Close to the Diagnosis of Type 1 Diabetes in Children With Multiple Autoantibodies. *Diabetes* 2017; **66**: 437-447 [PMID: 28108610 DOI: 10.2337/db16-0714]
- 30 **Baschal EE**, Eisenbarth GS. Extreme genetic risk for type 1A diabetes in the post-genome era. *J Autoimmun* 2008; **31**: 1-6 [PMID: 18450419 DOI: 10.1016/j.jaut.2008.03.003]
- 31 **Pociot F**, Lernmark Å. Genetic risk factors for type 1 diabetes. *Lancet* 2016; **387**: 2331-2339 [PMID: 27302272 DOI: 10.1016/S0140-6736(16)30582-7]
- 32 **Noble JA**. Immunogenetics of type 1 diabetes: A comprehensive review. *J Autoimmun* 2015; **64**: 101-112 [PMID: 26272854 DOI: 10.1016/j.jaut.2015.07.014]
- 33 **Nerup J**, Platz P, Andersen OO, Christy M, Lyngsøe J, Poulsen JE, Ryder LP, Nielsen LS, Thomsen M, Svejgaard A. HL-A antigens and diabetes mellitus. *Lancet* 1974; **2**: 864-866 [PMID: 4137711]
- 34 **Miyadera H**, Tokunaga K. Associations of human leukocyte antigens with autoimmune diseases: challenges in identifying the mechanism. *J Hum Genet* 2015; **60**: 697-702 [PMID: 26290149 DOI: 10.1038/jhg.2015.100]
- 35 **Bennett ST**, Lucassen AM, Gough SC, Powell EE, Undlien DE, Pritchard LE, Merriman ME, Kawaguchi Y, Dronsfield MJ, Pociot F. Susceptibility to human type 1 diabetes at IDDM2 is determined by tandem repeat variation at the insulin gene minisatellite locus. *Nat Genet* 1995; **9**: 284-292 [PMID: 7773291 DOI: 10.1038/ng0395-284]
- 36 **Kennedy GC**, German MS, Rutter WJ. The minisatellite in the diabetes susceptibility locus IDDM2 regulates insulin transcription. *Nat Genet* 1995; **9**: 293-298 [PMID: 7773292 DOI: 10.1038/ng0395-293]
- 37 **Lucassen AM**, Julier C, Beressi JP, Boitard C, Froguel P, Lathrop M, Bell JL. Susceptibility to insulin dependent diabetes mellitus maps to a 4.1 kb segment of DNA spanning the insulin gene and associated VNTR. *Nat Genet* 1993; **4**: 305-310 [PMID: 8358440 DOI: 10.1038/ng0793-305]
- 38 **Nisticò L**, Buzzetti R, Pritchard LE, Van der Auwera B, Giovannini C, Bosi E, Larrad MT, Rios MS, Chow CC, Cockram CS, Jacobs K, Mijovic C, Bain SC, Barnett AH, Vandewalle CL, Schuit F, Gorius FK, Tosi R, Pozzilli P, Todd JA. The CTLA-4 gene region of chromosome 2q33 is linked to, and associated with, type 1 diabetes. Belgian Diabetes Registry. *Hum Mol Genet* 1996; **5**: 1075-1080 [PMID: 8817351]
- 39 **Kavvoura FK**, Ioannidis JP. CTLA-4 gene polymorphisms and susceptibility to type 1 diabetes mellitus: a HuGE Review and meta-analysis. *Am J Epidemiol* 2005; **162**: 3-16 [PMID: 15961581 DOI: 10.1093/aje/kwi165]
- 40 **Smyth D**, Cooper JD, Collins JE, Heward JM, Franklyn JA, Howson JM, Vella A, Nutland S, Rance HE, Maier L, Barratt BJ, Guja C, Ionescu-Tîrgoviste C, Savage DA, Dunger DB, Widmer B, Strachan DP, Ring SM, Walker N, Clayton DG, Twells RC, Gough SC, Todd JA. Replication of an association between the lymphoid tyrosine phosphatase locus (LYP/PTPN22) with type 1 diabetes, and evidence for its role as a general autoimmunity locus. *Diabetes* 2004; **53**: 3020-3023 [PMID: 15504986]
- 41 **Vang T**, Miletic AV, Bottini N, Mustelin T. Protein tyrosine phosphatase PTPN22 in human autoimmunity. *Autoimmunity* 2007; **40**: 453-461 [PMID: 17729039 DOI: 10.1080/08916930701464897]
- 42 **van Belle TL**, Coppieters KT, von Herrath MG. Type 1 diabetes: etiology, immunology, and therapeutic strategies. *Physiol Rev* 2011; **91**: 79-118 [PMID: 21248163 DOI: 10.1152/physrev.00003.2010]
- 43 **Lempainen J**, Hermann R, Veijola R, Simell O, Knip M, Ilonen J. Effect of the PTPN22 and INS risk genotypes on the progression to clinical type 1 diabetes after the initiation of β -cell autoimmunity. *Diabetes* 2012; **61**: 963-966 [PMID: 22357962 DOI: 10.2337/db11-0386]
- 44 **Salveti M**, Ristori G, Bompreszi R, Pozzilli P, Leslie RD. Twins: mirrors of the immune system. *Immunol Today* 2000; **21**: 342-347 [PMID: 10871876]
- 45 **Christen U**, Bender C, von Herrath MG. Infection as a cause of type 1 diabetes? *Curr Opin Rheumatol* 2012; **24**: 417-423 [PMID: 22504578 DOI: 10.1097/BOR.0b013e3283533719]
- 46 **Coppieters KT**, Wiberg A, Tracy SM, von Herrath MG. Immunology in the clinic review series: focus on type 1 diabetes and viruses: the role of viruses in type 1 diabetes: a difficult dilemma. *Clin Exp Immunol* 2012; **168**: 5-11 [PMID: 22385231 DOI: 10.1111/j.1365-2249.2011.04558.x]
- 47 **Lempainen J**, Vaarala O, Mäkelä M, Veijola R, Simell O, Knip M, Hermann R, Ilonen J. Interplay between PTPN22 C1858T polymorphism and cow's milk formula exposure in type 1 diabetes. *J Autoimmun* 2009; **33**: 155-164 [PMID: 19473815 DOI: 10.1016/j.jaut.2009.04.003]
- 48 **Hyöty H**, Taylor KW. The role of viruses in human diabetes. *Diabetologia* 2002; **45**: 1353-1361 [PMID: 12378375 DOI: 10.1007/s00125-002-0852-3]
- 49 **Rodriguez-Calvo T**, Sabouri S, Anquetil F, von Herrath MG. The viral paradigm in type 1 diabetes: Who are the main suspects? *Autoimmun Rev* 2016; **15**: 964-969 [PMID: 27491567 DOI: 10.1016/j.autrev.2016.07.019]
- 50 **Kondrashova A**, Hyöty H. Role of viruses and other microbes in the pathogenesis of type 1 diabetes. *Int Rev Immunol* 2014; **33**: 284-295 [PMID: 24611784 DOI: 10.3109/08830185.2014.889130]
- 51 **Elboudwarej E**, Cole M, Briggs FB, Fouts A, Fain PR, Quach H, Quach D, Sinclair E, Criswell LA, Lane JA, Steck AK, Barcellos LF, Noble JA. Hypomethylation within gene promoter regions and type 1 diabetes in discordant monozygotic twins. *J Autoimmun* 2016; **68**: 23-29 [PMID: 26782299 DOI: 10.1016/j.jaut.2015.12.003]
- 52 **Wang Y**, Shaked I, Stanford SM, Zhou W, Curtsinger JM, Mikulski Z, Shaheen ZR, Cheng G, Sawatzke R, Campbell AM, Auger JL, Bilgic H, Shoyama FM, Schmeling DO, Balfour HH, Hasegawa K, Chan AC, Corbett JA, Binstadt BA, Mescher MF, Ley K, Bottini N, Peterson EJ. The autoimmunity-associated gene PTPN22 potentiates toll-like receptor-driven, type 1 interferon-dependent immunity. *Immunity* 2013; **39**: 111-122 [PMID: 23871208 DOI: 10.1016/j.immuni.2013.06.013]
- 53 **Cloutier JF**, Veillette A. Cooperative inhibition of T-cell antigen receptor signaling by a complex between a kinase and a phosphatase. *J Exp Med* 1999; **189**: 111-121 [PMID: 9874568]
- 54 **Gjörloff-Wingren A**, Saxena M, Williams S, Hammi D, Mustelin T. Characterization of TCR-induced receptor-proximal signaling events negatively regulated by the protein tyrosine phosphatase PEP. *Eur J Immunol* 1999; **29**: 3845-3854 [PMID: 10601992 DOI: 10.1002/(SICI)1521-4141(199912)29:12<3845::AID-IMMU3845>3.0.CO;2-U]
- 55 **Cloutier JF**, Veillette A. Association of inhibitory tyrosine protein kinase p50csk with protein tyrosine phosphatase PEP in T cells and other hemopoietic cells. *EMBO J* 1996; **15**: 4909-4918 [PMID: 8890164]
- 56 **Rawlings DJ**, Dai X, Buckner JH. The role of PTPN22 risk variant in the development of autoimmunity: finding common ground between mouse and human. *J Immunol* 2015; **194**: 2977-2984 [PMID: 25795788 DOI: 10.4049/jimmunol.1403034]
- 57 **Begovich AB**, Carlton VE, Honigberg LA, Schrodi SJ, Chokkalingam AP, Alexander HC, Ardlie KG, Huang Q, Smith AM, Spoorke JM, Conn MT, Chang M, Chang SY, Saiki RK, Catanese JJ, Leong DU, Garcia VE, McAllister LB, Jeffery DA, Lee AT, Batliwalla F, Remmers E, Criswell LA, Seldin MF, Kastner DL, Amos CI, Sninsky JJ, Gregersen PK. A missense single-nucleotide polymorphism in a gene encoding a protein tyrosine phosphatase (PTPN22) is associated with rheumatoid arthritis. *Am J Hum Genet* 2004; **75**: 330-337 [PMID: 15208781 DOI: 10.1086/422827]
- 58 **Wu H**, Cantor RM, Graham DS, Lingren CM, Farwell L, Jager PL, Bottini N, Grossman JM, Wallace DJ, Hahn BH, Julkunen H, Hebert

- LA, Rovin BH, Birmingham DJ, Rioux JD, Yu CY, Kere J, Vyse TJ, Tsao BP. Association analysis of the R620W polymorphism of protein tyrosine phosphatase PTPN22 in systemic lupus erythematosus families: increased T allele frequency in systemic lupus erythematosus patients with autoimmune thyroid disease. *Arthritis Rheum* 2005; **52**: 2396-2402 [PMID: 16052563 DOI: 10.1002/art.21223]
- 59 **Kyogoku C**, Langefeld CD, Ortmann WA, Lee A, Selby S, Carlton VE, Chang M, Ramos P, Baechler EC, Batliwalla FM, Novitzke J, Williams AH, Gillett C, Rodine P, Graham RR, Ardlie KG, Gaffney PM, Moser KL, Petri M, Begovich AB, Gregersen PK, Behrens TW. Genetic association of the R620W polymorphism of protein tyrosine phosphatase PTPN22 with human SLE. *Am J Hum Genet* 2004; **75**: 504-507 [PMID: 15273934 DOI: 10.1086/423790]
- 60 **Fiorillo E**, Orrú V, Stanford SM, Liu Y, Salek M, Rapini N, Schenone AD, Saccucci P, Delogu LG, Angelini F, Manca Bitti ML, Schmedt C, Chan AC, Acuto O, Bottini N. Autoimmune-associated PTPN22 R620W variation reduces phosphorylation of lymphoid phosphatase on an inhibitory tyrosine residue. *J Biol Chem* 2010; **285**: 26506-26518 [PMID: 20538612 DOI: 10.1074/jbc.M110.111104]
- 61 **Stanford SM**, Mustelin TM, Bottini N. Lymphoid tyrosine phosphatase and autoimmunity: human genetics rediscovers tyrosine phosphatases. *Semin Immunopathol* 2010; **32**: 127-136 [PMID: 20204370 DOI: 10.1007/s00281-010-0201-4]
- 62 **Habib T**, Funk A, Rieck M, Brahmandam A, Dai X, Panigrahi AK, Luning Prak ET, Meyer-Bahlburg A, Sanda S, Greenbaum C, Rawlings DJ, Buckner JH. Altered B cell homeostasis is associated with type 1 diabetes and carriers of the PTPN22 allelic variant. *J Immunol* 2012; **188**: 487-496 [PMID: 22105996 DOI: 10.4049/jimmunol.1102176]
- 63 **Menard L**, Saadoun D, Isnardi I, Ng YS, Meyers G, Massad C, Price C, Abraham C, Motaghed R, Buckner JH, Gregersen PK, Meffre E. The PTPN22 allele encoding an R620W variant interferes with the removal of developing autoreactive B cells in humans. *J Clin Invest* 2011; **121**: 3635-3644 [PMID: 21804190 DOI: 10.1172/JCI45790]
- 64 **Giancchetti E**, Palombi M, Fierabracci A. The putative role of the C185T polymorphism of protein tyrosine phosphatase PTPN22 gene in autoimmunity. *Autoimmun Rev* 2013; **12**: 717-725 [PMID: 23261816 DOI: 10.1016/j.autrev.2012.12.003]
- 65 **Arechiga AF**, Habib T, He Y, Zhang X, Zhang ZY, Funk A, Buckner JH. Cutting edge: the PTPN22 allelic variant associated with autoimmunity impairs B cell signaling. *J Immunol* 2009; **182**: 3343-3347 [PMID: 19265110 DOI: 10.4049/jimmunol.0713370]
- 66 **Zheng J**, Petersen F, Yu X. The role of PTPN22 in autoimmunity: learning from mice. *Autoimmun Rev* 2014; **13**: 266-271 [PMID: 24189282 DOI: 10.1016/j.autrev.2013.10.011]
- 67 **Dai X**, James RG, Habib T, Singh S, Jackson S, Khim S, Moon RT, Liggitt D, Wolf-Yadlin A, Buckner JH, Rawlings DJ. A disease-associated PTPN22 variant promotes systemic autoimmunity in murine models. *J Clin Invest* 2013; **123**: 2024-2036 [PMID: 23619366 DOI: 10.1172/JCI66963]
- 68 **Zhang J**, Zahir N, Jiang Q, Miliotis H, Heyraud S, Meng X, Dong B, Xie G, Qiu F, Hao Z, McCulloch CA, Keystone EC, Peterson AC, Siminovich KA. The autoimmune disease-associated PTPN22 variant promotes calpain-mediated Lyp/Pep degradation associated with lymphocyte and dendritic cell hyperresponsiveness. *Nat Genet* 2011; **43**: 902-907 [PMID: 21841778 DOI: 10.1038/ng.904]
- 69 **Rieck M**, Arechiga A, Onengut-Gumuscu S, Greenbaum C, Concannon P, Buckner JH. Genetic variation in PTPN22 corresponds to altered function of T and B lymphocytes. *J Immunol* 2007; **179**: 4704-4710 [PMID: 17878369]
- 70 **Serreze DV**, Chen YG. Of mice and men: use of animal models to identify possible interventions for the prevention of autoimmune type 1 diabetes in humans. *Trends Immunol* 2005; **26**: 603-607 [PMID: 16140038 DOI: 10.1016/j.it.2005.08.012]
- 71 **Pearson JA**, Wong FS, Wen L. The importance of the Non Obese Diabetic (NOD) mouse model in autoimmune diabetes. *J Autoimmun* 2016; **66**: 76-88 [PMID: 26403950 DOI: 10.1016/j.jaut.2015.08.019]
- 72 **Hasegawa K**, Martin F, Huang G, Tumas D, Diehl L, Chan AC. PEST domain-enriched tyrosine phosphatase (PEP) regulation of effector/memory T cells. *Science* 2004; **303**: 685-689 [PMID: 14752163 DOI: 10.1126/science.1092138]
- 73 **Brownlie RJ**, Miosge LA, Vassilakos D, Svensson LM, Cope A, Zamoyska R. Lack of the phosphatase PTPN22 increases adhesion of murine regulatory T cells to improve their immunosuppressive function. *Sci Signal* 2012; **5**: ra87 [PMID: 23193160 DOI: 10.1126/scisignal.2003365]
- 74 **Maine CJ**, Hamilton-Williams EE, Cheung J, Stanford SM, Bottini N, Wicker LS, Sherman LA. PTPN22 alters the development of regulatory T cells in the thymus. *J Immunol* 2012; **188**: 5267-5275 [PMID: 22539785 DOI: 10.4049/jimmunol.1200150]
- 75 **Maine CJ**, Marquardt K, Cheung J, Sherman LA. PTPN22 controls the germinal center by influencing the numbers and activity of T follicular helper cells. *J Immunol* 2014; **192**: 1415-1424 [PMID: 24453256 DOI: 10.4049/jimmunol.1302418]
- 76 **Lin X**, Pelletier S, Gingras S, Rigaud S, Maine CJ, Marquardt K, Dai YD, Sauer K, Rodriguez AR, Martin G, Kupriyanov S, Jiang L, Yu L, Green DR, Sherman LA. CRISPR-Cas9-Mediated Modification of the NOD Mouse Genome With Ptpn22R619W Mutation Increases Autoimmune Diabetes. *Diabetes* 2016; **65**: 2134-2138 [PMID: 27207523 DOI: 10.2337/db16-0061]
- 77 **Wu DJ**, Zhou W, Enouz S, Orrú V, Stanford SM, Maine CJ, Rapini N, Sawatzke K, Engel I, Fiorillo E, Sherman LA, Kronenberg M, Zehn D, Peterson E, Bottini N. Autoimmunity-associated LYP-W620 does not impair thymic negative selection of autoreactive T cells. *PLoS One* 2014; **9**: e86677 [PMID: 24498279 DOI: 10.1371/journal.pone.0086677]
- 78 **Zheng P**, Kissler S. PTPN22 silencing in the NOD model indicates the type 1 diabetes-associated allele is not a loss-of-function variant. *Diabetes* 2013; **62**: 896-904 [PMID: 23193190 DOI: 10.2337/db12-0929]
- 79 **Yeh LT**, Miaw SC, Lin MH, Chou FC, Shieh SJ, Chuang YP, Lin SH, Chang DM, Sytwu HK. Different modulation of Ptpn22 in effector and regulatory T cells leads to attenuation of autoimmune diabetes in transgenic nonobese diabetic mice. *J Immunol* 2013; **191**: 594-607 [PMID: 23752610 DOI: 10.4049/jimmunol.1203380]
- 80 **Zipris D**. Epidemiology of type 1 diabetes and what animal models teach us about the role of viruses in disease mechanisms. *Clin Immunol* 2009; **131**: 11-23 [PMID: 19185542 DOI: 10.1016/j.clim.2008.12.011]
- 81 **Fousteri G**, Jofra T, Di Fonte R, Kuka M, Iannacone M, Battaglia M. PTPN22 controls virally-induced autoimmune diabetes by modulating cytotoxic T lymphocyte responses in an epitope-specific manner. *Clin Immunol* 2015; **156**: 98-108 [PMID: 25513733 DOI: 10.1016/j.clim.2014.12.002]
- 82 **Jofra T**, Di Fonte R, Hutchinson TE, Dastmalchi F, Galvani G, Battaglia M, Salek-Ardakani S, Fousteri G. Protein tyrosine phosphatase PTPN22 has dual roles in promoting pathogen versus homeostatic-driven CD8 T-cell responses. *Immunol Cell Biol* 2017; **95**: 121-128 [PMID: 27725666]
- 83 **Pellegrini S**, Cantarelli E, Sordi V, Nano R, Piemonti L. The state of the art of islet transplantation and cell therapy in type 1 diabetes. *Acta Diabetol* 2016; **53**: 683-691 [PMID: 26923700 DOI: 10.1007/s00592-016-0847-z]
- 84 **Fousteri G**, Jofra T, Di Fonte R, Gagliani N, Morsiani C, Stabilini A, Battaglia M. Lack of the protein tyrosine phosphatase PTPN22 strengthens transplant tolerance to pancreatic islets in mice. *Diabetologia* 2015; **58**: 1319-1328 [PMID: 25748328 DOI: 10.1007/s00125-015-3540-9]
- 85 **Fousteri G**, Jofra T, Debernardis I, Stanford SM, Laurenzi A, Bottini N, Battaglia M. The protein tyrosine phosphatase PTPN22 controls forkhead box protein 3 T regulatory cell induction but is dispensable for T helper type 1 cell polarization. *Clin Exp Immunol* 2014; **178**: 178-189 [PMID: 24905474 DOI: 10.1111/cei.12393]

P- Reviewer: Angelini F, Gloria-Bottini F S- Editor: Ji FF
L- Editor: A E- Editor: Lu YJ





Published by **Baishideng Publishing Group Inc**
7901 Stoneridge Drive, Suite 501, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: <http://www.f6publishing.com/helpdesk>
<http://www.wjgnet.com>

