PTPN22 controls virally-induced autoimmune diabetes by modulating cytotoxic T lymphocyte responses in an epitope-specific manner

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Abstract
Ptpn22 is one of the most potent autoimmunity predisposing genes and strongly associates with type 1 diabetes (T1D). Previous studies showed that non-obese diabetic mice with reduced expression levels of Ptpn22 are protected from T1D due to increased number of T regulatory (Treg) cells. We report that lack of Ptpn22 exacerbates virally-induced T1D in female rat insulin promoter lymphocytic choriomeningitis virus (RIP-LCMV-GP) mice, while maintaining higher number of Treg cells throughout the antiviral response in the blood and spleen but not in the pancreatic lymph nodes. GP₃₃⁻₄₁-specific pentamer-positive cytotoxic lymphocytes (CTLs) are numerically reduced in the absence of Ptpn22 at the expansion and contraction phase but reach wild-type levels at the memory phase. However, they show similar effector function and even a subtle increase in the production of IL-2. In contrast, NP₃₉₆⁻₄₀₄-specific CTLs develop normally at all phases but display enhanced effector function. Lack of Ptpn22 also augments the memory proinflammatory response of GP₆₁⁻₈₀ CD4 T cells. Hence, lack of Ptpn22 largely augments antiviral effector T cell responses, suggesting that caution should be taken when targeting Ptpn22 to treat autoimmune diseases where viral infections are considered environmental triggers.

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1. Introduction
Ptpn22 encodes for the protein tyrosine phosphatase LYP (in humans, PEP in mice), which is involved not only in T- and B- but also in innate-cell signaling and it is associated with susceptibility to various autoimmune diseases [1,2].

Abbreviations: Ptpn22, protein tyrosine phosphatase non-receptor type 22; RIP, rat insulin promoter; LCMV, lymphocytic choriomeningitis virus; CTL, cytotoxic lymphocyte; Treg, T regulatory; WT, wild-type; KO, knockout; T1D, type 1 diabetes; pancLN, pancreatic lymph node; EM, effector memory; CM, central memory.

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With regard to type 1 diabetes (T1D), the Ptpn22 susceptibility allele C1858T has emerged as one of the strongest non-HLA (human leukocyte antigen) genetic risk factors [3]. Therefore, understanding the contribution of Ptpn22 in autoreactive T-cell development and function might provide new ways to treat T1D. Previous studies showed that reduced [4] or increased [5] levels of Ptpn22 can prevent T1D in non-obese diabetic (NOD) mice, the most commonly used model of spontaneous autoimmunity. Here, we tested the role of Ptpn22 in a virally-induced model of T1D, where an acute viral infection triggers the disease.

The rat insulin promoter (RIP)-lymphocytic choriomeningitis virus (LCMV) transgenic mouse model was developed more than two decades ago [6,7] and has in elucidating different immunological rules that govern islet autoimmunity triggered by an acute viral infection. The transgenic mice express the LCMV glycoprotein (GP) antigen under control of the RIP in pancreatic β cells. Viral infection with LCMV induces rapid CD8-dependent T1D that initiates right after viral clearance. This model has served to address not only the effectiveness but also the safety of several treatments known to abrogate T1D in NOD mice and has in elucidating how specific genetic determinants interact with environmental triggers (i.e., viral infections) [8].

Anti-LCMV-specific CD8* cytotoxic T lymphocytes (CTLs) can be easily tracked and studied in RIP-LCMV-GP mice by class I LCMV-specific pentamers and intracellular cytokine staining following LCMV-specific peptide stimulation. Pathogenic CTLs express the LCMV glycoprotein (GP) antigen under control of the RIP in pancreatic β cells. Viral infection with LCMV induces rapid CD8-dependent T1D that initiates right after viral clearance. This model has served to address not only the effectiveness but also the safety of several treatments known to abrogate T1D in NOD mice and has in elucidating how specific genetic determinants interact with environmental triggers (i.e., viral infections) [8].

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Ptpn22 expresses an effector memory (EM) (i.e., CD44hiCD62Llo) phenotype and is functionally characterized by co-production of TNF-α and interferon (IFN)-γ [9]. Whereas T1D in RIP-LCMV-GP mice occurs in a CD4-independent fashion [10], CD4-mediated T-cell help is important for efficient memory CTL development [11]. Progression to T1D in RIP-LCMV-GP mice is influenced by several factors and the most important ones regard the generation and function of LCMV-specific CTLs [12], and the production of proinflammatory cytokines, such as type I IFNs [13], IL-12 [14] and IFN-γ [15]. Interestingly, T1D can be also modulated in RIP-LCMV-GP mice with the induction of FOXP3^+ T regulatory (Treg) cells [16–18].

It appears that Ptpn22 modulates several innate and adaptive immune responses that are triggered by LCMV, suggesting that Ptpn22 might play a role in T1D development in RIP-LCMV-GP mice. For example, lack of Ptpn22 reduces DC activation and type I IFN production [19], but amplifies T- and B-cell activation [20], germinal center (GC) and T follicular helper (Tfh) cell development [21], and Treg [4,22,23] and memory T-cell generation [24,25]. Furthermore, lack of Ptpn22 enhances the activation and proinflammatory cytokine production by a subset of antigen-specific CTLs and CD4^+ T cells.

2. Materials and methods

2.1. Mice

Homozygous Ptpn22-deficient mice, referred throughout the manuscript as KO (knockout), were previously described [24]. Mice were interbred with RIP-LCMV-GP transgenic [6] and the heterozygous (HET) offspring were intercrossed to obtain RIP-LCMV-GP ^Ptpn22^WT (wild-type), HET and KO littermates that were used throughout the study. All mice were housed under SPF conditions in compliance with guidelines of the San Raffaele Institutional Animal Care and Use Committee (IACUC #479).

2.2. Viruses and infection

LCMV Armstrong plaque-purified was prepared by a single passage on BHK-21 cells and used throughout experiments. To induce T1D, 8–12-week-old mice were infected with a single dose of 10^3 PFU i.p. To measure viral load, mice were infected with 2 × 10^5 PFU i.p.

2.3. Blood glucose monitoring

Blood glucose was monitored with OneTouch Ultra at weekly intervals. Diabetes was defined as blood glucose values over 300 mg/dl.

2.4. Peptides

Peptides used for viral studies were the dominant D^b^-restricted LCMV epitopes GP33–41, and NP396–404 and the I-Ab-restricted epitope GP61–80 (all from Promimmune).

2.5. Immunohistochemistry

Tissues were immersed in Tissue-Tek OCT (Bayer) and quick frozen on dry ice. Using cryomicrotome and Superfrost Plus slides (Fisher Scientific), 6-μm tissue sections were cut. Sections were fixed with 100% acetone at room temperature, and after washing in TBS, an avidin/biotin-blocking step was included (Vector Laboratories). Primary and secondary antibodies (Vector Laboratories) were reacted with the sections for 60 min each, and color reaction was obtained by sequential incubation with Vector Blue AP III and AEC (Vector Laboratories)-biotin and guinea pig anti-swine insulin (DAKO). Goat anti-guinea pig AP was used to detect insulin [26].

2.6. Virus titration

LCMV titres of infected spleens were determined in a virus plaque assay as previously described [27]. Cells from the fibrosarcoma cell line MC57 were plated at a concentration of 2.5 × 10^5 in 24-well plates. Tissue samples (frozen at −80 °C in MEM-0% FCS) were thawed, homogenized, and added to the MC57 cells in 5-fold dilution steps. The virus was allowed to infect MC57 cells for 4 h, then methylcellulose (Methocel, Sigma, Mo., US) was diluted 1:2 in 2× Dulbecco...
modified Eagle medium and added to inhibit budding of virus. After 48 h of incubation at 37 °C, cell monolayers were fixed with 4% formaldehyde and permeabilized by incubation in 0.5% Triton X-100. Plaques of virus-infected cell clusters were detected immunohistochemically using the LCMV-specific anti-VL-4 mAb. Peroxidase-coupled anti-rat Ig antibody (Jackson ImmunoResearch, PA, US) was used as a second step, and a color reaction was performed using 3,3′-diaminobenzidine tablets (SIGMAFAST™ Sigma, Mo, US) according to the manufacturer’s instructions.

2.7. In vitro peptide restimulation

Single cell suspensions were prepared from the spleen and pancreatic lymph nodes (pancLNs). Cells were stimulated for 3 h with 1 μg/ml MHC class I-restricted viral peptides, and 2 μg/ml MHC class II-restricted viral peptides in the presence of brefeldin A.

2.8. Flow cytometry

Cells were stained with anti-CD4, -CD8, -CD25, -CD44, -CD62L, CD19, and CD107α mAbs (all from BD Biosciences, Biolegend and eBioscience) and then intracellularly with anti-FOXP3 mAb (eBioscience). DbGP33 and eBioscience) and then intracellularly with anti-FOXP3 mAb (Jackson ImmunoResearch, PA, US) was used as a second step, and a color reaction was performed using 3,3′-diaminobenzidine tablets (SIGMAFAST™ Sigma, Mo, US) according to the manufacturer’s instructions. All samples were acquired on a FACSCanto or LSRII flow cytometer (BD Biosciences) and analyzed with FlowJo (Tree Star, USA) software.

2.9. Statistics

Comparisons between groups were performed using the unpaired, two-tailed Student’s t test. Diabetes incidence was determined with Kaplan–Meier survival curves, which were compared with the log-rank test. In all cases Prism software (GraphPad, USA) was used. *p < 0.05, **p < 0.01, ***p < 0.001.

3. Results

3.1. Increased virally-induced T1D incidence in female RIP-LCMV-GP Ptpn22KO mice

In RIP-LCMV-GP transgenic mice infection with the Armstrong strain of LCMV induces rapid CD8-mediated T1D > 10 days post infection (dpi) [28]. To determine whether Ptpn22 controls T1D susceptibility in this model, RIP-LCMV-GP Ptpn22WT, HET and KO littermates were infected with LCMV. T1D incidence in female RIP-LCMV-GP Ptpn22KO mice was approximately 80%, greater than in WT and HET female littermates, where roughly 50% of the mice turned diabetic (A). In contrast, T1D incidence in all groups of male mice was similar (B). Pancreata from RIP-LCMV-GP Ptpn22WT and KO mice were examined by immunohistochemistry for the presence of infiltrating CD4+ and CD8+ T cells. Islets from diabetic RIP-LCMV-GP mice were heavily infiltrated with both CD4+ and CD8+ T cells, whereas non-diabetic mice contained islets with reduced insulitis, with CD4+ and CD8+ T cells present mostly around the islet periphery (Figs. 1C–D and data not included). Thus, lack of Ptpn22 increased virally-induced T1D in RIP-LCMV-GP female mice.

3.2. Treg-cell frequency transiently drops after acute infection with LCMV but remains higher in the absence of Ptpn22 in the blood and spleen but not in the pancLN

FOXP3+ Treg cell number drops in LCMV-infected mice during the first week after infection as a result of the robust type I IFN production that is provoked by the virus [29]. The reduction in Treg cell number is considered essential for the generation of optimal antiviral T-cell responses and for the virus clearance [30]. Ptpn22KO mice have increased number of Treg cells in the steady-state [22,23] and show a defect in type I IFN production following infection with LCMV [19]. First the kinetics of viral clearance between WT and Ptpn22KO were compared. A higher (2 × 10^5 PFU) viral dose was used as 10^5 PFU was relatively low to give us consistent results. At 3 days post infection (dpi), LCMV titres were similar between Ptpn22KO and WT mice, while virus was cleared in both groups by 8 dpi (Fig. 2A and data not included). Thus, despite the enhanced initial number of Treg cells and the defective innate immune response [19], Ptpn22KO mice are as effective as their WT littermates in controlling the virus.

To test the effect of LCMV infection on Treg cells in the absence of Ptpn22, blood was collected from RIP-LCMV-GP Ptpn22KO mice at 8, 15 and 70 dpi, time points that correspond to the expansion, contraction and memory phase, respectively [31]. Whereas the overall expansion of CD4+ T cells was not affected by the absence of Ptpn22 (data not included), circulating Treg-cell frequency dropped at 8 dpi by an average 50% in RIP-LCMV-GP Ptpn22KO mice, which was similar to the drop observed in WT mice (Figs. 2B–C). Interestingly, circulating Treg-cell frequency remained higher in RIP-LCMV-GP Ptpn22KO mice as compared to WT mice at all time-points analyzed (Fig. 2B). Whereas Treg-cell frequency and number remained higher also in the spleen of RIP-LCMV-GP Ptpn22KO mice, it did not differ from WT mice in the pancLNs (Figs. 2D–G) (similar results were obtained with male and female mice, only data from female mice is shown throughout the manuscript). These findings show that LCMV infection reduces Treg cells in RIP-LCMV-GP Ptpn22KO similarly to WT mice. Furthermore, Treg-cell frequency and number remains higher in the absence of Ptpn22 throughout the anti-LCMV response except the pancLNs.

3.3. Numeric reduction in primary but not memory GP33-41-specific pentamer-positive CTLs in RIP-LCMV-GP Ptpn22KO mice

The CD8+ LCMV-specific immune response, which determines T1D penetrance in this model, was evaluated over time. Antigen-specific pentamer staining was used to identify the frequency of LCMV-specific CD8+ CTLs at different time points after infection. Whereas lack of Ptpn22 did not affect the overall expansion of CD8+ T cells (data not included),
primary immunodominant GP33-41-specific CTLs examined at 8 and 15 dpi were reduced in the blood and spleen of RIP-LCMV-GP<sup>Ptpn22KO</sup> mice at the expansion phase (Figs. 3A–C and data not included), as previously shown [19]. However, GP33-41-specific CTLs were present at WT levels in the pancLNs (Figs. 3B–C). In contrast, the frequency of NP396-404-specific CTLs was identical between RIP-LCMV-GP<sup>Ptpn22KO</sup> and WT mice at the expansion and contraction phase in all tissues examined (Figs. 3D–F).

The frequency and number of LCMV-specific memory CTLs was also evaluated at the memory phase. LCMV-infected Ptpn22KO mice had similar cellularity in the spleen and pancLNs at the memory phase (data not included). Interestingly, the frequency of GP33-41-specific CTLs in three peripheral compartments (i.e., blood, spleen and pancLNs) was comparable between RIP-LCMV-GP<sup>Ptpn22KO</sup> and WT mice (Figs. 4A–C). Also, the frequency and number of memory NP396-404-specific CTLs was not affected by the absence of Ptpn22 (Figs. 4D–F). Furthermore, the distribution of central memory (CM) (i.e., CD44<sup>hi</sup>CD62L<sup>+</sup>) and EM on GP33-41- and NP396-404-specific CTLs did not differ between RIP-LCMV-GP<sup>Ptpn22KO</sup> and WT mice (data not included). Altogether, these results show that lack of Ptpn22 reduces the number of GP33-41-specific CTLs at the expansion and contraction phase in the blood and spleen but does not interfere with their expansion in the pancLN. Yet Ptpn22 allows the survival and accumulation of GP33-41-specific CTLs as memory cells at levels similar to WT in all lymphoid compartments. In contrast, Ptpn22 is dispensable for the priming and memory generation of NP396-404-specific CTLs.

### 3.4. Lack of Ptpn22 increases the effector function of LCMV-specific CTLs at the expansion phase

Given that the results so far cannot explain the increased susceptibility of RIP-LCMV-GP<sup>Ptpn22KO</sup> to virally-induced T1D, the functional activity of LCMV-specific CTLs was examined at the expansion phase. Rather unexpectedly, GP33-41-specific IL-2 production was increased in the absence of Ptpn22, whereas co-production of IFN-γ/TNF-α and IFN-γ/CD107α (degranulation marker) between RIP-LCMV-GP<sup>Ptpn22KO</sup> and WT mice was similar (Figs. 5A–B and D–E). In contrast, NP396-404-specific CTL proinflammatory responses were modestly enhanced in RIP-LCMV-GP<sup>Ptpn22KO</sup> mice (Figs. 5D–F). These findings show that GP33-41- and NP396-404-specific CTLs show modest increased effector function at the expansion phase, suggesting that lack of Ptpn22, by enhancing primary effector T cell responses, increases predisposition to virally-induced T1D.

### 3.5. Memory NP396-404-specific CTLs show increased effector function in the absence of Ptpn22

Next, the functional activity of the resulting memory LCMV-specific CTL responses was examined. Antigen-
specific co-production of IFN-γ/TNF-α, IL-2, and IFN-γ/ degranulation was examined in the spleen and pLN of RIP-LCMV-GP<sup>Ptpn22WT</sup> and <sup>KO</sup> mice 70 dpi. GP<sub>33-41</sub>-specific memory CTLs showed similar effector (%TNF-α and IFN-γ) and IL-2 cytokine production, and CD107α degranulation (Supplem. Figs. 1A–B). On the contrary, NP<sub>396-404</sub>-specific effector memory CTL responses were enhanced in RIP-LCMV-GP<sup>Ptpn22WT</sup> and <sup>KO</sup> mice 70 dpi with LCMV (n = 4 mice/group). Taken together, this data shows that lack of Ptpn22 does not affect the development and functional memory of GP<sub>33-41</sub>-specific CTLs, the effector and cytotoxic activity of memory NP<sub>396-404</sub>-specific CTLs.

3.6. Enhanced GP<sub>61-80</sub>-specific memory CD4<sup>+</sup> T-cell responses in RIP-LCMV-GP<sup>Ptpn22KO</sup> mice

Since Ptpn22<sup>KO</sup> mice generate enlarged GCs and a higher number of T<sub>FH</sub> cells upon antigen-specific immunization
splenic GC responses were initially compared between RIP-LCMV-GP<sup>Ptpn22KO</sup> and WT mice at the expansion phase. No differences in T<sub>FH</sub>, GC B cell and plasma cell formation were seen (Suppl. Fig. 2). Next, to test whether the lack of Ptpn22 has bestowed new properties to CD4<sup>+</sup> T cells that might have affected T1D susceptibility in RIP-LCMV-GP mice, GP<sub>61−80</sub>-specific memory CD4<sup>+</sup> T cell responses were tested. Interestingly, double cytokine-producing (TNF-α/IFN-γ) memory CD4<sup>+</sup> T cell responses were significantly increased in the spleen and pancLN of memory RIP-LCMV-GP<sup>Ptpn22KO</sup> mice, while IL-2 production was similar (Fig. 7). Of note, no FOXP3<sup>+</sup> Treg cells produced proinflammatory cytokines in response to GP<sub>66−77</sub> specific CD4<sup>+</sup> T cells (data not included) [29]. Taken together, these results show that in the absence of Ptpn22, memory LCMV-specific CD4<sup>+</sup> T-cell responses are also increased, demonstrating a critical role for Ptpn22 in the generation and effector function also of LCMV-specific memory CD4<sup>+</sup> T cells.

### 4. Discussion

Our study suggests an important role for Ptpn22 in T1D development in the RIP-LCMV-GP mouse model of virally-induced diabetes. Female RIP-LCMV-GP<sup>Ptpn22KO</sup> mice develop T1D with higher incidence as compared to their WT littermates, which is associated with increased effector and cytotoxic function by specific subsets of antigen-specific CTLs. In the absence of Ptpn22, GP<sub>33−41</sub>-specific pentamer-positive CTL generation is initially impaired, as previously described [19], but reaches WT levels later on. However, their proinflammatory function is not affected by the absence of Ptpn22, with the exception of IL-2, which is modestly increased at the expansion phase. Lack of Ptpn22 also augments the proinflammatory function of GP<sub>61−80</sub>-specific memory CD4<sup>+</sup> T cell responses. Thus, the findings reported here extend previous observations [19], and indicate that lack of Ptpn22 causes several T-cell extrinsic and intrinsic defects that shape the generation and/or function of effector/memory T cells in an antigen-specific manner after viral infection in vivo.

It was rather unexpected that the absence of Ptpn22 would increase T1D development in RIP-LCMV-GP mice. Previous studies indicated that Ptpn22<sup>KO</sup> mice, which contain a higher number of Treg cells in the steady-state [22,23], have impaired type I IFN production and diminished GP<sub>33−41</sub>-specific CTL generation [19], would be likely protected from virally-induced T1D. The effect of Ptpn22 on T1D incidence was apparent solely in female RIP-LCMV-GP mice, which was
possibly owed to the fact that WT female mice developed T1D with lower incidence as compared to male mice. We postulate that lack of Ptpn22 would have had the same effect also in male mice, if male RIP-GP<sup>Ptpn22<sub>WT</sub></sup> mice had developed T1D with lower incidence.

T1D incidence in RIP-LCMV-GP mice can be influenced by the housing conditions, the sex but more commonly, by alterations in the C57BL/6 genetic background. For example, of RIP-LCMV mice with SV129, can interfere with disease penetrance by in the C57BL/6 genetic background. For example, of RIP-LCMV housing conditions, the sex but more commonly, by alterations with lower incidence.

Therefore, female RIP-LCMV-GP<sup>Ptpn22<sub>WT</sub></sup> mice in our experiments possibly developed reduced T1D due to both hormonal and genetic alterations. In addition, given that lack of Ptpn22 augmented particularly the proinflammatory function of NP<sub>396-404</sub>-specific CTLs both at the expansion and memory phase, it would be interesting to evaluate disease progression in the RIP-LCMV-NP model of virally-induced T1D.

The production of type I IFNs at the initial stages of an antiviral immune response is essential to regulate several cell types including, as recently shown, the expansion of Treg cells [29]. During LCMV infection, type I IFNs directly repress Treg cell proliferation, a step that is necessary for the production of optimal antiviral T cell responses and efficient viral clearance [29]. Here, we defined that Treg-cell repression takes place also in LCMV-infected Ptpn22<sup>KO</sup> mice and that Treg-cell frequency drops to the same extent in Ptpn22<sup>KO</sup> and WT mice at the acute phase. Thus, lack of Ptpn22 has no effect on Treg-cell repression induced by LCMV infection despite reducing the production of type I IFNs [19]. Interestingly, we found that the frequency and number of Treg cells was higher in RIP-LCMV-GP<sup>Ptpn22<sub>KO</sub></sup> mice in all compartments analyzed except the pancLNs. This finding shows that Ptpn22 has a different effect on Treg cell activity generated that Ptpn22 has a different effect on Treg cell activity generated.

The fact that Treg-cell frequency remains higher in Ptpn22<sup>KO</sup> mice throughout the antiviral immune response also implies that Treg cells might be responsible for shaping the antiviral CTL immune response. Previous studies demonstrated that Treg cells regulate the numbers and effector functions of CD8<sup>+</sup> and CD4<sup>+</sup> T cells during pathogen-triggered immune responses. For example, excessive Treg-cell number led into reduced CTL activity and failure to clear pathogens [33,34], whereas reduced Treg-cell activity generated over-reactive CTLs that caused immunopathology [35]. Our data show that in the absence of Ptpn22, GP<sub>33-41</sub>-specific CTL pentamer-positive cells are reduced, suggesting that Treg cells might involved. However, the fact that GP<sub>33-41</sub>-specific CTL function is not impaired in the absence of Ptpn22 at the expansion phase made us generate an alternative hypothesis. Perhaps, in the absence of Ptpn22 LCMV-specific CTLs become hyper-activated and, as a consequence, down-regulate their T-cell receptor (TCR). Therefore, it is possible that the
pentamer staining did not reveal the actual number of LCMV-specific CTLs.

It is striking that the absence of Ptpn22 so differentially affected the development of LCMV-specific CTLs (GP33–41 versus NP396–404) and yet increased T1D incidence in female RIP-LCMV-GP Ptpn22KO mice. This discrepancy is not due to the additional presence of one of the two proteins as a target antigen in the pancreas because similar results can be obtained if plain WT and Ptpn22KO mice (not RIP-GP transgenic) are used (data not included). GP33–41 responses differ from NP396–404 responses in major histocompatibility class (MHC) I binding affinity and avidity [36]. Given that, Ptpn22 alters lower and to a lesser extent higher affinity CD8 T cell responses [25], it is possible that Ptpn22 differentially affected LCMV-specific CTLs due to differences in their overall affinity/avidity.

Our results appear to conflict with earlier studies that interpreted the reduced expansion of GP33–41-specific CTLs in the absence of Ptpn22 as a consequence of diminished type I IFN production [19]. Type I IFN signaling is a major promoter of CD8+ T-cell primary expansion that, however, has consequences on memory T-cell formation. In the absence of type I IFN, not only primary but also memory T-cell development is decreased [37]. Thus, the presence of a similar number of GP33–41-specific CTLs in RIP-LCMV-GP Ptpn22KO mice at the memory phase and a similar number of functional GP33–41-specific CTLs at the expansion phase was rather unexpected, as it was also surprising that NP396–404-specific CTLs enhanced function.

Together, our data suggests that Ptpn22 acts at many levels. Our findings possibly reflect not only intrinsic alterations in T cells, such as changes in TCR affinity threshold, but also changes in antigen presentation and the cytokine...
microenvironment, which shapes LCMV-specific CTL responses in an epitope-specific manner. Moreover, our results propose that blocking the activity of might not be of therapeutic value in preventing T cell–mediated autoimmune disorders triggered by viral infection.

5. Summary

The immunomodulatory effects of Ptpn22 are incredibly complex, and several murine studies so far suggest that lack of Ptpn22 may promote or inhibit autoimmunity depending on the experimental setting, which basically translates to the type of inflammatory cells that mediates tissue damage. Our data elucidate a novel role of Ptpn22 during T1D development triggered by an acute viral infection and further highlight the complexity of the responses that are controlled by this gene. We show that lack of Ptpn22 exacerbates T1D in female RIP-LCMV-GP mice, which is associated with changes in the frequency and effector function of specific CTL subsets and CD4+ T cells.

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Conflict of interest statement

The authors declare that there are no conflicts of interest.
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