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Regulation of autoimmune and anti-tumour T-cell responses by PTPN22

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Summary

A number of polymorphisms in immune-regulatory genes have been identified as risk factors for the development of autoimmune disease. *PTPN22* (that encodes a tyrosine phosphatase) has been associated with the development of several autoimmune diseases, including type 1 diabetes, rheumatoid arthritis and systemic lupus erythematosus. PTPN22 regulates the activity and effector functions of multiple important immune cell types, including lymphocytes, granulocytes and myeloid cells. In this review, we describe the role of PTPN22 in regulating T-cell activation and effector responses. We discuss progress in our understanding of the impact of PTPN22 in autoimmune disease in humans and mouse models, as well as recent evidence suggesting that genetic manipulation of PTPN22 expression might enhance the efficacy of anti-tumour T-cell responses.

Keywords: autoimmunity; signal transduction; T-cell; tumour immunology.

Introduction

Regulation of T-cell receptor (TCR) signalling and activation is essential for the maintenance of immunological tolerance and homeostasis. Disruption of these complex signalling networks can lead to undesirable outcomes, such as unregulated inflammation, autoimmunity or ineffective anti-tumour responses. The identification of HLA class II alleles as strong risk factors for the development of autoimmune diseases[1] clearly implicates T-cell activation as an important driver of autoreactive immune responses. Furthermore, polymorphisms in genes encoding molecules involved in the regulation of T-cell signalling and activation, such as CTLA4[2] and IL-2,[1] have been linked to autoimmunity, highlighting the need for appropriate T-cell responses in order to maintain tolerance.

In the past 15 years, polymorphisms in *PTPN22* (that encodes a cytoplasmic tyrosine phosphatase) have been identified as risk factors for the development of autoimmune diseases, such as type 1 diabetes (T1D), rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE).[3] Subsequently, important cell-intrinsic roles for PTPN22 (protein tyrosine phosphatase, non-receptor type, 22) in a number of immune cell populations, including B-cells,[4,5] neutrophils,[6] dendritic cells[7,8] and myeloid cells,[9] have been identified. In this review, we focus on the mechanisms by which PTPN22 regulates T-cell activation. We describe recent progress in the field highlighting the importance of PTPN22 in regulating both autoimmune and anti-tumour T-cell responses.

T-cell activation and PTPN22

T-cell activation results when the TCR engages antigenic peptide presented by major histocompatibility complex (MHC) molecules on the surface of antigen-presenting cells (APCs). TCR signalling is initiated by the Src tyrosine kinases, Lck and Fyn, that phosphorylate immunoreceptor tyrosine-based activatory motifs (ITAMs) in TCR-associated CD3 and zeta chains. ITAM phosphorylation enables the recruitment and phosphorylation of the zeta-associated

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Abbreviations: PTPN22, protein tyrosine phosphatase, non-receptor type, 22; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; SNP, single nucleotide polymorphism; T1D, type 1 diabetes; TCR, T-cell receptor; TGFβ, transforming growth factor β; ZAP70, zeta chain associated protein kinase of 70 kDa protein kinase of 70 kDa (ZAP70), and the propagation of downstream signals ultimately leading to gene expression and effector functions (reviewed in[10,11]).

The activity and function of Src family kinases is regulated by phosphorylation of key tyrosine residues within the kinase domain (e.g. Lck Y394) and the C-terminus (e.g. Lck Y505; reviewed in[11]). In this regard, when phosphorylated by Csk, the inhibitory Y505 residue forms an intermolecular association with the Lck src-homology (SH)2 domain keeping Lck in a 'closed' conformation.[11] Dephosphorylation of Lck Y505 by CD45 enables Lck to attain an 'open' or 'primed' conformation.[11] By contrast, auto- or transphorylation of the active site Y394 is essential for optimal Lck kinase activity.

PTPN22 is a cytoplasmic, non-receptor protein tyrosine phosphatase that is expressed predominantly in cells of haematopoietic origin.[12] In T-cells, PTPN22 as well as additional phosphatases including SHP-1 (PTPN6) and PTPN2 can dephosphorylate Lck Y394, thereby limiting TCR proximal signalling.[13,14] A number of additional PTPN22 substrates have been identified, including ZAP70, TCRζ and VAV1.[15] In order to dephosphorylate TCR proximal kinases Lck and ZAP70, cytoplasmic PTPN22 is thought to be recruited to the cell membrane through association with C-terminal Src kinase (CSK) that in turn binds to transmembrane adapter proteins such as phosphoprotein associated with glycosphingolipid-enriched microdomains (PAG).[12,16] Interestingly, a well-described autoimmune-associated polymorphism in *PTPN22* (C1858T) results in an amino acid substitution that disrupts PTPN22-CSK interactions (described in further detail below).

As well as impacting upon canonical TCR signalling pathways, PTPN22 also influences 'inside-out' signalling to integrins such as LFA-1. In the absence of PTPN22, TCR triggering results in enhanced activation of the small GTPase Rap1 and a subsequent increase in LFA-1-dependent adhesion.[17] As a consequence, PTPN22-deficient T-cells have an increased propensity to form productive conjugates with APCs.[18] Interestingly, PTPN22 also regulates integrin 'outside-in' signalling. In migrating T-cells, PTPN22 localizes to the leading edge and regulates the activation of Lck, ZAP70 and VAV1 following LFA-1-ICAM-1 engagement.[19]

The generation of PTPN22-deficient mice has increased our understanding of the role PTPN22 plays in limiting T-cell activation and the maintenance of T-cell homeostasis. Under resting conditions, *Ptpn22*-deficient mice accumulate increased numbers of effector/memory phenotype T-cells as compared with wild-type counterparts.[17,20] Initial studies using TCR cross-linking antibodies indicated that increased activation was seen for effector T-cells lacking PTPN22, whereas the responses of naïve WT and *Ptpn22*$^{-/-}$ T-cells were indistinguishable.[20] These data suggested that PTPN22 was important for the regulation of effector but not naïve T-cell activation. Consistent with these findings, PTPN22 expression is elevated in effector and memory T-cells relative to naïve T-cells.[21,22] More recently, studies using the OT-I TCR transgenic mouse strain [that expresses an MHC class I restricted ovalbumin (ova)-specific TCR] have shown that naïve T-cell activation is regulated by PTPN22. Thus, initial T-cell activation in response to high-affinity ova-peptide antigens was unaffected by loss of PTPN22 expression, consistent with previous data using cross-linking antibodies.[18] By contrast, PTPN22 was important for limiting naïve T-cell responses to weak agonist ova-peptide variants. Furthermore, several studies have determined that the extent of T-cell proliferation and activation under lymphopenic conditions *in vivo* is regulated by PTPN22.[18,23] Interestingly, in effector CD8^{+} cytotoxic T-cells, the absence of PTPN22 reduced the threshold for activation in response to very low affinity, self-antigen.[18] These data are consistent with a central role for PTPN22 in maintaining T-cell homeostasis and in limiting autoreactive T-cell responses.

PTPN22 polymorphisms in autoimmunity

PTPN22 single-nucleotide polymorphisms (SNPs) have been identified as risk factors for the development of autoimmunity in humans.[24] Bottini and colleagues first identified a link between the *PTPN22* C1858T SNP, which results in the substitution of tryptophan for arginine at position 620 (R620W), and type 1 diabetes.[3] Many studies have subsequently confirmed an association of the PTPN22 R620W variant with T1D and other autoimmune conditions such as RA and SLE.[25–27] Whilst much work has focused on the relatively common R620W PTPN22 variant, other PTPN22 SNPs have also been linked with some degree to autoimmunity. For example, a SNP in the *PTPN22* promoter region (rs2488457) has been identified as a risk factor for the development of RA in Asian populations (reviewed in[28]). By contrast, a rare missense SNP in the PTPN22 catalytic domain (rs33996649) serves to lessen the risk of RA and SLE.[29] PTPN22 R620W is not associated with all autoimmune conditions, for example multiple sclerosis[30]; there seems to be a particularly strong link of R620W with diseases characterized by the presence of autoantibodies.[31] Interestingly, in mice, PTPN22 regulates the numbers of follicular T helper (Tfh) cells that are critical for B-cells to make antibody responses within the germinal centre.[32] In these experiments, the absence of PTPN22 permitted increased Tfh cell proliferation and elevated levels of IL-21 production.[32]

The location of R620W (corresponding to position R619W in mouse) within the regulatory P1 PEST [proline (P), glutamic acid (E), serine (S), threonine (T)-rich] domain of PTPN22 abrogates its interaction with CSK, a kinase that together with PAG and Dok adaptors also negatively regulates TCR signalling.[16,33] The loss of this interaction could predict a loss of normal PTPN22 function; however, the findings from a number of studies are more complex. An early study suggested that PTPN22 R620W had elevated phosphatase activity indicating gain-of-function, whilst T-cells from carriers of the C1858T SNP produced lower levels of IL-2 upon TCR stimulation.[34] While some studies support this initial description of PTPN22 R620W function,[35–38] other studies have reported the converse to be true; that R620W confers a loss of PTPN22 function.[19,39,40] Knock-in mice engineered to express the PTPN22 R619W variant display an overall phenotype similar to that of PTPN22 knock-out mice,[8,41] including T-cell hyper-responsiveness, suggesting that in mice the variant results in loss of PTPN22 function. However, it should be noted that mass spectrometry analysis indicates that the complete absence of PTPN22 has distinct effects on the mouse T-cell phosphoproteome as compared with PTPN22 R619W expression.[41] It is therefore likely that the precise impact of the R619W/R620W polymorphism on signalling pathways is highly context dependent.

Mouse models of PTPN22 function in autoimmunity

Researchers have attempted to clarify the role of PTPN22 in autoimmunity using mouse models. Expression of PTPN22 R619W does not result in the development of spontaneous autoimmunity on a C57BL/6 genetic background yet, when expressed in an autoimmune-prone strain (129/Sv), knock-in mice develop systemic autoimmunity.[41] Similarly, deletion of PTPN22 in C57BL/6 mice does not result in overt autoimmunity;[17,20] however, when combined with a mutation in an additional phosphatase CD45 (E613R) the mice succumb to a lupus-like disease.[40] Thus, in mice, the absence of PTPN22 or expression of disease-associated variants pre-disposes to spontaneous autoimmunity only in a permissive genetic background.

PTPN22-deficient mice have been crossed to additional autoimmune-prone genetic backgrounds, such as the non-obese diabetic (NOD)[42–44] and the ZAP70-mutant SKG strains.[45] A summary of autoimmune models carried out in PTPN22-mutant mouse strains is shown in Table 1. The results of these studies paint a complicated picture of the role of PTPN22 in the regulation of autoimmunity. Under some circumstances, the absence of PTPN22 confers a protective effect[6,43,45,46] whilst, in others, PTPN22-deficiency or PTPN22 R619W expression enhances the severity of autoimmunity.[17,32,40–42,47] These apparently contradictory results are likely explained, at least in part, by the fact that PTPN22 regulates both inflammatory and anti-inflammatory T-cell responses. For example, PTPN22-deficient mice have increased numbers of peripheral regulatory T-cells (Tregs),[17,46,48] and these Tregs are more suppressive.[17] Consistent with these data, diminished autoimmune inflammation in PTPN22-mutant animals in the EAE and NOD models was associated with enhanced regulatory T-cell numbers and activity.[43,46]

PTPN22-dependent regulation of Th differentiation also impacts upon disease severity in mouse models. For example, combined deletion of PTPN22 with the ZAP70 SKG mutation, a hypomorphic mutant allele of ZAP70 that gives rise to a $CD4^+$ T-cell-driven model of arthritis,[49] resulted in less severe disease.[45] PTPN22 deficiency appeared to bias $CD4^+$ Th cell differentiation away from the Th17 lineage, which is pathogenic in the SKG model, to a more Th1/Treg biased response, resulting in lower levels of inflammation.[45] At a mechanistic level, it is possible that elevated IL-2 secretion by *Ptpn22*$^{-/-}$ T-cells biases against Th17 polarization, instead favouring Th1/Treg differentiation. Similarly, the PTPN22 R620W variant favoured Th1 differentiation and diminished Th17 differentiation in human T-cells.[38] Thus, the precise nature of the disease-driving T-cell response and the balance between inflammatory and regulatory $CD4^+$ T-cells populations is critical for the outcome of disease in PTPN22-deficient and knock-in mouse models.

A number of studies have sought to determine the role of PTPN22 in T-cell development and central tolerance. Overall numbers and distributions of thymocyte subsets are unaffected in *Ptpn22*$^{-/-}$ mice expressing a polyclonal T-cell repertoire.[17,20] PTPN22-deficiency resulted in a small increase in the positive selection of DO11·10 and HY TCR transgenic single-positive thymocytes;[20] however, no increases in absolute numbers of single-positive thymocytes were apparent in the OT-1 system.[18] There was no impact of PTPN22 on negative selection of HY thymocytes[20] or in transgenic mice expressing PTPN22 R620W.[50] Finally, TCR sequencing analyses suggested that the absence of PTPN22 did not impact upon thymocyte selection processes in the ZAP70 SKG mouse model.[45] Together, these studies suggest that PTPN22 plays only a minor role in the thymus, and that disease-associated PTPN22 polymorphisms likely impact on peripheral rather than central tolerance mechanisms.

Non-cell intrinsic effects of PTPN22 on T-cells

PTPN22 function in additional cell types likely has an important effect on T-cell-driven inflammation. For example, in myeloid cells, rather than act as a negative regulator, PTPN22 enhances production of type 1 interferons (IFNs).[9,51] Conversely, PTPN22 negatively regulates type 1 IFN-receptor signalling pathways.[23,52] A clear example of cell-extrinsic effects of PTPN22 on T-cell function comes from studies of chronic viral infection. In

Table 1. PTPN22 and models of autoimmunity

Model	PTPN22 status	Genetic background	Impact on disease	Immunological features	References
EAE	KO	C57Bl/6	Protection	Protection involves increased Tregs	46
Colitis	KO	C57Bl/6	Exacerbated	Increased T-cell expansion	17
Lupus like disease	KO + CD45 E613R	C57Bl/6	Exacerbated	Enhanced effector/memory T-cells	40
Diabetes	Knock-down	NOD	Protection	Protection involves increased Tregs	43
Diabetes	Overexpression	NOD	Protection	Reduced Th1 functionality	44
Diabetes	R619W KI (CRISPR)	NOD	Exacerbated	Not assessed	42
Diabetes RIP-LCMV	KO	C57Bl/6	Exacerbated	Increased T effector function	47
Systemic autoimmunity	R619W (and STZ diabetes)	C57Bl/6x129/Sv	Exacerbated	B-cell restricted R619W expression sufficient to induce autoimmunity	41
SKG arthritis	KO	SKG	Protection	Biasing of Th17 differentiation toward Th1/Treg	45
SKG arthritis	Transgenic R620W	SKG	No difference	–	50
KBxN arthritis	KO	C57Bl/6	Exacerbated	Increased T follicular helper cells	32
KBxN arthritis	KO	C57Bl/6	Protected	Reduced neutrophil activation	6

this regard, several studies reported that PTPN22-deficient mice were more efficient at clearing chronic lymphocytic choriomeningitis virus (LCMV) infection.[51,53] *Ptpn22*$^{-/-}$ mice infected with the persistent LCMV clone 13 had increased numbers and function of virus-specific $CD4^+$ T-cells[51] and $CD8^+$ T-cells.[53] However, cell transfer studies and mixed bone marrow chimera experiments indicated that the ability of *Ptpn22*$^{-/-}$ T-cells to resist exhaustion, and therefore clear virus load more efficiently, was not cell-intrinsic.[51,53] Excessive production of type 1 IFN following infection can result in T-cell exhaustion.[54,55] Thus, reduced production of type 1 IFN by PTPN22-deficient myeloid cells enabled prolonged T-cell responses to clone 13 LCMV. Therefore, in addition to modulating TCR signalling directly, PTPN22 influences T-cell activation in a cell-extrinsic manner, complicating our experimental interpretation of both infectious disease and autoimmune mouse models.

PTPN22 and anti-tumour responses

There are several parallels between the regulation of autoimmunity and effective tumour immunosurveillance,[56,57] and while one is detrimental to the host, the

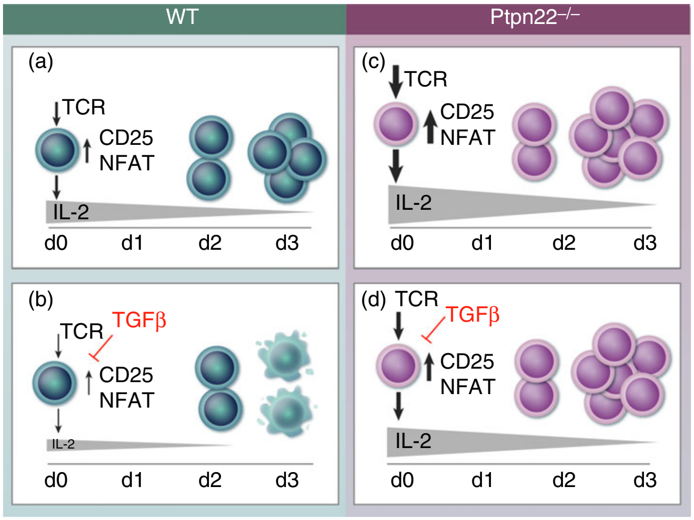

Figure 1. $CD8^+$ T-cells lacking PTPN22 have sufficiently strong T-cell receptor (TCR) signals to overcome transforming growth factor β (TGFβ)-mediated suppression. (a) Control T-cells stimulated through the TCR upregulate expression of transcription factors (TFs), activation markers such as CD25 and translocate NFAT into the nucleus within 24 hr. Subsequently, cells start to secrete IL-2 and proliferate. (b) TGFβ added at the start of control cell culture inhibits TCR-driven TFs, activation marker upregulation and NFAT translocation, resulting in lower levels of IL-2 production, thereby less cell proliferation and more cell death by d3. (c) TCR stimulation is stronger in *Ptpn22*$^{-/-}$ cells, resulting in more IL-2 and more cell proliferation. (d) TGFβ is less able to suppress strong TCR signals, allowing *Ptpn22*$^{-/-}$ cells to secrete enough IL-2 to proliferate and survive by d3.

other is desirable. Autoimmune T-cells respond to self-antigens and resist immune-regulatory mechanisms, such as those mediated by Tregs.[58,59] By contrast, anti-tumour T-cell responses are frequently hampered by a failure to respond to low-affinity tumour-associated antigens (TAA) adequately, and a hostile tumour microenvironment, characterized by the presence of suppressive cell types (Tregs) and ligands (PD-L1/2), limited nutrient and oxygen levels and high levels of immunosuppressive cytokines such as transforming growth factor β (TGFβ).

Adoptive cell transfer (ACT) of genetically engineered tumour-reactive T-cells or *ex vivo* expanded tumour-infiltrating lymphocytes (TILs) has had substantial success as a cancer immunotherapy.[60] Furthermore, modulation of intracellular signalling pathways in T-cells has the potential to improve the efficacy of anti-tumour ACT. Importantly, data indicate that, similar to their role in the regulation of auto-reactivity, inhibitory phosphatases limit T-cell anti-tumour activity.[61,62] In a recent study, we investigated the impact of PTPN22-deficiency on anti-tumour T-cell responses. Previous data showed that TGFβ plays a critical role in controlling autoreactive and anti-tumour T-cell responses, particularly to weak, self-ligand-mediated responses.[59,63] Interestingly, PTPN22-deficient CD8$^+$ T-cells were highly resistant to the suppressive effects of TGFβ.[64] This reduced susceptibility to TGFβ was not a consequence of alterations in canonical TGFβ-receptor signalling. Rather, enhanced TCR-driven IL-2 production in the absence of PTPN22 interfered with the suppressive function of TGFβ (Fig. 1). As a consequence of enhanced TCR signalling and concomitant reduced susceptibility to TGFβ, upon adoptive transfer, tumour-reactive PTPN22-deficient CD8$^+$ T-cells were better able to control the growth of established tumours that secreted TGFβ than wild-type T-cells.[64] These data suggest that deleting PTPN22 in human TILs or TAA-specific T-cells may improve the efficiency of T-cell immunotherapy of human cancer.

Concluding remarks

PTPN22 has emerged as a key regulator of T-cell activation, and effector responses in infection, autoimmunity and anti-tumour immunity. The deleterious role of PTPN22 polymorphisms in autoimmunity is well established, yet recent evidence in mice suggests that deletion of PTPN22 could also be harnessed as an approach to improve anti-tumour immunity. Future studies targeting PTPN22 in human T-cells will be required to determine the utility of such approaches in human disease. Furthermore, fundamental questions regarding the role of PTPN22 in T-cell memory and longevity remain outstanding. Thus, it is clear that deletion of PTPN22 enhances T-cell effector responses. Does this push T-cells to a short-lived effector phenotype and is development of T-cell memory affected? Finally, it has become apparent that PTPN22 has complex positive- and negative-regulatory effects in different immune cell types and signalling pathways. In future studies, the use of lineage-specific knockout or mutant mice should help clarify the precise role of PTPN22 in T-cells and other immune populations.

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Disclosures

None.

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