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Regulation of TCR signalling by tyrosine phosphatases: from immune homeostasis to autoimmunity

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Summary

More than half of the known protein tyrosine phosphatases (PTPs) in the human genome are expressed in T cells, and significant progress has been made in elucidating the biology of these enzymes in T-cell development and function. Here we provide a systematic review of the current understanding of the roles of PTPs in T-cell activation, providing insight into their mechanisms of action and regulation in T-cell receptor signalling, the phenotypes of their genetically modified mice, and their possible involvement in T-cell-mediated autoimmune disease. Our projection is that the interest in PTPs as mediators of T-cell homeostasis will continue to rise with further functional analysis of these proteins, and PTPs will be increasingly considered as targets of immunomodulatory therapies.

Keywords: protein tyrosine phosphatase; T-cell activation; T-cell receptor signalling; autoimmunity; tyrosine phosphorylation

Tyrosine phosphorylation in T-cell activation: the balance between tyrosine kinases and tyrosine phosphatases

Activation of T cells is largely mediated through signal transduction downstream from the T-cell receptor (TCR) expressed on the cell surface. The TCR is a transmembrane receptor complex comprised of α and β chains, which bind ligands, and CD3 (ε, γ and δ) and ζ chains containing motifs that are phosphorylated on tyrosine, called immunoreceptor tyrosine-based activation motifs. Signal transduction through the TCR is initiated when the receptor binds to a peptide–MHC complex presented by an antigen-presenting cell. This interaction initiates a cascade of signalling events, which induces the proliferation, mobilization and differentiation of T cells. For an updated and comprehensive review of signalling through the TCR the reader is referred to recent authoritative publications.[1–4]

A dynamic wave of tyrosine phosphorylation phenomena is critical for ignition of intracellular signalling in T cells. Engagement of the TCR leads to the activation of the Src family protein tyrosine kinases (PTKs) LCK and FYN, which phosphorylate the immunoreceptor tyrosine-based activation motifs of the TCR. This provides docking sites for the SH2 domains of ZAP-70, a Syk family PTK, allowing ZAP-70 to be phosphorylated and activated by LCK. Once activated, ZAP-70 phosphorylates the adaptor proteins SLP-76 and LAT, which nucleate signalling complexes, leading to the phosphorylation and activation of multiple downstream effectors. This results in calcium mobilization, activation of mitogen-activated protein kinases (MAPKs), transcriptional regulation and cytoskeletal rearrangements.

Protein tyrosine phosphatases (PTPs) are the natural counterpart of PTKs. Much like PTKs, depending upon the phosphorylation site and the signalling context, they can enhance or reduce the function of their protein target(s). The modern view of phosphorylation networks is one of dynamic 'always-on' grids where the stoichiometry of each phosphorylation site is continuously controlled by the changing balance between the activities of kinases and phosphatases. For example, the activation state of the Src family kinases (SFKs) is balanced between the activities of CSK and CD45, which respectively phosphorylate and dephosphorylate the inhibitory C-terminal site (Y505 of LCK), and the negative regulators LYP and SHP-1, which dephosphorylate an activating tyrosine in the catalytic domain (Y394 of LCK). Acute changes in PTP activity/expression are in principle sufficient to alter the network status and even trigger true signalling waves. The recent 'kinetic-segregation' model postulates that PTPs are responsible for the very initiation of signalling after engagement of the TCR.[5] In this model, acute removal of

PTPs from membrane areas where the interactions between the T cells and antigen-presenting cells occur results in an imbalance in the phosphatase–kinase equilibrium, which is sufficient to trigger a self-amplifying wave of activation of the SFKs.

The human genome encodes more than 100 PTPs classified into four classes (see refs. 6 and 7 for reviews of PTP classifications). T cells are known to express at least 60 of these enzymes, many of which have known roles as positive or negative regulators of TCR signalling.[8,9] The study of these PTPs in autoimmunity has obvious significance because TCR signalling impinges upon the pathogenesis of autoimmunity at multiple levels. For example, increased/decreased TCR signalling can alter selection at the thymic level, activation and differentiation of effector T cells, suppressive activity of regulatory T cells, and triggering and maintenance of peripheral anergy.[10–12] Here, after briefly reviewing the role of each PTP in TCR signalling (summarized in Fig. 1 and Table 1), we will also summarize whether there is any evidence available of an involvement of the enzyme in autoimmunity (summarized in Table 2). The classification system adopted in this review (Fig. 2) is the one described in Alonso *et al.*[6]

Class I enzymes

Receptor PTPs

CD45

CD45, encoded by the *PTPRC* gene, is a type 1 leucocyte-specific glycoprotein and a transmembrane PTP. CD45 is highly expressed in all nucleated haematopoietic cells and comprises about 10% of lymphocyte surface proteins.[13] The protein structure consists of a large extracellular domain, a short transmembrane segment and a cytoplasmic portion containing two PTP domains called D1 and D2; only the membrane-proximal domain D1 has tyrosine phosphatase activity, and it is necessary for TCR-mediated signal transduction.[14]

The role of CD45 in T-cell activation has been intensely studied and excellent focused reviews are available.[15–17] The best-characterized substrates of CD45 in T cells are the SFKs LCK and, to a lesser extent, FYN.[18–21] The negative regulatory site on SFKs (Y505 of LCK) is a bona fide substrate of CD45 in T cells, and there is substantial evidence of CD45 being a positive regulator of TCR signalling through dephosphorylation of this site.[22,23] CD45-deficient T-cell lines and thymocytes from $CD45^{-/-}$ mice exhibit increased phosphorylation of the inhibitory sites of LCK and FYN, and the thymic phenotype of $CD45^{-/-}$ mice (see below) is completely rescued by the expression of the constitutively active LCK Y505F mutant.[18,19,21,24–26] However, there is *in vitro* and *in vivo* evidence that CD45 is also able to dephosphorylate the positive regulatory site of LCK (Y394), and data in CD45-deficient cell lines suggest that CD45 may also behave as a negative regulator of T-cell activation.[27–30]

Deficiency of CD45 in both humans and mice leads to a severe-combined immunodeficiency, supporting a major positive regulatory role for CD45 in T-cell activation.[31–35] CD45-deficient mice, obtained by targeting exon 6,[33] exon 9[35] or exon 12,[34] exhibit a block in the double-positive to single-positive transition due to reduced signalling through the TCR. In CD45 knockout (KO) mice reconstituted with a titration of the CD45RO transgene, rescuing just 3% of the physiological CD45 expression was able to restore T-cell development.[36] When CD45 expression was increased to 30% of wild-type levels, increased CD4 and CD8 single-positive expansion was observed, suggesting a key positive role for CD45 in positive selection. However, in this system, increased levels of CD45 expression led to reduced phosphorylation of both LCK Y505 and Y394 sites, supporting the idea that CD45 can regulate both of the LCK tyrosine phosphorylation sites. A model has been postulated where high CD45 expression in T cells may be necessary to maintain the LCK Y394 site in a dephophorylated state to terminate TCR signalling.[36] Recently, a mouse with a CD45 'lightning' mutation was generated, in which the surface expression of CD45 is low, but the expression of all the isoforms (see below) is maintained. The authors showed that CD45 is differently required during basal and inducible TCR signalling. Once again, CD45 was found to have dual negative and positive roles in the regulation of thymic selection.[37]

A well-known observation is that multiple, highly conserved isoforms of CD45 are expressed on T cells at different developmental and activation stages, as the result of differential splicing of exons 4, 5 and 6.[13,38] Inclusion of exons 4, 5 or 6 is indicated by the presence of the letters A, B or C, respectively, in the isoform name. The most commonly observed are the larger isoform RB (which includes only exon 5), expressed on primary naive T cells, and the shortest isoform RO (which lacks all three exons), expressed in activated and memory T cells.[39] The molecular basis of this complex isoform regulation is becoming clear and the heterogeneous nuclear ribonucleoprotein L-like protein (hnRNPLL) has been recently identified as a key modulator of the expression pattern of CD45 isoforms.[40–42] On the other hand, the functional significance of the changes in CD45 isoform expression during T-cell differentiation/activation remains unexplained and several apparently contrasting observations have been reported. Early biochemical experiments showed that different isoforms of CD45 have similar PTP activity *in vitro*.[18] Studies carried out in $CD45^{-/-}$ mice made transgenic for various isoforms of CD45 showed that rescue of thymic development and peripheral T-cell numbers/functions was dependent on expression levels of

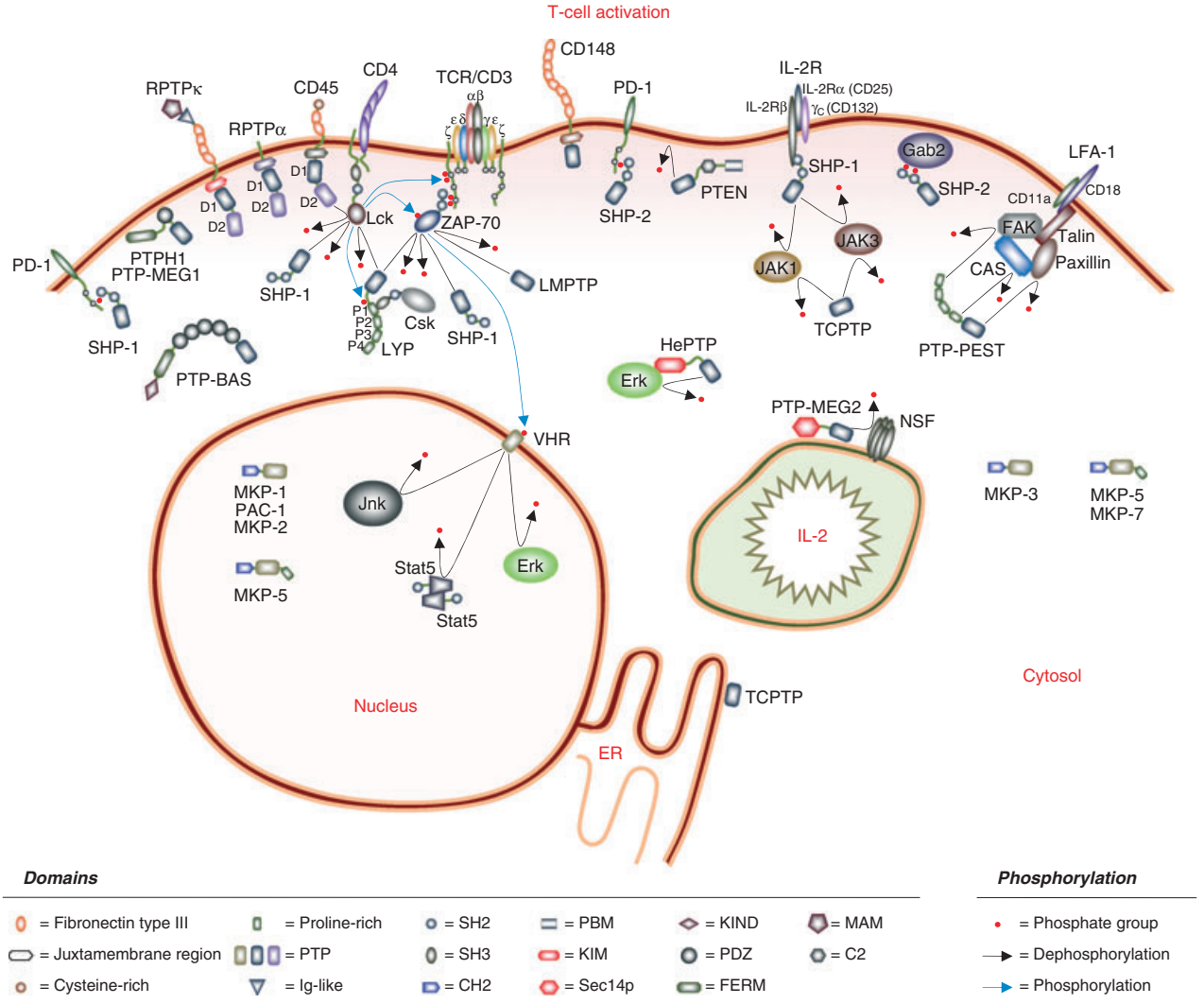

Figure 1. Schematic representation of the diverse functions of the protein tyrosine phosphatases (PTPs) regulating T-cell activation. The activation of a T cell involves tyrosine phosphorylation at multiple levels, and PTPs play diverse roles that work in concert together to cause the response of the T cell to the extracellular environment, to cause T-cell mobilization and to cause the production and response to cytokines such as interleukin-2 (IL-2). PTPs involved in these processes include transmembrane PTPs and intracellular membrane-proximal, cytosolic and nuclear PTPs. The initial response of a T cell to the external environment is finely tuned by PTPs regulating the early wave of phosphorylation events immediately proximal to the T-cell receptor (TCR), and many of the PTPs are found near the plasma membrane. These PTPs control the phosphorylation status of the Src family kinases (SFKs), the immunoreceptor tyrosine-based activation motifs (ITAMS) of the ζ chains and ZAP-70. Further downstream, PTPs control both membrane-proximal and cytosolic signalling effectors. Activation of mitogen-activated protein kinases (MAPKs) is spatially regulated by classical and dual-specific PTPs localized to the cytosol and/or nucleus. T-cell mobility is controlled by cytoskeletal rearrangements, involving multiple PTPs with protein–protein interaction domains and FERM (band 4.1–ezrin–radixin–moesin) domains that allow their association with complexes regulating the cytoskeleton and/or the plasma membrane. Post-transcriptionally, secretion of cytokines such as IL-2 requires phosphotyrosine-mediated vesicle formation. The autocrine response of T cells to extracellular IL-2 is mediated through tyrosine phosphorylation of signalling molecules downstream from the IL-2 receptor. An additional layer of modulation of the T-cell response is added through triggering of inhibitory receptors, whose function is mediated by cytosolic PTPs that can bind to the inhibitory motifs on these receptors.

the transgene, but was generally isoform-independent.[43–45] In contrast, CD45-deficient cell lines expressing the RO isoform were found to produce more interleukin-2 (IL-2) than cells expressing the RABC isoform after TCR engagement with MHC–peptide.[46] Additional studies in transgenic CD45$^{-/-}$ mice also found differences in phenotypic rescue between high- and low-molecular-weight isoforms.[47,48] Finally, in *in vitro* studies using mouse T cells, Seki *et al.*[49] showed that CD45 expressed on CD8^{+} T cells was less active than CD45 expressed on CD4^{+} T cells and correlated this difference to the distinctive expression pattern of CD45 isoforms between CD8^{+} (primarily

Table 1. Protein tyrosine phosphatases (PTPs) in T-cell activation

PTP	Gene name	Role in T-cell activation
CD45	*PTPRC*	Positively regulates TCR signalling by dephosphorylation of inhibitory site of LCK and FYN
CD148	*PTPRJ*	Positively regulates TCR signalling by dephosphorylation of inhibitory site of LCK; may also negatively regulate TCR signalling by dephosphorylation of LAT and PLCγ1
RPTPα	*PTPRA*	Positively regulates TCR signalling by dephosphorylation of inhibitory site of LCK and FYN
RPTPκ	*PTPRK*	Needed for development of $CD4^+$ T cells; mechanism unclear
LAR	*PTPRF*	Negatively regulates TCR signalling in thymocytes by dephosphorylation of LCK and FYN
LYP/Pep	*PTPN22*	Negatively regulates TCR signalling by dephosphorylation of inhibitory site of LCK, FYN, ZAP-70 and others; binds CSK
PTP-PEST	*PTPN12*	Negatively regulates TCR signalling by dephosphorylation of Cas, Pyk2, FAK, paxilin; binds CSK
SHP-1	*PTPN6*	Negatively regulates T-cell activation through ITIM/ITSM receptors, cytokine receptors, dephosphorylates LCK, ZAP-70 and others
SHP-2	*PTPN11*	Positively regulates T-cell activation by increasing ERK activation; binds Gab2; may also inhibit T-cell activation through ITIM/ITSM receptors
TCPTP	*PTPN2*	Negatively regulates T-cell activation by inhibiting IL-2 production
PTPH1	*PTPN3*	Inhibits TCR signalling when over-expressed by dephosphorylating immunoreceptor tyrosine-based activation motifs; dephosphorylates valosin-containing protein and interacts with TACE
PTP-MEG1	*PTPN4*	Inhibits T-cell activation when over-expressed
PTP-BAS	*PTPN13*	Inhibits apoptosis by binding CD95/FAS; regulates cytokine secretion by inhibiting STAT proteins
PTP-MEG2	*PTPN9*	Promotes secretion – necessary for secretory vesicle formation
HePTP	*PTPN7*	Negatively regulates TCR signalling by dephosphorylation of ERK and p38
MKP-1	*DUSP1*	Negatively regulates T-cell activation by dephosphorylation of MAPKs in nucleus
PAC-1	*DUSP2*	Negatively regulates T-cell activation by dephosphorylation of p38 and ERK in nucleus
MKP-2	*DUSP4*	Negatively regulates IL-2 signalling and proliferation of $CD4^+$ T cells through regulation of STAT5 phosphorylation
MKP-3	*DUSP6*	Negatively regulates T-cell activation by dephosphorylation of ERK in cytosol; may mediate TLR4-induced inhibition of TCR signalling
MKP-5	*DUSP10*	Negatively regulates T-cell activation by dephosphorylation of JNK in cytosol and nucleus
MKP-7	*DUSP16*	Regulates the balance between Th1/Th2 cells through dephosphorylation of JNK in cytosol
VHR	*DUSP3*	Dephosphorylates p38, ERK and STAT5; promotes cell-cycle progression
PTEN	*PTEN*	Opposes PI3K activity by dephosphorylating PIP_3; functions as tumour suppressor
LMPTP	*ACP1*	Positively regulates signalling by dephosphorylation of inhibitory site of ZAP-70; may prevent TCR clustering by inhibiting cytoskeletal rearrangement through FAK

ERK, extracellular signal-regulated kinase; IL-2, interleukin-2; ITIM/ITSM, immunoreceptor tyrosine-based inhibitory motifs/immunoreceptor tyrosine-based switch motifs; JNK, Jun N-terminal kinase; MAPK, mitogen-activated protein kinase; STAT5, signal transducer and activator of transcription; TCR, T-cell receptor; Th1, T helper type 1; TLR4, Toll-like receptor 4.

expressing CD45RBC) and $CD4^+$ (primarily expressing the RO and RB isoforms) T cells.

The phosphatase activity of CD45 is believed to be physiologically inhibited by dimerization in *trans* involving a specific juxtamembrane 'wedge' motif. Strong evidence in favour of a role for CD45 in autoimmunity was provided by the Weiss group who described the phenotype of mice carrying an inactivating point mutation (CD45E613R) in the inhibitory wedge motif. These mice express a constitutively active form of CD45 and display an autoimmune syndrome resembling human systemic lupus erythematosus (SLE).[50] Although thymic development was normal in these mice, double-positive thymocytes showed enhanced TCR signalling,[51] confirming a positive role for CD45 in T-cell development. In contrast, TCR activation was down-regulated in peripheral T cells.

T cells from patients with SLE show decreased CD45 expression or phosphatase activity compared with healthy controls, and show abnormal patterns of CD45 phosphorylation and isoform expression.[52–54] Altered CD45 isoform expression has been also associated with infantile cholestasis.[55]

A C77G polymorphism of CD45 abolishes the silencing of exon 4, causing an enhanced expression of the high-molecular-weight form of CD45 in all T-cell subpopulations.[56,57] This single nucleotide polymorphism (SNP) was first associated with multiple sclerosis by Jacobsen *et al.*,[58] but the association was not confirmed in subsequent studies.[59–62] The SNP is not associated with type 1 diabetes (T1D),[63,64] Graves' disease,[63] SLE,[65] Hashimoto's thyroiditis[66] or myasthenia gravis.[67] An association was found with autoimmune hepatitis,[68] and another study reported an increased frequency of the SNP in systemic sclerosis.[69] Another very rare polymorphism, C59A, causes aberrant splicing of *PTPRC* and was found in several members of a family with multiple sclerosis.[58]

Table 2. T cell protein tyrosine phosphatases (PTPs) and autoimmunity

PTP	Gene name	Autoimmune phenotype in mice	Autoimmune phenotype in humans
CD45	*PTPRC*	SLE-like disease in mice with constitutively active CD45	Genetic association with autoimmune hepatitis, myasthenia gravis and multiple sclerosis
LYP/Pep	*PTPN22*		Genetic association with multiple autoimmune diseases, including T1D, rheumatoid arthritis, SLE, Graves' disease, Hashimoto's thyroiditis, myasthenia gravis, generalized vitiligo, Wegener's granulomatosis
PTP-PEST	*PTPN12*	T-cell deletion reduces susceptibility to EAE	
SHP-1	*PTPN6*	*me/me* mice show systemic autoimmunity	
SHP-2	*PTPN11*		Located within linkage disequilibrium block that associates with coeliac disease, rheumatoid arthritis, T1D and Crohn's disease
TCPTP	*PTPN2*	T-cell deletion leads to spontaneous autoimmunity	Genetic association with T1D, rheumatoid arthritis and coeliac disease
MKP-1	*DUSP1*	KO mice show delayed EAE development	
MKP-5	*DUSP10*	KO mice protected from EAE	
PTEN	*PTEN*	Autoimmunity in KO heterozygous mice	
LMPTP	*ACP1*		Genetic association with T1D, Crohn's disease and ulcerative colitis

EAE, experimental autoimmune encephalitis; KO, knockout; SLE, systemic lupus erythematosus; T1D, type 1 diabetes.

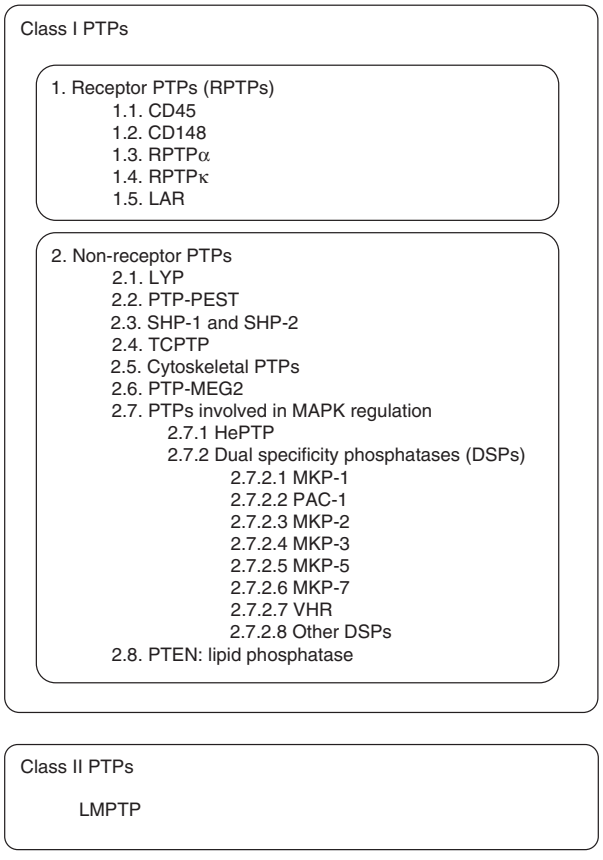

Figure 2. Classification scheme of the protein tyrosine phosphatases (PTPs) described in this review.

CD148

CD148, encoded by the *PTPRJ* gene, is a ubiquitous transmembrane PTP. It is structurally characterized by an extracellular domain consisting of eight fibronectin type III domains with multiple glycosylation sites, a cytoplasmic domain with a juxtamembrane wedge motif, and a single PTP domain.[70,71] Naive T cells exhibit low expression of CD148 and inducibly express the phosphatase after TCR stimulation.[72] Some differences in expression patterns of CD148 between human and mouse T cells have been reported.[73,74] A recent expression study confirmed that in mice, the expression of CD148 is high in double-negative thymocytes, drops significantly in single-positive thymocytes, and is nearly absent in peripheral blood T cells. In contrast, human thymocytes show an opposite pattern, with high expression in single-positive thymocytes and peripheral blood T cells.[75] Over-expression studies in Jurkat cells indicate that CD148 inhibits phosphorylation of phospholipase Cγ1 and LAT, causing down-regulation of TCR signalling.[76] In over-expression studies in CD45-negative JS-7 T cells, CD148 was also able to dephosphorylate the negative regulatory tyrosine residue of SFKs, suggesting that in certain circumstances, CD148 might be able to promote TCR signalling.[75] Interestingly, the extracellular domain of CD148 mediates the exclusion of the phosphatase from the immunological synapse. After T-cell–antigen-presenting cell disengagement, the access of CD148 to its substrates is reconstituted, causing down-regulation of TCR signalling, suggesting a role for CD148 in tempering long-term signalling in T cells.[77]

RPTPα

RPTPα, encoded by the *PTPRA* gene, is a ubiquitous transmembrane PTP expressed at low levels in lymphoid tissues.[78] Like CD45, RPTPα functions to

dephosphorylate SFKs on their inhibitory tyrosine residue.[79] However, studies have shown that CD45 and RPTPα are not redundant PTPs.[80,81] RPTPα could not compensate for loss of CD45 in dephosphorylation and activation of LCK or FYN in a CD45-deficient T-cell line, and showed lower *in vitro* activity than CD45 on Src-derived phosphopeptides and on recombinant LCK.[80] Unlike CD45, RPTPα KO mice show a benign immune phenotype.[81] Resting thymocytes from RPTPα-deficient mice showed enhanced phosphorylation of FYN on both tyrosines 417 and 528, and increased FYN activity, indicating that RPTPα may act as a negative regulator of FYN in unstimulated thymocytes. After TCR stimulation, the same thymocytes showed no differences in tyrosine phosphorylation, but had impaired proliferation and IL-2 response. A recent study suggested that RPTPα is itself regulated by CD45 through dephosphorylation at Tyr789.

RPTPκ

RPTPκ, encoded by the *PTPRK* gene, is a ubiquitous transmembrane PTP whose expression is induced by transforming growth factor-β.[82,83] An important role for RPTPκ in T-cell development was hypothesized following the discovery that *Ptprk* is deleted in the LEC rat, a model that displays a monogenic recessive immunodeficiency (called T helper immunodeficiency or *Thid*).[84,85] The *Thid* phenotype is characterized by hypoplasia of the thymus and spleen, reduced levels of IgG, selective deficiency in CD4 single-positive T cells, and strongly reduced T helper function.[86] The CD4 single-positive T-cell deficiency is attributed to anomalous development of T cells in the thymus, and was replicated in the mouse by bone marrow reconstitution of irradiated animals with double-negative cells transduced with dominant-negative RPTPκ.[84] However the role of *Ptprk* in the *Thid* phenotype has been partially called into question after the discovery that the genomic deletion of the LEC rat also inactivates a neighbouring gene encoding *Themis*, a recently identified key regulator of thymic development.[87] *In vitro*, a reduction of extracellular signal-regulated kinase (ERK) phosphorylation has been described in LEC thymocytes and in T cells after knock-down of *Ptprk*; however, the biochemical basis of this phenomenon and the substrate of RPTPκ in T cells are unclear at the moment.[88]

LAR

LAR, a transmembrane PTP encoded by the *PTPRF* gene, is expressed in thymocytes and has been suggested to negatively regulate TCR signalling in thymocytes through dephosphorylation of LCK and FYN.[89,90]

Non-receptor PTPs

LYP

The lymphoid phosphatase (LYP) is a cytosolic PTP encoded by the *PTPN22* gene.[91] The structure of LYP includes an N-terminal PTP domain, an interdomain region, and a C-terminal domain that contains four proline-rich motifs, termed P1–P4.[91,92] The P4 motif is located within a C-terminal homology domain (CTH) that is also present in the phosphatases PTP-PEST and BDP1.[93] LYP and its mouse orthologue Pep are expressed only in haematopoietic cells.[91,92]

In T cells, LYP/Pep function as potent negative regulators of T-cell activation through inhibition of early signalling downstream of the TCR. Initial over-expression studies in cell lines revealed that Pep had an inhibitory role in TCR signalling by dephosphorylation of positive regulatory tyrosines on LCK, FYN and ZAP-70.[94–96] Substrate trapping experiments later identified LCK (Y394), ZAP-70 (Y493), the CD3ζ chain, VAV, CD3ε, and valosin-containing protein as substrates of LYP in T cells.[97] LYP/Pep are powerful inhibitors of TCR signalling in *ex vivo* over-expression and inhibition systems.[98–103] The phenotype of the *Ptpn22* knockout mouse further supports the view of Pep as a negative regulator of TCR signalling.[104] These mice display increased positive selection, an expanded $CD4^+$ and $CD8^+$ effector/memory T-cell compartment, and hyper-responsiveness of effector/memory T cells to TCR engagement. Interestingly, a similar enhanced response to TCR engagement was not observed in naive T cells.

In T cells, numerous studies have shown that a high stoichiometry complex is formed between the P1 motif of LYP/Pep and the SH3 domain of CSK.[94,95,99,103,105–107] Due to the known inhibitory role of CSK in regulating the SFKs, it has been proposed that the constitutive Pep–CSK complex functions to synergistically repress LCK and FYN activity through combined phosphorylation of the inhibitory tyrosine by CSK and concurrent dephosphorylation of the activating phosphotyrosine by LYP.[95,96] However, recent studies from our group focused on the W620 variant of the human phosphatase, which lacks association with CSK (see below), suggest that CSK might behave as an inhibitor of the phosphatase activity as well. In the proposed model, CSK recruits LCK to LYP, which leads to phosphorylation of LYP on an inhibitory tyrosine residue Y536, and consequent reduction of the phosphatase activity. Hence the CSK–LYP complex is part of a positive LCK–LYP feedback loop, which might function to maintain LCK in an activated state after TCR stimulation and so sustain signalling through the TCR.[103]

Recent molecular and structural analyses have provided insight into additional modes of regulation of LYP. Crystal structure analysis revealed that the catalytic

domain contains a LYP-specific loop.[101,102,108] In this region a serine (S35) was identified that is phosphorylated by PKC, resulting in a decrease of catalytic activity.[101] Another structure solved by our group showed that the catalytic cysteine (C227) forms a disulphide bond with an additional cysteine residue (C129), which can also regulate the activity through a reversible oxidation mechanism.[108] LYP also seems to be regulated by intramolecular interactions between the catalytic domain and the proximal interdomain region, suggesting a possible mechanism of action of post-translational modifications outside the catalytic domain.[109]

The critical role of PTPs in immune homeostasis is exemplified in the discovery of the association of *PTPN22* with multiple human autoimmune diseases. This was first documented in 2004 when an SNP (C1858T) in the *PTPN22* gene was reported to increase the risk of T1D,[105] rheumatoid arthritis[99] and SLE.[110] The association with T1D, rheumatoid arthritis and SLE has been confirmed in multiple populations (reviewed in ref. 111). The T1858 allele was also found to increase the risk of juvenile idiopathic arthritis,[112,113] Graves' disease,[114–117] Hashimoto's thyroiditis,[118] Addison's disease,[115,119] myasthenia gravis,[120–122] generalized vitiligo,[123,124] systemic sclerosis,[125] alopecia areata,[126] psoriatic arthritis[127,128] and Wegener's granulomatosis.[129] Interestingly, the *PTPN22* C1858T allele is not associated with multiple sclerosis, coeliac disease, psoriasis and ulcerative colitis,[130,131] and has a protective effect against Crohn's disease and Behçet's disease.[132–134]

The presence of the C1858T SNP causes a substitution from arginine to tryptophan at amino acid 620 (R620W), which impairs the binding of LYP to CSK. The functional effect of the substitution is still somehow controversial. Some observations from our group and others suggest that LYP-W620 is a gain-of-function form of the phosphatase.[100] T cells from patients with T1D carrying the T1858 allele showed decreased T-cell activation as evidenced by reduced TCR-induced IL-2 secretion[100,135] and decreased calcium mobilization after TCR engagement.[136] Reduced TCR-mediated calcium mobilization and IL-10 secretion was also seen in memory T cells from healthy C/T carriers compared with homozygous C/C healthy subjects. However, this pattern was only seen in memory and not naive T cells. Consistent with the data from primary T cells, over-expression studies comparing the LYP-R620 and LYP-W620 variants showed that LYP-W620 is indeed a more potent inhibitor of TCR signalling and T-cell activation.[100,103] These findings are in contrast to two recent reports claiming that the W620 variant is a hypomorphic allele.[137,138] In one study also based on over-expression of the two phosphatase variants, Jurkat cells co-transfected with LYP-W620 and CSK were less responsive to TCR stimulation than cells co-transfected with CSK and LYP-R620.[137] In another study, a mouse carrying the W619 knock-in mutation of Pep (the homologous site to LYP-W620) was characterized. T cells from these mice showed increased proliferation and phosphorylation of ERK in response to TCR engagement compared with WT mice.[138] The authors found reduced expression of Pep as a result of increased calpain and proteasome-mediated cleavage in mice carrying the W619 allele. They also show reduced expression of LYP in homozygous carriers of the T1858 allele, and increased proliferation and phosphorylation of ERK in T cells of these individuals in response to TCR stimulation.

PTP-PEST

PTP-PEST, encoded by the *PTPN12* gene, is a ubiquitous cytosolic PTP expressed in most non-haematopoietic and haematopoietic cell types.[139–141] The structure of PTP-PEST is characterized by an N-terminal PTP domain, a central protein–protein interaction domain containing proline-rich motifs, and a conserved C-terminal tail.

Studies in non-immune cells have shown that PTP-PEST is involved in the regulation of cell migration and cytoskeletal reorganization by dephosphorylation of focal adhesion proteins, such as Cas[142] and paxillin.[143] In human and mouse naive $CD4^+$ and $CD8^+$ T cells, PTP-PEST expression is down-regulated after TCR activation.[144] In T cells early studies showed that PTP-PEST regulates signalling proteins involved in TCR activation, such as Cas, Pyk2 and FAK and behaves as a negative regulator of TCR signalling.[145] Studies in $CD4^+$ T cells from TCR transgenic mice showed that over-expressed PTP-PEST inhibited immunological synapse formation, correlating with an impaired phosphorylation of WASP.[146] Over-expression studies in Jurkat T cells and primary human T cells also pointed to a possible role of PTP-PEST as a negative regulator of TCR activation.[144] However, the physiological role of PTP-PEST in T-cell function in mice could not be confirmed until recently because global KO of PTP-PEST in mice causes early embryonic lethality.[147]

The Veillette group recently generated a conditionally deleted allele of *Ptpn12* in T cells and showed that PTP-PEST plays a critical role in secondary T-cell activation without altering T-cell development and primary T-cell response.[148] The phenotype was attributed to increased phosphorylation of Pyk2 and correlated with a decrease in T-cell aggregation during secondary T-cell activation. Importantly, mice deficient in PTP-PEST in T cells were less susceptible to development of experimental autoimmune encephalitis (EAE) compared with wild-type mice, providing evidence that PTP-PEST may contribute to the development of autoimmune diseases through action at the T-cell level.

SHP-1 and SHP-2

Although structurally similar, the cytoplasmic SH2-domains containing phosphatases SHP-1 and SHP-2 are distinct PTPs, both in their expression profiles and in their function. SHP-1 is encoded by the *PTPN6* gene. It is expressed in all haematopoietic lineages at all stages, and at lower levels in epithelial cells and in the olfactory neuroepithelium.[92,149–151] Several isoforms have been reported and two distinct transcription initiation sites regulate *PTPN6* expression in haematopoietic or non-haematopoietic tissues.[152,153] SHP-2, on the other hand, is ubiquitously expressed.[154,155]

Both SHP-1 and SHP-2 are cytosolic PTPs comprised of two tandem N-terminal SH2 domains, a central catalytic PTP domain, and a C-terminal tail. They are about 60% homologous. Both are regulated by intramolecular folding, in which the N-terminal SH2 domain binds to the catalytic pocket of the PTP domain, preventing substrate binding and reducing the phosphatase activity.[156–160] Engagement of this SH2 domain by substrate binding releases this inhibition and activates the phosphatases. The C-terminal region may also be involved in intramolecular regulation of SHP-1, as truncation of the C-terminus leads to increased *in vitro* activity.[159,161] Both SHP-1 and SHP-2 are regulated by phosphorylation in the C-terminal region. Phosphorylation on Tyr536 and Tyr564 of SHP-1 and Tyr542 and Tyr580 of SHP-2 functions to regulate the activity of the phosphatase or provide docking sites for interactors containing SH2 domains, including Grb2.[162–166]

SHP-1 contains a C-terminal motif (SKHKED, amino acids 557–562) that mediates a constitutive localization of about 20–30% of SHP-1 to lipid rafts.[167] The localization to lipid rafts appears to be essential for SHP-1-mediated inhibition of TCR signalling. Extensive literature is already available regarding the role of SHP-1 in the immune system, and the reader is referred to several excellent reviews.[168–171] In T cells, SHP-1 acts as an inhibitor of TCR signal transduction and a regulator of the T-cell activation threshold.[172,173] Thymocytes and mature peripheral T cells deficient in SHP-1 show increased responses to TCR stimulation, demonstrating increased activation of SFKs and other signalling intermediates, increased IL-2 production and increased proliferation.[172,174,175] After TCR engagement, SHP-1 is activated by LCK-mediated phosphorylation and is recruited to the TCR complex, where it can dephosphorylate signalling molecules such as LCK, ZAP-70, PI3K, VAV, SLP-76 and CD3ζ.[170,176,177] The inhibitory role of SHP-1 is dependent upon the strength of the TCR signal.[177] Weaker, antagonistic signals cause rapid recruitment of SHP-1 to the TCR. There, in a negative feedback regulation loop, SHP-1 is phosphorylated on Tyr564 by LCK. This in turn promotes interaction between SHP-1 and the SH2 domain of LCK, and subsequent dephosphorylation and inactivation of LCK by SHP-1. On the other hand, stronger, agonistic TCR signals lead to ERK activation, followed by phosphorylation of LCK on Ser. This induces a conformational change in LCK, inhibiting binding of LCK to SHP-1 and the subsequent inactivation of LCK, leading to more sustained signalling through the TCR.[177] In T-cell development, SHP-1 participates in setting the thresholds for both positive and negative selection of thymocytes.[172,173,178,179] SHP-1 deficiency causes hyperresponsiveness of thymocytes to TCR stimulation, and leads to increased positive and negative selection. A more recent study shows that conditional knockout of SHP-1 in mature single-positive T cells limits the production of $CD8^+$ effector T cells, but does not affect the formation of long-lived central memory cells.[180]

SHP-1 inhibits T-cell activation through additional mechanisms as well. SHP-1 is a downstream mediator of signalling through inhibitory receptors in immune cells. These receptors are characterized by motifs called immunoreceptor tyrosine-based inhibitory motifs (ITIMs) or immunoreceptor tyrosine-based switch motifs (ITSMs) in their intracellular region, which become phosphorylated on tyrosine and recruit SHP-1 through its SH2 domains. Examples of such receptors expressed in T cells are CEACAM1, CD5, PD-1, BTLA and CD22.[181–187] SHP-1 also regulates signalling through cytokine receptors, for example, inhibiting the IL-2 receptor (IL-2R) signalling pathway by binding to the IL-2Rβ chain and reducing phosphorylation of the IL-2Rβ and the downstream Janus PTKs JAK1 and JAK3.[188]

The well-described phenotype of the *motheaten* mouse (*me*/*me*) has demonstrated the critical role of SHP-1 as a regulator of haemopoietic cell function.[169,174,175,189] A splicing mutation at the SHP-1 locus leads to a frameshift in the coding sequence of the transcript, resulting in no expressed protein. *me*/*me* mice are characterized by systemic inflammation and autoimmunity, with developmental abnormalities in macrophages, granulocytes, T cells, B cells, natural killer cells, erythrocytes and mast cells.[174] The phenotype of the *motheaten* mouse and several other studies have suggested that SHP-1 expression levels or activity can affect autoimmunity in humans and mice, however the mechanism of action of SHP-1 in autoimmunity is probably only partially mediated by an action on TCR signalling. A subset of patients with SLE exhibit lower expression levels of SHP-1 and CD45 in B cells.[39] Another study showed that T cells from psoriatic skin lesions have lower expression of SHP-1, which correlates with increased sensitivity to interferon-α through increased activation of JAK and signal transducer and activator of transcription (STAT).[190] Mice with partial inhibition of SHP-1 ($me^{v+/-}$) show worsened MOG-peptide-induced EAE, which includes an increased T-cell response.[191]

SHP-2, encoded by the *PTPN11* gene, is considered a key regulator of receptor-mediated signalling in many cell types. Indeed, the importance of SHP-2 is demonstrated by the embryonic lethality of mice with homozygous deletion of the PTP[192] and the requirement of SHP-2 for lymphocyte development.[193] In T cells, SHP-2 has generally been regarded as a positive regulator of signalling through the TCR. Conditional deletion of SHP-2 in T cells impairs thymocyte differentiation and proliferation, reduces the expansion of $CD4^+$ T cells, and inhibits T-cell activation as evidenced by impaired TCR-induced ERK activation, proliferation, production of activation markers and production of IL-2.[194] SHP-2 has also been suggested to inhibit T-cell adhesion by dephosphorylating ADAP and VAV1 proteins through association with the LAT-Gads-SLP-76 signalling complex.[195] Aside from the TCR, SHP-2 also mediates cytokine receptor signalling. Upon interleukin receptor engagement, SHP-2 binds to the adaptor protein Gab2, an association that promotes the activation of ERK.[196–198] In contrast to its generally regarded role as a potentiator of T-cell activation, SHP-2, like SHP-1, is also involved in inhibitory receptor signalling in T cells and other immune cells. In T cells, for example, SHP-2 has been found to interact with and mediate the inhibitory effect of ITIM-containing and ITSM-containing receptors such as PECAM-1,[199] PD-1[183] and BTLA.[186,187] A genome-wide association meta-analysis showed the *PTPN11* gene was included within a linkage disequilibrium block with shared association for coeliac disease and rheumatoid arthritis,[131] and a genome-wide association analysis showed that *PTPN11* was included in a linkage disequilibrium block with T1D association and with weak Crohn's disease association;[200] however, fine mapping and characterization of the responsible variants is still under investigation.

TCPTP

T-cell protein tyrosine phosphatase (TCPTP) is encoded by *PTPN2*, which recently emerged as a major autoimmunity gene. This PTP is ubiquitously expressed, with the highest expression found in haematopoietic and placental tissues.[201] Two different TCPTP splice variants have been identified: a 45 000 molecular weight form, which is mostly localized in the nucleus[201,202] and a 48 000 molecular weight form localized in the endoplasmic reticulum.[201,203]

The major TCPTP substrates in T cells have been identified as JAK1 and JAK3, and TCPTP has been shown to regulate downstream phosphorylation of STAT proteins, suggesting a role for this phosphatase in cytokine receptor signalling. $TCPTP^{-/-}$ T cells showed decreased phosphorylation of STAT5 in response to IL-2 stimulation and of STAT1 in response to interferon-α and interferon-γ stimulation.[204] It has also been suggested that TCPTP dephosphorylates nuclear STAT1, which is dependent upon arginine methylation of the STAT1 protein.[205]

Some insights into the role of TCPTP in T-cell activation emerged from the characterization of the global TCPTP KO mouse. These mice die between the second and third weeks after birth and show significant splenomegaly, lymphadenopathy and thymic involution, with a reduction in $CD4^+$ $CD8^+$ thymocytes evident by 3 weeks of age.[206] A defect in T-cell proliferation after anti-CD3 or concanavalin A stimulation was also described in these mice.[206,207] However, no defects in early TCR signalling (calcium mobilization and CD3 induced tyrosine phosphorylation) were found.[207] These findings correlated well with over-expression studies showing that TCPTP does not affect TCR-induced IL-2 gene activation,[203] suggesting that TCPTP is not involved in early TCR signalling. In contrast, a recent study with mice carrying a conditional deletion of TCPTP in T cells suggested that TCPTP is a key regulator of early TCR signalling through dephosphorylation of the active regulatory site of the SFKs LCK and FYN.[208] Notably, these mice showed spontaneous development of anti-nuclear antibodies and T-cell infiltration of the lungs and liver. Transfer of $CD8^+$ T cells was able to replicate this autoimmune phenotype in syngeneic animals. The importance of this study lies in its support of the concept that a loss-of-function of TCPTP in T cells is sufficient to trigger autoimmunity.

The first association between *PTPN2* and autoimmune disease was described in a genome-wide association study in which an SNP rs2542151 5·5 kb upstream of *PTPN2* was found to be associated with coeliac disease, T1D and rheumatoid arthritis.[200] These associations were replicated in other studies.[209,210] A new follow-up analysis confirmed the association between the rs2542151 SNP of *PTPN2* and T1D and found two new SNPs in the *PTPN2* gene associated with T1D.[211] A recent study showed that $CD4^+$ T cells from healthy controls carrying the rs1893217 SNP showed reduced pSTAT phosphorylation in response to IL-2 stimulation, correlating with decreased *PTPN2* RNA levels. This suggests that this genetic variant functionally alters the IL-2 signalling pathway in T cells, resulting in reduced expression of FoxP3.[212] However, it is currently unclear how this finding can be reconciled with the known negative role of TCPTP in STAT5 activation and the recent finding that deletion of TCPTP in T cells leads to increased numbers of regulatory T cells in mice.[208]

Cytoskeletal PTPs

Four cytosolic PTPs – PTPH1, PTP-MEG1, PEZ and PTP-BAS contain a FERM domain (band 4.1–ezrin–radixin–moesin), and are referred to as the cytoskeletal PTPs.[203] They are expressed in T cells and all lymphoid organs but their expression varies during development.

PTPH1 and PEZ are more expressed early in development, whereas PTP-MEG1 expression is higher in more mature lymphoid cells.[203] The four enzymes contain an N-terminal FERM domain, a central region, and a C-terminal PTP domain. Of these, PTPH1 and PTP-MEG1 contain a central PDZ (postsynaptic density-95-discs-large-ZO-1) domain, whereas PTP-BAS contains five central PDZ domains, as well as a very N-terminal putative kinase non-catalytic C-lobe domain (KIND). Both PTPH1 and PTP-MEG1 associate with the plasma membrane through their FERM domain.[203] The function of PEZ (encoded by the *PTPN14* gene) in T cells has not yet been defined but the data available for the other three PTPs are summarized below.

PTPH1, encoded by the *PTPN3* gene, is expressed in a variety of tissues including haematopoietic, colorectal, gastric and hepatic tissues.[213] PTPH1 has been considered a negative regulator of TCR signalling through dephosphorylation of the TCRζ chain.[214,215] Over-expression of PTPH1 in Jurkat cells inhibited TCR-induced activation of MAPKs and activation of an IL-2 promoter.[215] The FERM domain is required for this effect, because deletion of this region inhibited the localization of PTPH1 to the plasma membrane[203] and its ability to inhibit TCR signalling.[215] Additional substrates/interactors of PTPH1 have been proposed, suggesting that PTPH1 may have additional roles in the function of T cells and other cell types. PTPH1 dephosphorylates the valosin-containing protein, a hexameric ATPase, which has numerous functions, including regulation of the cell cycle and membrane vesicle fusion.[216] Through its PDZ domain, PTPH1 binds to the C-terminal tail of the tumour necrosis factor α-convertase (TACE), a metalloprotease-disintegrin involved in ectodomain shedding of proteins.[217] PTPH1 was also recently shown to dephosphorylate p38γ and promote Ras signalling.[218]

PTP-MEG1, encoded by the *PTPN4* gene, was first cloned from a megakaryoblastic cell line and HUVEC cDNA libraries.[219] PTP-MEG1 is expressed in most tissues, including lymphoid tissue[220] and was shown to inhibit TCR-induced T-cell activation when over-expressed in Jurkat cells.[215,221]

PTP-BAS, encoded by the *PTPN13* gene, is expressed in most tissues, and with a molecular weight of about 270 000 it is the largest non-receptor PTP.[222] PTP-BAS has been ascribed multiple functions, among which are inhibition of apoptosis through regulation/inhibition of the cell surface expression of FAS/CD95.[223] A study in $CD4^+$ T cells showed that PTP-BAS regulates cytokine signalling through dephosphorylation and inhibition of STAT4 and STAT6 activation.[224]

Surprisingly, a recent study in KO mice failed to support a role for the cytoskeletal PTPs in TCR signalling. Mice lacking the PTP domain of PTPH1 or PTP-MEG1 showed no difference in T-cell development or TCR-mediated signal transduction,[221,225] although the PTPH1 KO mice did exhibit enhanced growth due to increased growth hormone signalling.[226] Double-deficient *PTPN3*/*PTPN4* and triple-mutant mice that were null for *PTPN3*/*PTPN4* and lacking the PTP domain of PTP-BAS mice also showed no alterations in T-cell development or TCR-induced cytokine production or proliferation.[220]

PTP-MEG2

PTP-MEG2, encoded by the *PTPN9* gene, was originally cloned from a megakaryocyte cell line[227] and is expressed in many cell types, including T cells. It is unique among the PTPs, containing an N-terminal lipid-binding domain with homology to cellular retinaldehyde-binding protein and yeast protein Sec14p with phosphatidylinositol transfer activity.[227] Through this domain, PTP-MEG2 is found co-localized with PIP_3[228] on the cytoplasmic face of secretory vesicles and regulates secretory vesicle size and fusion via dephosphorylation of *N*-ethylmaleimide sensitive factor on an inhibitory Y83 residue.[229] Through dephosphorylation and activation of *N*-ethylmaleimide sensitive factor, PTP-MEG2 promotes homotypic fusion of secretory vesicles. Over-expression of PTP-MEG2 in Jurkat cells was shown to cause enlargement of the size of secretory vesicles, which required the catalytic activity of the phosphatase.[230] PTP-MEG2 binds to and is activated by PIP_2, PIP_3 and phosphatidylserine, providing a mechanism by which phosphorylation of inositides is coupled to downstream vesicle trafficking events.[228,229,231] Characterization of PTP-MEG2 knockout mice confirmed the profound effect of PTP-MEG2 on vesicle formation.[232] PTP-MEG2-deficient mice are embryonic lethal, however, PTP-MEG2 deficiency in haematopoietic cells was studied by transferring haematopoietic progenitors from fetal livers into irradiated $Rag2^{-/-}$ mice.[232] T cells isolated from the recipient mice were defective in their secretion of IL-2 and several other cytokines, although the intracellular levels of IL-2 were unaffected. Electron microscopy analysis revealed that T cells from these mice have reduced numbers of mature secretory vesicles.

PTPs involved in regulation of MAPKs

There are three major subfamilies of MAPKs that are expressed in the immune system: ERK, p38 and Jun N-terminal kinase (JNK) (reviewed in [233–235]). All contain a TxY motif in the activation loop of the kinase that can be phosphorylated on the threonine and the tyrosine. MAPKs are activated by phosphorylation on both residues. Their inactivation is mediated by dephosphorylation by three types of phosphatases – pSer/pThr phosphatases (which do not belong to the PTP family), and two types of PTPs, the pTyr-specific PTPs, and the dual-specific PTPs (DSPs). The DSPs can dephosphorylate pTyr, pSer

or pThr and include a subclass of PTPs that contain a MAPK-binding domain. A second subclass of 'atypical' DSPs lacks this domain, but some atypical DSPs still function to dephosphorylate MAPKs. Although regulators of the MAPKs appear to be critical for proper function of T cells and other cell types, no associations between any of these phosphatases and human autoimmunity have been reported. This review will highlight some of the MAPK regulators involved in T-cell activation.

HePTP

HePTP, encoded by the *PTPN7* gene, is a cytosolic PTP containing an N-terminal kinase interaction motif (KIM) and a PTP domain.[236] Two other members of this subclass are STEP and PTP-SL. All three of these PTPs dephosphorylate MAPKs on the activating phosphotyrosine residue.[237,238] Of this family, only HePTP is expressed exclusively in haematopoietic cells, in all lineages,[239,240] with high expression in T cells.[241]. HePTP is considered a negative regulator of T-cell activation through dephosphorylation of the pY in the activation loop of the MAPKs ERK and p38.[238] This inhibitory action requires the association of HePTP through the KIM with ERK1, ERK2 and p38, and provides selectivity, as HePTP does not interact with JNK.[238,241–243] In resting T cells, through its KIM, HePTP associates with the inactive forms of ERK and p38 in the cytosol.[238,241] This complex is disrupted by phosphorylation of HePTP on S23 by PKA (in KIM)[244,245] or on T45 and S72 by MAPKs/ERK outside the KIM.[238] Upon TCR stimulation, phosphorylation of HePTP on S23 causes the MAPKs to dissociate. HePTP remains in cytosol, while ERK and p38 move to the nucleus.[246] An additional regulation mechanism of HePTP during TCR signalling is through phosphorylation by PKCθ. HePTP translocates to the immune synapse upon TCR stimulation, where it is phosphorylated on S225 by PKCθ. This then targets HePTP to lipid rafts, where it inhibits TCR signalling.[247] HePTP$^{-/-}$ mice have no T-cell development, differentiation, or functional phenotype, with the exception of increased TCR-induced ERK and p38 activation.[243]

Dual specificity phosphatases

MKP-1

MKP-1, encoded by the *DUSP1* gene, is a nuclear DSP that predominantly dephosphorylates and inactivates p38 and JNK in response to stress.[248] MKP-1 has been considered a negative regulator of the innate immune response.[249] A study of the Mkp-1$^{-/-}$ mouse recently demonstrated the importance of MKP-1 in T-cell function.[250] Mkp-1-deficient mice showed normal T-cell development; however, T cells from these mice showed increased activation of JNK coupled with reduced expression of NFATc1. Both CD4$^+$ and CD8$^+$ T cells showed reduced IL-2 production and proliferation after TCR engagement. T cells from KO mice also demonstrated increased TCR-induced activation-induced cell death. Mkp-1 deficiency impaired effector functions of T helper type 1 (Th1), Th17 and CD8$^+$ T cells, but not Th2 cells. Consistent with their reduced T-cell function, Mkp-1$^{-/-}$ mice exhibited reduced antigen-specific T-cell responses *in vivo*. These mice exhibited defective viral clearance when challenged with influenza virus infection, and also delayed autoimmune development in the EAE model, possibly as a result of decreased CD4$^+$ T-cell function.

PAC-1

PAC-1, encoded by the *DUSP2* gene, is a nuclear DSP cloned from human T cells. It is primarily expressed in haematopoietic cells[251] and its expression is induced in activated leucocytes.[252,253] *In vitro* and over-expression studies showed that PAC-1 dephosphorylates and inactivates p38 and ERK.[254,255] Hence PAC-1 is believed to be the nuclear counterpart of HePTP and leads to nuclear inactivation of MAPKs, followed by their return to the cytosol, and reassociation with HePTP.[246] Unexpectedly, PAC-1-deficient mice show normal T-cell compartments.[253] However, studies in these mice showed that PAC-1 rather promotes inflammatory signalling in myeloid cells by suppressing the activation of JNK while increasing the activation of p38 and ERK1/2.

MKP-2

MKP-2, encoded by the *DUSP4* gene, is a nuclear DSP, expressed in both haematopoietic and non-haematopoietic tissues, which dephosphorylates ERK and JNK.[255] A role for MKP-2 in IL-2 signalling and CD4$^+$ T-cell proliferation was recently proposed by a study of *Dusp4*-deficient mice. CD4$^+$ T cells from these mice exhibited increased STAT5 phosphorylation, resulting in elevated CD25 expression and IL-2 signalling, and hyperproliferation of CD4$^+$ T cells.[256]

MKP-3

A role for the cytosolic MKP-3, encoded by the *DUSP6* gene, in setting the threshold for thymocyte-positive selection has been proposed.[257] Retroviral expression of Mkp-3 decreased ERK and JNK activation in T cells *in vitro*, while expression of a dominant-negative form of Mkp-3 increased their activation. In the same study, transduction of bone marrow cells with a construct encoding dominant-negative Mkp-3, followed by transfer of these cells into irradiated mice, resulted in increased positive selection of resulting thymocytes. MKP-3 may

also function as a regulator of cross-talk between TLR4 and TCR signalling in $CD4^+$ T cells, mediating an inhibitory effect of TLR4 signalling on subsequent TCR signalling by inhibition of ERK1/2 activation.[258]

MKP-5

MKP-5, encoded by the *DUSP10* gene, is constitutively expressed in naive $CD4^+$ T cells and is down-regulated by TCR stimulation.[259] The role of this DSP in T cells has been studied in mice lacking Mkp-5.[259] JNK, but not p38, was hyperactive in Th1 and Th2 cells from these mice. Naive $CD4^+$ T cells from these mice exhibited reduced proliferation upon TCR stimulation, however Th1, Th2 and $CD8^+$ effector T cells produced increased levels of cytokines after stimulation. These mice were protected from development of EAE, possibly through decreased T-cell proliferation.

MKP-7

Recent studies of MKP-7, encoded by the *DUSP16* gene, suggest that this DSP is involved in T helper cell differentiation.[260] MKP-7 shuttles between the nucleus and cytosol and preferentially dephosphorylates and inactivates JNK.[261] A recent study in mouse T cells showed that Mkp-7 is expressed in $CD4^+$ T cells, with lower expression in naive cells, increased expression in *in vitro* differentiated Th2 cells, and nearly absent expression in *in vitro* differentiated Th1 cells.[260] Several data support the concept that MKP-7 regulates the balance between Th1/Th2 cells through dephosphorylation of JNK. Overexpression of Mkp-7 *in vitro* enhanced Th2 differentiation, as evidenced by mRNA production of GATA-3 and IL-4, while causing only modest changes in Th1 differentiation, as shown by mRNA production of interferon-γ. $CD4^+$ T cells from transgenic mice over-expressing the active form of the phosphatase showed enhanced Th2, but not Th1, differentiation, while over-expression of inactive dominant negative Mkp-7 impaired Th2 differentiation. The authors of this study also demonstrated that upon immunization with OVA, transgenic mice over-expressing active Mkp-7 also displayed Th2-skewed production of OVA-specific IgG2a, IgG1 and IgE.[260]

VHR

VHR, encoded by the *DUSP3* gene, is an atypical DSP constitutively expressed in central and peripheral lymphoid organs.[262] VHR specifically inactivates ERK2 and JNK by dephosphorylation of the pTyr in the MAPK activation loop. Through this regulation of ERK2 and JNK, VHR acts as an inhibitor of T-cell activation.[263] VHR is recruited to the immune synapse upon TCR engagement, where it is phosphorylated on tyrosine by ZAP-70, a modification that is required for the inhibition of ERK2 and JNK. VHR also has additional roles in T cells and other cell types. It is required for cell cycle progression through dephosphorylation of ERK and JNK, and unlike many other DSPs, its expression is regulated by the cell cycle rather than by TCR or mitogenic stimuli.[264] VHR has also been recently reported to dephosphorylate STAT5.[265]

Other DSPs

Other DSPs have been implicated in the negative regulation of T-cell activation, for example MKP-6 (encoded by the *DUSP14* gene) has been shown to bind to CD28 in T cells and inhibit CD28 co-stimulation.[266] VHX (encoded by the *DUSP22* gene) was shown to inhibit activation of ERK2 and downstream NFAT/AP-1 reporter activity when over-expressed in Jurkat cells.[267]

PTEN: a lipid phosphatase

PTEN (phosphatase and tensin homologue), a ubiquitous phosphoinositide lipid phosphatase, is a unique member of the PTP family. By dephosphorylating PtdIns(3,4,5)P_3 (PIP_3), PTEN acts as an antagonist to the activity of phosphoinositide 3-kinase (PI3K).[268] PTEN is a well-known tumour suppressor that is involved in the regulation of T-cell function. Stimulation of the TCR, co-stimulatory molecules, or cytokine receptors of T cells activates PI3K, resulting in the production of PIP_3, a lipid second messenger critical for the propagation of downstream signal transduction. PTEN dephosphorylates and regulates the levels of PIP_3, controlling the strength and duration of signalling and activation of downstream pathways. PTEN effectively suppresses multiple T-cell functions, including cell cycle progression, adhesion, migration and survival.[269,270] Knockout of *Pten* causes embryonic lethality, and the partial deficiency of *Pten* in heterozygous mice leads to a lethal autoimmunity associated with reduced Fas-mediated apoptosis.[271,272] Conditional KO of *Pten* in T cells causes lymphadenopathy, splenomegaly, thymic enlargement, T-cell lymphoma, T-cell hyperproliferation, production of autoreactive T cells, impaired apoptosis, increased phosphorylation of ERK and AKT, and increased cytokine production.[269]

Class II enzymes: the LMPTP

The ubiquitously expressed low-molecular-weight PTP (LMPTP) is encoded by the *ACP1* gene. Two major isoforms have been isolated, called LMPTP-A (also called the Fast isoform, or ACP1-F) and LMPTP-B (also called the Slow isoform, or ACP1-S) arising from a splicing event in which either exon 3 or exon 4 is excised. The *ACP1* gene has a well-known polymorphism with three common codominant alleles, *called *A, *B, and *C* (reviewed in refs

273–275). These alleles affect both the total enzymatic activity and the ratio between isoforms A and B.[276,277]

LMPTP is involved in the regulation of growth factor signalling through dephosphorylation of a variety of growth factor receptors, which include platelet-derived growth factor receptor (PDGFR),[275,278] fibroblast growth factor receptor (FGFR),[279] insulin receptor (IR)[280] and ephrin receptor.[281] In T cells, LMPTP plays a positive regulatory role in TCR signalling through dephosphorylation of ZAP-70 on the negative regulatory tyrosine Y292.[282] Phosphorylation on this site provides a binding site for the c-Cbl ubiquitin ligase complex that inhibits TCR signalling by dephosphorylation and inactivation of ZAP-70 and through internalization of the TCR. The dephosphorylation of ZAP-70 by LMPTP consequently prolongs signal transduction through the TCR. Additionally, LMPTP may regulate T-cell cytoskeletal reorganization through dephosphorylation of FAK, which participates in regulating cytoskeletal rearrangement.[283] LMPTP was shown to dephosphorylate and inhibit FAK, which led to impairment of LFA-1-dependent T-cell adhesion and LFA-1 and TCR co-clustering. LMPTP may therefore control T-cell activation by preventing the cytoskeletal reorganization needed for LFA-1 and TCR clustering. The authors of this study propose a model where LMPTP enhances TCR signalling in the initial phases by dephosphorylation of ZAP-70, and then subsequently tempers signalling by reducing the cytoskeletal rearrangements needed for movement of membrane-associated signalling machinery.

The activity of LMPTP in T cells is enhanced by phosphorylation by the SFKs LCK and FYN on Y131. Y132 is also phosphorylated to a lesser extent.[284,285] Studies in other cell types have shown that phosphorylation of LMPTP on Y132 has no effect on the catalytic activity, and instead provides a docking site for the recruitment of Grb2, which promotes ERK activation, suggesting that LMPTP may regulate ERK activity in T cells as well.[286]

The *ACP1* polymorphism is associated with numerous disorders including cardiovascular, metabolic, neurological and autoimmune diseases.[274] Among autoimmune diseases, *ACP1* associates with inflammatory bowel diseases and T1D. Some studies suggest that ACP1 may influence Th1/Th2 orientation, in a gender-dependent manner.[287] The ACP1*A allele, which is associated with low LMPTP activity, makes females more susceptible to allergy (a Th2-mediated disorder), and males more susceptible to T1D and Crohn's disease (a Th1-mediated disorder).[288] Genotypes leading to high expression of LMPTP-A are positively associated with Crohn's disease in females and ulcerative colitis in males.[287] Additionally, *ACP1* genotype appears to influence the clinical manifestation of T1D.[289] Females with medium-high activity genotypes have earlier age of onset of T1D, while low activity genotypes are associated with higher glycaemic levels at initial diagnosis, and increase susceptibility to T1D in offspring of older mothers.[290]

Future directions

In conclusion, a large amount of data support the importance of PTPs in regulation of TCR signalling. Although the emphasis is still often on single enzymes and single substrates, systems biology and proteomics are increasingly applied to the study of phosphorylation networks and PTPs. Important difficult-to-address issues which benefit from a systemic approach include the frequent redundancy between PTPs and the possible pleiotropic actions of single PTPs at several levels of a signalling pathway. Our knowledge about post-translational regulation of PTP activity also has progressed tremendously in the last few years, and in the future increasing emphasis is expected on dynamic or even real-time monitoring of PTP activity during signalling. Finally, of the large number of PTPs that are *bona fide* regulators of TCR signalling, only a subset has been investigated for a possible role in autoimmunity. As this subset continues to expand, we predict that an increasing number of PTPs will be identified as important autoimmunity genes, biomarkers, or drug targets.

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Disclosures

The authors declare having no conflicts of interest to disclose.

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