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PTPN22: the archetypal non-HLA autoimmunity gene

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Abstract

PTPN22 encodes a tyrosine phosphatase that is expressed by haematopoietic cells and functions as a key regulator of immune homeostasis by inhibiting T-cell receptor signalling and by selectively promoting type I interferon responses after activation of myeloid-cell pattern-recognition receptors. A single nucleotide polymorphism of *PTPN22*, 1858C>T (rs2476601), disrupts an interaction motif in the protein, and is the most important non-HLA genetic risk factor for rheumatoid arthritis and the second most important for juvenile idiopathic arthritis. *PTPN22* exemplifies a shared autoimmunity gene, affecting the pathogenesis of systemic lupus erythematosus, vasculitis and other autoimmune diseases. In this Review, we explore the role of *PTPN22* in autoimmune connective tissue disease, with particular emphasis on candidate-gene and genome-wide association studies and clinical variability of disease. We also propose a number of *PTPN22*-dependent functional models of the pathogenesis of autoimmune diseases.

Introduction

Recognition that the *PTPN22* gene is a major risk factor for autoimmunity began with the association of a missense single nucleotide polymorphism (SNP) (1858C>T, rs2476601) with an increased risk of type 1 diabetes mellitus,[1] rheumatoid arthritis (RA)[2] and systemic lupus erythematosus (SLE).[3] Since then, this susceptibility locus has been found to affect multiple connective tissue and autoimmune diseases. At the genome-wide level, *PTPN22* 1858C>T ranks as the most important non-MHC single-gene contributor to RA susceptibility and the second most important for juvenile idiopathic arthritis (JIA).[4,5]

The frequency of the *PTPN22* 1858T allele varies among different populations. In Europe, a northeast to southwest gradient exists, with the highest frequencies in northern and eastern Europe (>10%) and the lowest in southern Europe (2–3%).[6–8] Approximately 6–10% of US, Australian and New Zealand white populations, and 4–5% of Hispanic populations, have the 1858T allele.[6,8] *PTPN22* 1858T is rare in Native American (<1%), African (<1%), Middle Eastern (0–3%) and Asian populations (<1%).[6–10]

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Competing interests

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Author contributions

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In addition to autoimmune diseases, *PTPN22* 1858C>T also affects susceptibility to infectious diseases. Carriers of the 1858T allele are at increased risk of bacterial infections, including invasive pneumococcal infections, bacterial pulmonary infections in patients with chronic muco cutaneous candidiasis, and lepromatous and tuberculoid leprosy.[7] Remarkably, carriers of the 1858T allele are resistant to the development of pulmonary tuberculosis,[11,12] and the allele has not been found to affect susceptibility to brucellosis, Chagas disease or hepatitis C.[7]

Reviews on the immunological function and molecular regulation of *PTPN22* are available.[7,13] Here we briefly review the functions of Tyrosine-protein phosphatase nonreceptor type 22 (PTPN22; also known as lymphoid phosphatase) in T cells, B cells and myeloid cells. We then describe the role of PTPN22 in autoimmunity, with emphasis on clinical manifestations of connective tissue autoimmune diseases, including RA, JIA, SLE, systemic sclerosis (SSc) and vasculitis. We also describe how the autoimmune-associated *PTPN22* 1858T variant affects the function of immune cells, and describe current mechanistic models for its role in the pathogenesis of autoimmunity.

PTPN22 structure and function

PTPN22 belongs to a family of genes encoding protein tyrosine phosphatases (PTPs).[14] PTPs function as regulators of tyrosine phosphorylation-based cell-signal transduction by removing phosphate groups from tyrosine residues on intracellular proteins. PTPs are the natural counterparts of protein tyrosine kinases, which catalyse the addition of phosphate groups on tyrosine residues. *PTPN22* encodes a nonreceptor PTP expressed only by haematopoietic cells. PTPN22 contains three domains, including: an N-terminal PTP catalytic domain; an interdomain region; and a C-terminal domain with four proline-rich regions that function as motifs for interaction with other proteins (Figure 1). The autoimmune-associated SNP *PTPN22* 1858C>T encodes an arginine to tryptophan substitution at amino acid 620 (Arg620Trp) in the first proline-rich motif of the PTPN22 protein.[1]

PTPN22 has dual roles in the regulation of immune cell signalling (Figure 2).[7,13] In the adaptive immune system, PTPN22 inhibits T-cell activation by restricting signalling downstream of the T-cell receptor (TCR). By contrast, in the innate immune system, PTPN22 selectively promotes myeloid-cell type I interferon production by enhancing signalling downstream of pattern recognition receptors.[15]

T cells

Studies of human and mouse cells show that PTPN22 is a potent inhibitor of T-cell activation by inhibitory dephosphorylation of key mediators of signal transduction immediately downstream of the TCR (Figure 2a). T-cell activation by TCR engagement requires a ‘wave’ of tyrosine-based phosphorylation events mediated by kinases of the Src family (Lck and Fyn being the most important) and the Syk family (ZAP-70 being the most important). These kinases cause phosphorylation of immunoreceptor tyrosine-based activation motifs (ITAMs) of the TCR-associated CD3ζ-chain and trigger multiple intracellular signalling pathways.[14] PTPN22 inhibits early TCR signalling by

dephosphorylating the activation loops of Lck, Fyn, ZAP-70 and ITAMs of the CD3ζ-chain. PTPN22 knock-down or pharmacological inhibition in human cells and deletion in mouse cells enhances TCR signalling.[2,16–19] In T cells, PTPN22 forms a high-stoichiometry complex with tyrosine-protein kinase CSK (also known as C-terminal SRC kinase), which is also an inhibitor of TCR signalling. This complex is mediated by a proline-rich motif of PTPN22 and the SH3 domain of CSK, both of which bind PTPN22 to its substrates and regulate its activity.[18,20,21]

The effect of PTPN22 on TCR signalling might differ between T-cell subpopulations. Studies showed that compared with wild-type mice, *Ptpn22*$^{-/-}$ mice had increased numbers of effector memory CD4^{+} and CD8^{+} T cells that are hyper-responsive to TCR engagement,[16] and increased numbers of follicular helper T cells that produce more IL-21.[22] CD4^{+}CD25^{+}Foxp3^{+} regulatory T (T_{REG}) cells are also affected by deletion of *Ptpn22* — compared with *Ptpn22*-sufficient mice, *Ptpn22*$^{-/-}$ mice have more T_{REG} cells,[19,23] and those cells are more suppressive and adhesive.[19]

B cells

The function of PTPN22 in B cells is not as clear as it is for T cells. Ptpn22 deficiency in mice has been shown to have no effect on B-cell receptor (BCR) signalling or B-cell development.[16,24] Increased spontaneous germinal-centre formation in the spleen and Peyer's patches was attributed to increased T-cell help;[16,22] however, primary B cells from humans with the PTPN22 Arg620Trp substitution and from mice with the homologous mutation, Ptpn22 Arg619Trp, had alterations in BCR signalling and the B-cell repertoire, suggesting PTPN22 regulates these processes.[25–30] The lack of effect of Ptpn22 deficiency on B-cell function in the knockout mouse could be due to compensation by other phosphatases during development, or to features of the C57BL/6 strain from which the knockout was generated.

Myeloid cells

PTPN22 is a selective promoter of type I interferon production by pattern-recognition receptor-activated human and mouse macrophages and dendritic cells (DCs; Figure 2b).[15] Efficient type I interferon induction after TLR engagement requires activation of a signalling cascade involving phosphorylation of interferon response factors (IRFs), IRF3 and IRF7. This cascade is dependent upon the Lys63-linked autoubiquitination of the E3 ubiquitin ligase TNF receptor-associated factor 3 (TRAF3). PTPN22 bound TRAF3 and selectively promoted TRAF3 Lys63-linked autoubiquitination in bone marrow-derived macrophages (BMDMs) after engagement of TLRs, enabling PTPN22 to mediate production of type I interferon without affecting expression of proinflammatory cytokines, such as IL-1β and TNF.[15] In contrast to TCR signalling, the effect of PTPN22 in the TLR signalling pathway is not mediated by PTPN22 catalytic activity, but instead is reliant upon scaffolding properties within the C-terminal domain of the protein. Knockdown of PTPN22 in human blood monocyte-derived macrophages, mouse BMDMs and mouse DCs, and Ptpn22-deficiency in mouse BMDMs and DCs, impaired type I interferon production after TLR engagement.[15] However, treatment of mouse BMDMs and a macrophage cell line with pharmacological inhibitors of Ptpn22 had no effect on TLR-stimulated type I interferon

production. Although *Ptpn22* deletion in mice did not lead to spontaneous autoimmunity or other pathology,[16] *Ptpn22*$^{-/-}$ mice had impaired type I interferon responses to TLR ligands *in vivo* and had reduced host responses to infection with lymphochoriomeningitis virus.[15] *Ptpn22*$^{-/-}$ mice have also been shown to have diminished type I interferon-dependent suppression of colitis and arthritis-related inflammation after TLR activation.[15]

PTPN22 1858C>T disease associations

PTPN22 is associated with many, but not all, connective tissue autoimmune diseases (Box 1). *PTPN22* 1858C>T is not associated with ankylosing spondylitis,[31,32] a single case–control study reported no association with primary antiphospholipid syndrome,[33] and meta-analysis of two case–control studies showed no association with primary Sjögren's syndrome.[8]

Rheumatoid arthritis

In connective tissue autoimmune disease research, the majority of genetic studies of *PTPN22* 1858C>T have examined its association with RA. Begovich *et al*.[2] reported the first association of *PTPN22* with RA, showing in a case–control study that the *PTPN22* 1858T allele increased the risk of rheumatoid factor (RF)-seropositive disease (OR 1.65) in white American individuals. Subsequent haplotype analyses in RA cohorts confirmed that *PTPN22* 1858C>T is the SNP that confers disease risk.[34–36] Notably, this SNP is responsible for the association between RA and a locus on chromosome 1p13 that had been previously identified by genetic linkage analysis.[37] Although the low frequency of homozygous individuals in most studies means the confidence intervals of the odds ratios often overlap with the odds ratios for heterozygous individuals, a single copy of the 1858T variant approximately doubles the risk of RA compared with 1858C homozygocity (OR 1.5–2.0),[2,38–42] indicating that the variant is a co-dominant allele.

Autoantibody status—Although *PTPN22* 1858C>T is associated with both autoantibody seropositive and seronegative RA, most studies have reported stronger associations of *PTPN22* with RF-positive or anti-cyclic citrullinated peptide (CCP) antibody-positive RA.[2,43–49] A stratified meta-analysis validated the association of *PTPN22* 1858T with both RF and anti-CCP autoantibody-positive RA.[8] *PTPN22* 1858T is more common in RF-positive than in RF-negative patients (OR 1.21), and is also more common in patients with anti-CCP antibodies than those without (OR 1.45).[8] Ultimately, a genome-wide association study (GWAS) of patients with RA revealed the risk effect of *PTPN22* 1858T is only of genome-wide significance in patients who test positive for anti-citrullinated peptide antibodies (ACPAs).[50]

Prediction of RA development—Studies of European early arthritis and inception cohorts revealed that, by itself, the *PTPN22* 1858T allele is not a good predictor of progression from undifferentiated arthritis to RA. For example, in one study, *PTPN22* 1858T was not associated with progression from undifferentiated arthritis to RA during a 1-year follow-up period; however, a trend of increased progression of disease in ACPA-positive cases was detected, but was not proven to be statistically significant.[51] In other studies, with mixed cohorts of patients with undifferentiated arthritis and other defined

arthritis syndromes, no differences were found in *PTPN22* 1858T allele frequency between RA and non-RA cases diagnosed at study entry or within a 2-year,[52] or longer,[53] follow-up period. In one report, the combination of *PTPN22* 1858T and anti-CCP antibody seropositivity was highly specific for RA, as only 1 of 184 patients with an arthritis other than RA was positive for this combination.[53] Findings were similar in another case–control study, in which blood samples were taken from patients with RA prior to disease onset.[46] *PTPN22* 1858T carriage alone had 80.3% specificity for the development of RA; however, *PTPN22* 1858T and anti-CCP antibody seropositivity were not co-present in healthy individuals (n = 368, 100% specificity). *PTPN22* genotyping alone is not as effective as anti-CCP antibody analysis (98.6% specificity) in predicting RA,[46] yet the strong association of *PTPN22* 1858T with anti-CCP antibody positive RA indicates that genotyping *PTPN22* might enhance the sensitivity of testing and enable better prediction of progression to RA in patients with early signs of arthritis. Most studies showed an earlier (2–7.5 years) age at onset of RA in carriers of the *PTPN22* 1858T allele,[38,44,48,54,55] but not all studies showed the same effect.[45,56,57] This heterogeneity might result from lack of stratification of the RA cases by clinical variability, as the 1858T allele might exert a stronger effect on the age of onset of autoantibody-positive RA. Although some studies have detected an effect of *PTPN22* on the presence of radiographic erosions or the rate of joint destruction in RA,[47,57,58] a meta-analysis indicated no such association in either anti-CCP antibody seropositive or seronegative individuals.[59]

Response to therapy—Most studies report no effect of *PTPN22* 1858T on the response of patients with RA to treatments including methotrexate,[58] rituximab,[60] anti-TNF biologic agents (adalimumab, etanercept or infliximab),[61] other DMARDs or prednisolone.[55] Only one study has shown an effect of *PTPN22* genotype on the likelihood of patients being maintained on methotrexate mono therapy; however, this study included only a small number of patients homozygous for *PTPN22* 1858T.[62]

Juvenile idiopathic arthritis

With a Norwegian case–control study, Viken *et al.*[63] reported the first association of *PTPN22* 1858C>T with JIA (OR 1.41). Several other studies confirmed the genome-wide significance of *PTPN22* 1858T as a risk factor for oligoarticular and RF-negative polyarticular JIA in white European, American and Australian individuals, and ranked it as the second most important non-HLA genetic contributor to the risk of developing JIA.[5,64,65] When patients with JIA were stratified by subgroup classification,[66] *PTPN22* 1858T was associated with oligoarticular JIA, but not with systemic-onset or enthesitis-related JIA.[39,67] It should be noted that the lack of association might reflect the limited power of these studies; only a small number of patients with rare subtypes of disease were included. Meta-analysis showed the presence of *PTPN22* 1858T increased the risk of both RF-positive and RF-negative polyarticular JIA.[39,67]

Psoriatic arthritis

PTPN22 1858C>T has a weak association with psoriatic arthritis (PsA) in white Canadian and Swedish populations (OR 1.22, shown by meta-analysis).[8,68,69] A case–control study in Sweden showed the association of the PTPN22 1858T with PsA was stronger in RF-

negative or anti-CCP antibody-negative patients, and that carriers had more numerous deformed joints and were more likely to have been diagnosed with dactylitis.[69] In this study, the frequency of PTPN22 1858T was similar in patients with monoarthritic, oligoarthritic and polyarthritic disease.

Systemic lupus erythematosus

The first report of an association of *PTPN22* 1858T with SLE was from a case–control study of white North American individuals by Kyogoku *et al.*[3] The association was replicated in case–control analyses of white and Hispanic populations (OR 1.46–1.56),[8,70] and was shown to be of genome-wide significance in white North American and Swedish populations (OR 1.35).[71] Consistent with the role of *PTPN22* as a major autoimmunity gene, the 1858T allele seems to be a risk factor for comorbid SLE and autoimmune thyroid disease.[72,73]

Several studies have found no association between *PTPN22* 1858C>T and manifestations of SLE;[3,56,74–76] however, in a case-only analysis, patients with SLE and the *PTPN22* 1858T allele had a greater risk of renal disorder than those homozygous for *PTPN22* 1858C (OR = 1.93).[77] Furthermore, a GWAS to identify SNPs associated with anti-double-stranded DNA (dsDNA) antibody seropositive SLE found an association of *PTPN22* 1858T with seropositive SLE in a case-only analysis.[78] Another study found a positive association between *PTPN22* 1858T and anti-cardiolipin IgG, and a trend towards an increased frequency of *PTPN22* 1858T in patients with lupus nephritis or in individuals seropositive for anti-dsDNA autoantibodies, although this trend was not shown to be statistically significant.[73]

Systemic sclerosis

A weak association occurs between *PTPN22* 1858C>T and SSc (OR 1.15–1.16, by meta-analysis of European individuals),[8,79,80] but has no genome-wide significance.[81–83] Unlike in RA studies,[8] the association with SSc is not affected by the presence of autoantibodies, as meta-analysis did not reveal a difference in allele frequency when comparing anti-centromere antibody seropositive and seronegative or anti-topoisomerase I autoantibody seropositive and seronegative SSc.[8,80]

Vasculitis syndromes

PTPN22 1858C>T is associated with only some forms of vasculitis. One study showed a strong association (OR 1.62) between *PTPN22* 1858T and biopsy-proven giant cell arteritis in white European individuals.[84] No specific association was found when patients were stratified by the presence of polymyalgia rheumatica, visual ischaemic manifestations or irreversible occlusive disease. Another study showed no association of *PTPN22* 1858C>T with Takayasu arteritis in Turkish individuals.[85] Among the anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAV), *PTPN22* 1858T is associated with granulomatosis with polyangiitis (GPA) (OR 1.91), but not with eosinophilic granulomatosis with polyangiitis (also known as Churg–Strauss syndrome) or microscopic polyangiitis.[86–88] In a GWAS of white individuals, *PTPN22* was associated with AAV in a discovery cohort (the association was not of genome-wide significance), but no such association was found in

a replication cohort. However, this study included a group of patients with either GPA or microscopic polyangiitis.[89] The association with GPA is stronger in patients with organ pathology (lung, kidney, eye or peripheral nervous system).[86,88] A single case–control study of white Spanish individuals showed no association of *PTPN22* 1858T with IgA vasculitis.[90] Intriguingly, two studies reported that *PTPN22* 1858T can protect against Behçet disease (OR 0.65).[91,92]

Idiopathic inflammatory myopathy

A single case–control study reported an association of *PTPN22* 1858C>T with idiopathic inflammatory myopathy in white individuals from the UK (OR 1.8).[93] Although the sample sizes were small when stratified into subgroups, the study suggested the association was restricted to polymyositis and juvenile dermatomyositis, and not to dermatomyositis or myositis overlapping with another connective tissue disease.[93] *PTPN22* 1858T was not associated with dermatomyositis in a GWAS of patients with adult or juvenile dermatomyositis.[94]

Other immune-mediated disorders

The discovery that *PTPN22* 1858C>T contributes to genetic susceptibility to many, but not all, autoimmune diseases suggests fundamental similarities and differences underlie their pathogenesis. Aside from the connective tissue diseases, *PTPN22* 1858T is associated with many other autoimmune diseases (Box 1).[6–8] Intriguingly, a number of autoimmune diseases are not associated with the 1858T allele, and the allele is protective against two autoinflammatory disorders, Crohn disease and Behçet disease.[95] Generally, *PTPN22* has stronger associations with autoimmune disorders in which autoantibodies have a major role in pathogenesis. An interesting hypothesis proposed by Zheng *et al.*[8] is that the effect of *PTPN22* depends upon the tissue where the autoimmunity manifests as pathology. Autoimmune diseases affecting connective tissues, joints, muscles, blood, pancreas, kidney or thyroid show a stronger association with *PTPN22* than diseases of the gastrointestinal tract or immune-privileged sites, such as the central nervous system and the eye.[8]

Functional models for PTPN22 in disease

At the molecular level the functional effect of *PTPN22* 1858C>T is still under investigation. In human lymphocytes the SNP disrupts the interaction between PTPN22 and CSK,[1,18,20] a potent inhibitor of TCR signalling that phosphorylates inhibitory tyrosine residues of Lck and Fyn.[21,96] The interaction with CSK is believed to modulate the inhibitory function of PTPN22 in TCR signalling; however, whether the effect of CSK is to promote or inhibit the action of PTPN22, and the molecular mechanism by which CSK regulates PTPN22, is still a matter of debate.[18,20,96] The effect of the PTPN22 Arg620Trp substitution on TCR signalling is controversial, with some studies suggesting increased suppression of signalling by the Trp620 variant,[18,20,28] and other studies suggesting the opposite.[24,30]

At the cellular level, the mechanism of action of PTPN22 Trp620 is also under investigation. Reports of genotyped human primary cells and newly-described mouse models mimicking the human PTPN22 Trp620 variant have suggested several overlapping models of how

PTPN22 Trp620 causes autoimmunity (Figure 3). It should be noted that translating information from mouse models to human PTPN22 biology must be considered with caution as no clear characterization of the functional differences between the human PTPN22 and mouse Ptpn22 proteins exists.

Skewed T-cell differentiation model

One functional explanation for the role of PTPN22 Trp620 in the pathogenesis of autoimmune diseases is that it alters the balance of effector T-cell and T_{REG}-cell compartments (Figure 3a). Experiments on *Ptpn22*$^{-/-}$ mice showed that the loss of Ptpn22 causes alterations in the number and function of T_{REG} cells and follicular helper T cells.[19,22,23] The complexity of the effect of Ptpn22 in T cells is demonstrated by data from nonobese diabetic (NOD) mouse studies. Overexpression of T-cell-specific, transgenic wild type *Ptpn22*,[97] or knockdown of *Ptpn22*,[98] protected NOD mice from diabetes. Although these findings seem contradictory, they suggest that the balance between or within autoimmune-promoting effector T-cell and autoimmune-protecting T_{REG}-cell compartments is finely regulated by PTPN22 expression or activity. A study of primary human T cells showed that individuals homozygous for PTPN22 Trp620 had increased type 1 T helper (T_H1) cell-mediated IFN-γ responses and reduced suppression of T_H1 cells by T_{REG} cells.[99]

Altered B-cell repertoire model

PTPN22 ArgTrp620 could contribute to the generation of autoreactive B cells (Figure 3b). Ptpn22 Trp619 (homologous to human PTPN22 Trp620) knock-in mice have been made with various genetic backgrounds.[25,30] Although the Ptpn22 Trp619 mouse on an inbred C57BL/6 background does not develop spontaneous autoimmunity, mice on a mixed C57BL/6×129 background develop spontaneous systemic autoimmunity characterized by circulating autoantibodies and immune-cell infiltration in multiple tissues, including the lungs and liver.[25] Importantly, conditional overexpression of Ptpn22 Trp619 only in B cells was sufficient to cause spontaneous autoimmunity in the mixed background,[25] suggesting a critical effect of Ptpn22 in regulating B-cell function that is disrupted by the Trp619 variant. In mice with a C57BL/6 or mixed background, the Arg619Trp mutation led to hyper-responsiveness of peripheral B cells to anti-IgM antibody stimulation.[25,30] Considering that some of the strongest associations of *PTPN22* 1858C>T are with autoimmune diseases characterized by production of circulating autoantibodies (RA, SLE and type 1 diabetes), dysregulation of B-cell clonal deletion and receptor editing is likely to contribute to *PTPN22*-associated autoimmune diseases.[100] It was reported that, compared with those without the allele, individuals with *PTPN22* 1858T have expanded anergic B-cell numbers, as well as transitional and naive B cells with diminished BCR signalling and resistance to BCR-stimulated apoptosis.[27] The same study showed expanded transitional B-cell numbers in *PTPN22* 1858T carriers,[27] although this effect was not found in another study.[101] These data suggest the PTPN22 Trp620 variant contributes to the escape of autoreactive B cells from deletion at developmental checkpoints. Furthermore, a SNP (rs34933034) augmenting CSK expression that leads to enhanced activation of mature B cells is also a risk factor for SLE, highlighting that alterations in the PTPN22–CSK complex and signalling pathway might disrupt B-cell homeostasis and promote pathogenic alterations in the B-cell repertoire.[102] Finally, *PTPN22* 1858C>T is associated with an increased risk of chronic

lymphocytic leukaemia (CLL).[103] PTPN22 is proposed to inhibit antigen-induced apoptosis of human CLL blasts;[104] therefore, PTPN22 Trp620 might promote both CLL and autoimmunity by protecting autoreactive B cells from antigen-receptor-induced death.

Altered immune regulation model

PTPN22 Trp620 has also been shown to impair production of type I interferon by myeloid cells (Figure 3c).[15] Type I interferons might be critical for maintaining immune homeostasis by antagonizing the action of IL-1β and TNF.[105] Human cells expressing PTPN22 Trp620 have deficient TLR-induced type I interferon production, and in a model of IL-1β-dependent synovial inflammation, overexpression of transgenic human PTPN22 Trp620 in mice impaired amelioration of inflammatory arthritis by treatment with polyinosinic-polycytidylic acid, a type I interferon-inducing TLR agonist.[15]

Other *PTPN22* polymorphisms

PTPN22 788G>A

SNPs of *PTPN22* other than 1858C>T (Figure 1) have been associated with connective tissue autoimmune diseases. *PTPN22* 788G>A (rs33996649) is a rare missense SNP does that not co-occur with *PTPN22* 1858C>T and, intriguingly, it reduces the risk of both RA[106] and SLE[107] but is not associated with SSc[80] or giant cell arteritis.[84] *PTPN22* 788G>A encodes a loss-of-function Arg263Gln substitution in the PTPN22 catalytic domain, which changes the conformation of the active site and reduces the phosphatase activity of the protein.[107]

PTPN22 –1123G>C

PTPN22 –1123G>C (rs2488457) is a SNP in the promoter region of the *PTPN22* gene and its function has not yet been characterized. In white Europeans, *PTPN22* –1123G>C is often coexpressed with *PTPN22* 1858C>T, and genetic studies showed that in this group of individuals *PTPN22* –1123G>C is only a minor contributor to RA risk.[108] However, this SNP might be an important risk factor in Asian populations, as in case–control studies it has been shown to increase the risk of RA in Chinese individuals[109,110] and ankylosing spondylitis in a Taiwanese population.[111]

Future directions

More molecular work is required to understand the function of PTPN22 in immune-cell homeostasis, and to clarify the effect of the PTPN22 Trp620 variant in immune-cell signalling. Autoimmune pathogenesis promoted by *PTPN22* 1858C>T probably involves concerted anomalies in the differentiation of T-cell subsets, B-cell repertoire and the balance between immunoregulatory and proinflammatory cytokine production. Selective expression of the PTPN22 Trp620 variant in lymphocyte subsets and other cell types in autoimmune disease models will help to clarify the cellular mechanism of action of PTPN22 in disease, and indicate whether the effect on disease pathogenesis varies between autoimmune diseases.

Studies also suggest that PTPN22 has important novel functions in myeloid cells, an area that should be further explored. For example, a report showed that neutrophils from individuals with *PTPN22* 1858T release increased levels of reactive oxygen species (when primed with TNF) and Ca^{2+} after stimulation with a chemotactic bacterial peptide mimic.[112] PTPN22 might also promote IFN-γ-dependent Janus kinase–signal transducer and activator of transcription (JAK–STAT) signalling in myeloid cells, as knockdown of human THP-1 monocytes decreased STAT1 and STAT3 phosphorylation after stimulation with IFN-γ.[113]

Further experiments should also test whether PTPN22 is clinically relevant as a therapeutic target or a biomarker for autoimmunity. Although *PTPN22* 1858C>T does not seem to be a predictive marker for disease development, several studies have suggested that PTPN22 expression profiles could be used as biomarkers for RA, SLE or vasculitis. In one study, the ratio between the full-length PTPN22 and a shorter isoform (called LYP2) was higher in peripheral blood mononuclear cells from patients with RA than from healthy individuals.[114] Another study showed that transcript levels encoding an isoform of PTPN22 that lacks catalytic activity (PTPN22.6) correlated with RA disease activity, as assessed by C-reactive protein-based 28-joint disease activity score (DAS28-CRP3).[115] Additionally, altered histone H3 lysine 4 trimethylation of *PTPN22*,[116] and higher levels of the *PTPN22* transcript,[117] have been detected in patients with SLE, compared with healthy individuals. Additionally, high *PTPN22* transcript numbers in $CD8^+$ T cells correlated with poor prognosis of SLE and AAV.[118]

Conclusions

PTPN22 is a major genetic risk factor for multiple connective tissue and other autoimmune diseases, including RA, JIA, PsA, SLE, SSc and some forms of vasculitis. In RA, *PTPN22* is the strongest non-HLA genetic predisposition factor. Carriers of the 1858T variant are more likely to develop ACPA-negative or RF-positive disease and experience disease onset at an earlier age. Patients with early arthritis who have both the 1858T allele and ACPA seropositivity are highly likely to develop RA. Once RA has developed, the presence of the *PTPN22* 1858T allele does not substantially affect disease progression or severity, or whether patients will respond to anti-TNF therapy or other treatments. *PTPN22* 1858C>T is also a strong genetic risk factor for SLE. Carriers of the 1858T allele are at increased risk of co-occurrence of SLE and autoimmune thyroid disease. *PTPN22* does not seem to affect clinical manifestations of SLE, with the possible exceptions of the development of anti-dsDNA autoantibodies and renal disorder,[73] an area for further investigation. Further exploration of the immunological functions of PTPN22 will hopefully explain how it confers risk of disease and reveal any potential as a therapeutic or prognostic target for connective tissue diseases.

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Key points

- *PTPN22* encodes a protein tyrosine phosphatase that inhibits antigen-receptor signalling in T cells and promotes pattern-recognition receptor-induced type I interferon production by myeloid cells
- *PTPN22* 1858C>T is a risk factor for connective tissue autoimmune diseases, including rheumatoid arthritis (RA), juvenile idiopathic arthritis, psoriatic arthritis, systemic lupus erythematosus, systemic sclerosis and some forms of vasculitis
- In white populations, *PTPN22* 1858C>T is the most important non-HLA genetic risk factor for RA and the second most important for juvenile idiopathic arthritis
- Individuals with *PTPN22* 1858T are more likely to develop RA with seropositivity for anti-citrullinated protein antibodies or rheumatoid factor, and have this disease at an earlier age than those without the variant
- Interactions between the protein encoded by *PTPN22* 1858T and tyrosine-protein kinase CSK are impaired, the functional consequences of which are still under investigation
- Autoimmune pathogenesis promoted by *PTPN22* 1858C>T probably involves the differentiation of T-cell subsets, the B-cell repertoire and the balance between immunoregulatory and proinflammatory cytokine production

Box 1

PTPN22 1858C>T disease association*

Increased risk (OR)

- Addison disease (1.43)
- Alopecia areata (1.38)
- Giant cell arteritis (1.62)[84]
- Graves disease (1.59)
- Granulomatosis with polyangiitis (1.91)[88]
- Hashimoto thyroiditis (1.63)[119]
- Idiopathic inflammatory myopathy (1.77)
- Idiopathic thrombocytopenic purpura (1.93)
- Juvenile idiopathic arthritis (1.54)
- Myasthenia gravis (1.53)
- Psoriatic arthritis (1.22)
- Rheumatoid arthritis (1.65)
- Systemic lupus erythematosus (1.46)
- Systemic sclerosis (1.16)
- Type 1 diabetes mellitus (1.84)
- Vitiligo (1.98)

Decreased risk (OR)

- Behçet disease (0.42)[91]
- Crohn disease (0.84)

Not affected‡

- Celiac disease
- Multiple sclerosis
- Psoriasis
- Ulcerative colitis

Probably not affected§

- Ankylosing spondylitis
- Aplastic anaemia[120]
- Chronic urticaria[121]

- Churg–Strauss syndrome[88]
- Microscopic polyangiitis[88]
- Pemphigus
- Primary antiphospholipid syndrome[33]
- Primary biliary cirrhosis
- Primary sclerosing cholangitis
- Primary Sjögren's syndrome
- Takayasu arteritis[85]
- Uveitis

*Unless otherwise indicated, data were obtained from Zheng *et al*.[8]

‡Diseases categorized as "not affected" did not have a statistically significant association with *PTPN22* 1858C>T in a meta-analysis of multiple studies.

§Diseases categorized as "probably not affected" were addressed by single studies, and did not have a statistically significant association with *PTPN22* 1858C>T.[8]

Review criteria

PubMed was searched for articles and abstracts from 2004 to the present, using the terms “PTPN22” and “lymphoid tyrosine phosphatase”. Studies relevant to autoimmunity were identified using the search terms “autoimmunity”, “autoimmune disease”, “arthritis”, “lupus”, “sclerosis” and “vasculitis”. Only English-language reports were included. Full-length papers were downloaded and reviewed and their reference lists were scanned for further relevant references. The list was last updated in April 2014.

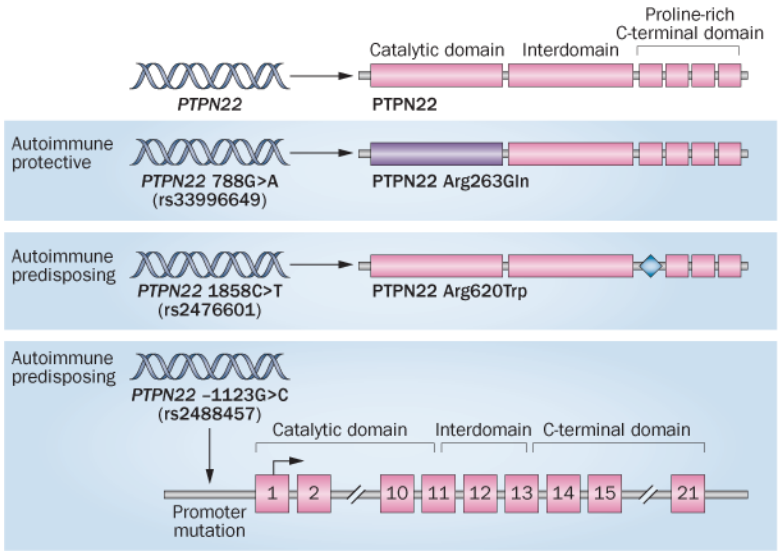

Figure 1.

Variants of human *PTPN22*. *PTPN22* encodes a tyrosine phosphatase with an N-terminal catalytic domain, an interdomain region and a C-terminal domain with four proline-rich regions. Several SNPs in the *PTPN22* gene are associated with autoimmune disease. The autoimmune-protective 788G>A SNP (rs33996649) causes an Arg263Gln substitution in the PTPN22 catalytic domain (purple). The autoimmune-predisposing 1858C>T SNP (rs2476601) causes an Arg620Trp substitution in the first proline-rich motif (blue diamond). The autoimmune-predisposing −1123G>C SNP (rs2488457) is in the promoter region of the *PTPN22* gene. Abbreviations: PTPN22, tyrosine-protein phosphatase nonreceptor type 22; SNP, single-nucleotide polymorphism.

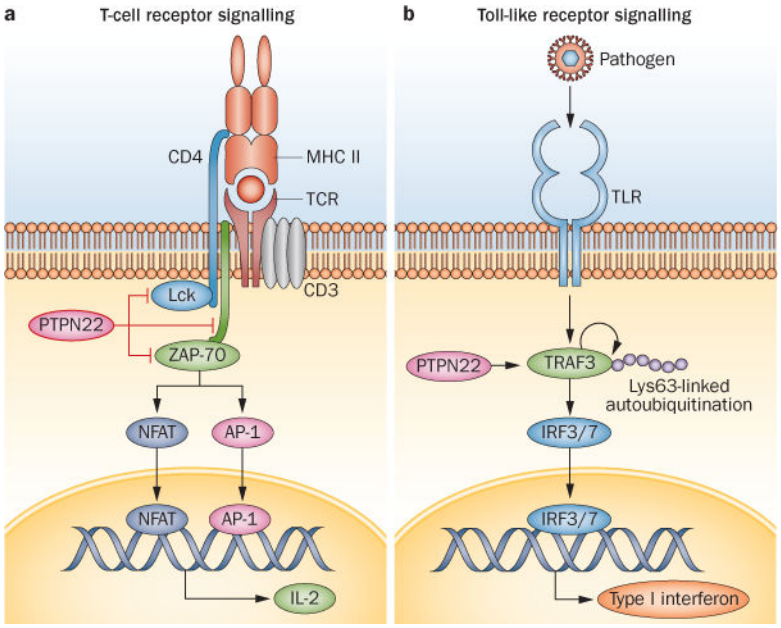

Figure 2.

PTPN22 regulation of cell signalling. PTPN22 has dual roles in the regulation of immune-cell signalling. **a** | In T cells, PTPN22 restricts signalling by inhibitory tyrosine dephosphorylation of key promoters of signalling downstream of the TCR: the SRC family tyrosine protein kinase Lck; the SYK family kinase ZAP-70 and the TCR-associated CD3ζ-chain. The catalytic activity of PTPN22 is essential for this role. **b** | In myeloid cells, PTPN22 acts as a selective promoter of the type I interferon response by promoting the Lys63-linked autoubiquitination of TRAF3 and phosphorylation of IRF3 and IRF7 downstream of pattern-recognition receptors. In contrast to lymphocytes, the catalytic activity of PTPN22 is not substantially involved in the promotion of TLR signalling in myeloid cells. Instead, myeloid cells rely on scaffolding properties within the C-terminal domain of the protein. Abbreviations: IRF3, interferon regulatory factor 3; IRF7, interferon regulatory factor 7; NFAT, nuclear factor of activated T cells; PTPN22, tyrosine-protein phosphatase nonreceptor type 22; TCR, T-cell receptor; TLR, Toll-like receptor; TRAF3, TNF-receptor-associated factor 3.

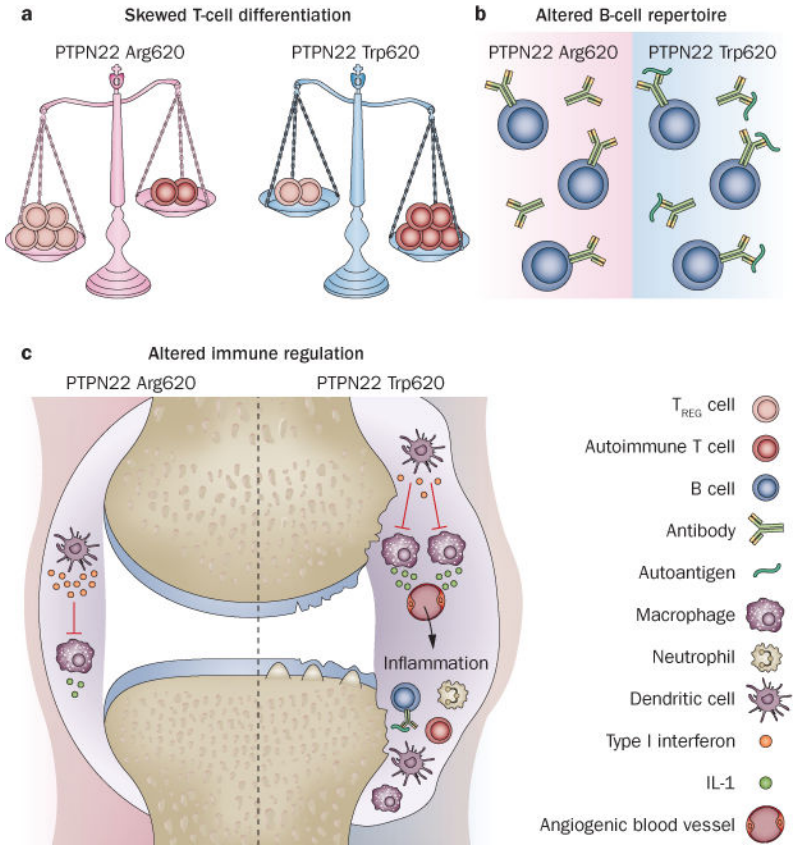

Figure 3.

Models of PTPN22-regulated autoimmune disease. **a** | The PTPN22 ArgTrp620 promotes the expansion of pathogenic, autoimmune T cells. **b** | PTPN22 ArgTrp620 alters the B-cell repertoire, promoting autoantibody production. **c** | PTPN22 ArgTrp620 impairs type I interferon production by myeloid cells, which during homeostasis functions to antagonize the effect of proinflammatory cytokines, for example, to protect against arthritis in the synovium. Abbreviations: PTPN22, tyrosine-protein phosphatase nonreceptor type 22; T_{REG} cell, regulatory T cell.