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The contribution of *PTPN22* to rheumatological disease

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Abstract

One of the unresolved questions in modern medicine is why certain individuals develop a disorder such as rheumatoid arthritis or lupus, while others do not. Contemporary science holds genetics partly responsible and blames the remainder on environmental and stochastic factors. Among the many genes that increase the risk of autoimmune conditions, the risk allele encoding the W620 variant of *PTPN22* is shared between multiple rheumatologic diseases, suggesting a fundamental role in the development of immune dysfunction. Here, we discuss how the presence of the *PTPN22* risk allele may shape the signs and symptoms of these diseases. Besides the emerging clarity in how *PTPN22* tunes T and B cell antigen receptor signaling, we discuss recent discoveries of important functions of *PTPN22* in myeloid cell lineages. Taken together, these new insights are revealing important clues to the molecular mechanisms of prevalent diseases like rheumatoid arthritis and lupus and may open new avenues for the development of personalized therapies that spare the normal function of our immune system.

In 2004, we and others published the discovery that a single-nucleotide polymorphism C1858T (rs2476601) in the *PTPN22* gene is associated with type 1 diabetes [1], rheumatoid arthritis (RA) [2] and systemic lupus erythematosus (SLE) [3]. These initial findings have been extensively replicated, and today there are close to 1,000 published papers confirming and refining the genetic association of *PTPN22* with numerous autoimmune diseases. Indeed, *PTPN22* is now recognized as the most influential non-major histocompatibility complex (MHC) gene to promote the development of autoimmunity, including most rheumatologic conditions. Here we summarize the progress in our understanding of the role of *PTPN22* in rheumatologic diseases, highlighting how *PTPN22* likely operates through multiple mechanisms of action. The strength and direction of the association between *PTPN22* and various diseases (Fig. 1) reflects the differential contribution of these mechanisms and introduces a vision for novel pathogenetic disease classification.

AUTHOR CONTRIBUTIONS

All authors drafted the article, revised it critically for important intellectual content, approved the final version to be published, and take responsibility for the integrity of the data and the accuracy of the data analysis.

***PTPN22* in rheumatoid and juvenile idiopathic arthritis**

A statistically significant association of the *PTPN22* 1858T allele (encoding the W620 variant) with rheumatoid arthritis (RA) was first reported by Begovich and co-workers in 2004 [2]. The odds ratio was 1.65 in their discovery cohort (n=475 RA, 475 controls) and as high as 2.63 for the homozygous TT genotype versus CC in their replication cohort (n=840 from 463 white families). Rheumatoid factor (RF)-positive RA patients had a higher odds ratio than RF-negative patients. Numerous papers have validated these findings [4] and documented an association with anti-citrullinated protein antibodies (ACPA) [5–9] as well as smoking [10, 11], erosive disease [12], and earlier onset [8, 13]. However, the presence of the *PTPN22* risk allele 1858T did not correlate with response to anti-TNF agents [9] or methotrexate [14].

Despite the now well-established geographical gradient in T allele frequency with the highest prevalence in white Caucasians of northern European descent and considerably lower frequencies in southern Europeans [15] and Hispanics, particularly low frequencies (<1%) in Asians, and near absence in people of African origin, a significant association of the T allele with RA has been documented in populations world-wide, including RA patients from South Asia [16], Tunisia [17], and Turkey [18]. However, in some populations the T allele frequency is too low (<1%) for a meaningful analysis [19]. Interestingly, another polymorphism (rs2488457) located in the promoter region of *PTPN22* is instead associated with RA in a Chinese population [20].

The *PTPN22* 1858T allele is also associated with juvenile idiopathic arthritis (JIA) [4, 21] with a somewhat lower odds ratio of ~1.3 in a meta-analysis that included over 4,000 patients and 6,000 controls [22], as well as in a more recent meta-analysis [23], in which RF-positive polyarticular JIA had a stronger odds ratio of 2.12. Interestingly, this subtype of JIA is most similar to RA. Other association studies have treated all seven recognized forms of JIA as a single entity.

***PTPN22* in spondylarthropathies**

While most susceptibility loci identified in psoriasis (PsO) tend to be equally associated with skin psoriasis and with psoriatic arthritis (PsA), *PTPN22* is an exception: the association of the 1858T allele with general skin psoriasis is weak or absent whereas its association with PsA is statistically highly significant with odds ratios of up to 1.32 [24, 25]. This suggests that PsA has additional components in its pathogenesis compared to skin-restricted disease and more involvement of cells and pathways influenced by *PTPN22*. Also somewhat surprising considering the partially shared pathogenic mechanisms between PsA and ankylosing spondylitis (AS), the latter does not associate with *PTPN22*. The known role of *PTPN22* in CD8 memory T cell function [26] and interleukin-17-producing T helper (Th17) cell differentiation [27] suggest the possibility that the differential association of *PTPN22*-W620 with PsA vs. PsO or AS depends on alterations in the function of CD8 T cells -which are thought to play a more prominent role in PsA vs. PsO or AS [28]- or that *PTPN22*-W620 contributes to differential phenotypes of Th17 in PsA vs. PsO or AS [29].

***PTPN22* in SLE**

The first reported association of the *PTPN22* 1858T allele with SLE by Kyogoku and co-workers [3] found that a single copy of the T allele increases risk of SLE with an odds ratio of 1.37 (95% confidence interval 1.07–1.75), while TT homozygotes have a much higher odds ratio of 4.37 (95% confidence interval 1.98–9.65). The association with SLE has now been replicated in nearly 20 studies and two recent meta-analyses give an overall odds ratio of ~1.5 [30, 31]. SLE patients with an 1858T allele were noted in different studies to have higher IFN α levels and lower TNF α [32], somewhat more prevalent nephritis [33], and a higher incidence of anti-phospholipid syndrome with anti-cardiolipin autoantibodies [34].

***PTPN22* in vasculitides**

The rs2476601 *PTPN22* polymorphism is also positively associated with ANCA-associated vasculitis (AAV) [35–38]. Specifically, *PTPN22* 1858T is associated with two of the three distinct autoimmune vasculitides associated with ANCAs [39]: microscopic polyangiitis (MPA) and granulomatosis with polyangiitis (GPA, formerly known as Wegener's granulomatosis), but has not been reported in eosinophilic granulomatosis with polyangiitis (eGPA, formerly known as Churg-Strauss syndrome). *PTPN22* association was equal between patients of both the anti-proteinase 3 and anti-myeloperoxidase serotypes. Although an initial paper [40] reported a lack of association, several later studies have documented and replicated a significant association of 1858T with biopsy-proven giant cell arteritis (GCA) [41, 42] with an odds ratio of 1.62 (95% confidence interval 1.29–2.04). These findings have been replicated in Spanish, Scandinavian, British, American, and Australian patient samples. There was no difference in risk between patients with or without polymyalgia rheumatica or visual ischemic manifestations. In contrast, *PTPN22* did not associate with Takayasu's arteritis, Behcet's disease, or IgA vasculitis.

***PTPN22* in other rheumatologic and autoimmune conditions**

PTPN22 1858T is also strongly associated with type 1 diabetes, autoimmune thrombocytopenia, vitiligo, idiopathic inflammatory myopathies, Graves' disease, myasthenia gravis, and Addison's disease. On the other hand, the association with systemic sclerosis (SSc) is weaker and has only been found in larger cohorts and meta-analyses [43]. Other diseases that lack an association with *PTPN22* 1858T include multiple sclerosis, pemphigus vulgaris, ulcerative colitis (UC), primary sclerosing cholangitis, primary biliary cholangitis (formerly known as primary biliary cirrhosis), and acute anterior uveitis, all of which represent diseases in epithelial, mucosal, or immune privileged organs [44]. Intriguingly, in Crohn's disease the direction of association is reversed, and *PTPN22* 1858T plays a protective role. Fig. 1 summarizes the spectrum of association between *PTPN22* and various rheumatologic/autoimmune diseases. The observed variability likely reflects fundamental differences in disease pathogenesis, although it is possible that in some diseases, *PTPN22* 1858T promotes both pathogenic and disease-protective pathways, ultimately attenuating the strength of the association.

Other polymorphisms in *PTPN22*

Besides the C1858T polymorphism, two additional *PTPN22* SNPs have been found to have disease associations, particularly in populations with a low frequency of the 1858T allele. The G-1123C polymorphism (rs2488457) is located in the 5' promoter region of *PTPN22* and associates with RA [20], JIA [45], and UC [46] in Chinese populations—in which the rs2476601 SNP does not associate with autoimmunity. The impact of this non-coding SNP on the transcription, stability, or translation of the mRNA remains to be fully clarified. Interestingly, both SNPs rs2476601 and rs2488457 were recently reported as potential cis-expression quantitative trait loci (eQTLs) in whole blood from Spanish RA patients [47], and another study demonstrated that *PTPN22* expression is significantly decreased in whole blood from RA patients carrying the risk alleles of SNPs rs2476601 and rs2488457 compared to healthy controls [48].

The second (rs33996649) is a missense G788A mutation that encodes an R263Q substitution in the catalytic domain of the protein. This variant changes the conformation of the *PTPN22* active-site, and therefore, unlike the 1858T allele, results in reduced catalytic activity of *PTPN22* [49]. It is therefore interesting that in European populations, the 788A allele displays a pattern of autoimmune disease association that is distinct from the 1858T allele. In contrast to 1858T, the 788A allele protects against both SLE and RA [50]. The 788A allele also protects against UC, which 1858T does not associate with, and the 788A does not associate with Crohn's disease, which the 1858T is protective against [50, 51]. Single studies have so far shown no associations with SSc, GCA, IgA vasculitis, uveitis, or Graves' disease [50].

Structure and molecular functions of *PTPN22*

The *PTPN22* gene encodes a 110-kDa protein (Fig. 2) known as the lymphoid tyrosine phosphatase (LYP) [52], although now more commonly referred to simply as *PTPN22*. It is found in all leukocyte lineages, its mRNA being particularly abundant in neutrophils, natural killer (NK) cells, and B cells. The *PTPN22* protein has a classical and strictly phosphotyrosine-specific protein tyrosine phosphatase (PTP) domain in its N-terminus followed by a linker region and a long C-terminus of unknown structure. Within the last 200 residues of *PTPN22*, there are four proline-rich sequence motifs, termed P1 - P4, the first of which (PPPLPERTPESFIVV) binds with high affinity to the Src homology 3 (SH3) domain of the C-terminal c-Src kinase, Csk [53]. While Csk phosphorylates the negative regulatory C-terminus of Lck [54] and other Src family kinases that mediate signaling from a variety of immune receptors, including the T cell receptor (TCR) and B cell antigen receptors and Fc receptors [55], *PTPN22*, in a complementary manner, dephosphorylates the same kinases at their activation loop tyrosines [56] (Fig. 2). This gives *PTPN22* a strong inhibitory function in the T cell receptor and Fc receptor signaling pathways, while the role of *PTPN22* in B cell receptor (BCR) signaling remains less defined. In the context of TCR signaling, *PTPN22* can also dephosphorylate subunits of the receptor (e.g. CD3 ϵ) and other proximal signaling molecules, such as Vav, zeta chain-associated protein of 70 kDa (ZAP-70), and valosin-containing protein (VCP). The elimination of *PTPN22* in the mouse results in accumulation of effector/memory T cells later in life [57]. These cells show enhanced responsiveness to

TCR engagement. PTPN22 knockout (KO) mice also display enhanced numbers of follicular helper T cells and germinal centers, and KO CD4⁺ T cells provide increased T cell help to B cells. [58] Additionally, PTPN22 deletion in mice results in expansion of CD4⁺CD25⁺Foxp3⁺ regulatory T cells, which display enhanced suppressive and adhesive functions [59]. No effects on B cell receptor signaling or B cell development were reported [57].

The C1858T polymorphism switches amino acid residue 620 in PTPN22 from Arg (R) to Trp (W) [1], changing the P1 motif to PPPLPEWTPESFIVV. This change is significant because R620 is a key residue for binding the Csk SH3 domain. Indeed, the PTPN22*W620 protein no longer binds Csk [1]. We reported that PTPN22*W620 isolated from primary T cells from healthy or diabetes patients had higher catalytic activity than PTPN22*R620 [60]. The consequences of increased catalytic activity, lost Csk binding, and other mechanisms (described below) are likely different and potentially all important for increasing the risk of autoimmunity. Mutagenic and chemical biology approaches—for example, generation of chemical activators of PTPN22 catalytic activity or probes that would disrupt the interaction between PTPN22 and CSK—would aid in the dissection of the impact of these mechanisms on PTPN22 function.

Indicative of even more complexity (Fig. 2), PTPN22 has also been reported to associate with the TNF receptor associated protein TRAF3 [61], the adapter protein Grb2 [62], the cytoskeletal protein PSTPIP [63], and the citrullinating enzyme protein deiminase 4 (PAD4) [64]. The physiological relevance of these interactions remain to be fully elucidated, but binding to TRAF3 has been shown to restrict the physical location of PTPN22 and Csk to enhance signaling from the T cell antigen receptor [61] and the interleukin-6 receptor [65]. The binding of PTPN22 to proline, serine, threonine phosphatase-interacting protein 1 (PSTPIP1), the gene for which is mutated in familial recurrent arthritis (FRA) [66, 67] and pyogenic arthritis, pyoderma gangrenosum, and acne (PAPA) syndrome [68], may direct PTPN22 to its recently recognized role in dephosphorylating the inflammasome subunit NACHT, LRR and PYD domains-containing protein 3 (NLRP3) [69]. This dephosphorylation was found to stimulate inflammasome activation and subsequent interleukin-1 β production [69]. Importantly, PTPN22*W620 also bound NLRP3, but was more effective in dephosphorylating it, leading to increased IL-1 β production. Finally, the binding of PTPN22 to PAD4 reportedly only involved the major allele PTPN22*R620, while the disease-predisposing variant did not bind [64]. The authors propose that this difference may result in increased protein citrullination in RA patients carrying the 1858T allele.

Another likely important aspect of the biology of PTPN22 is its regulation by mechanisms that modulate T cell function, such as its direct transcriptional suppression by the regulatory T cell transcription factor Foxp3 [70] and by inhibition of translation of its mRNA by the T cell modulating micro-RNA mir-181a [71]. These findings emphasize the importance of PTPN22 fine-tuning in the complex, but important, regulation of T cell immunity.

T and B cell mechanisms by which PTPN22*W620 may drive autoimmunity

The scientific community has not yet reached a consensus on how exactly PTPN22*W620 increases the risk of autoimmunity. Most investigators have focused on T cells. Some have proposed that PTPN22*W620 alters T cell antigen receptor signaling during thymic selection to promote the survival of autoreactive T cells that later participate in self-reactivity [72, 73]. One study suggested that Treg are less effective in 1858T carriers at suppressing activation of effector T cells [27] (Fig. 3). Several *in vitro* studies with human T cells have showed that PTPN22*W620 decreases TCR signaling, as a gain-of-function effect would predict [60, 74]. This was seen as diminished tyrosine phosphorylation of early signaling molecules and reduced calcium mobilization [60]. In contrast, experiments in mouse T cells largely came to the opposite conclusion [75]. Despite these differences in TCR signaling effects between the two species, the disease-predisposing allele causes many of the same perturbations in T and B cell immunity in both species [75]. In addition, other pathways activated by TCR signaling in human T cells (including the extracellular signal-regulated kinase [ERK] and protein kinase B [PKB/AKT] pathways) were found to be enhanced in 1858T carriers. This suggests that the PTPN22 W620 mechanism of action in T cells and the consequent immunopathogenic effects are complex. Indeed, inhibition of autoimmune-protective IL-10 release, enhancement of IL-2 and IFN γ release, and expansion of the memory T cell compartment have been variably reported in studies of W620 in human T cells [60, 74, 76, 77].

Intriguingly, while loss of PTPN22 in B cells does not seem to impact BCR signaling [78], multiple reports suggest that the W620 variation results in inhibition of human B cell activation. Although the underlying molecular mechanism remains to be further clarified, these observations suggest that PTPN22 W620 can impinge on the pathogenesis of autoimmunity by impairing the elimination of autoreactive B cells [78–80]. This conclusion is also supported by experiments in humanized mice [79]. Furthermore, overexpression of Ptpn22 W619 only in B cells was sufficient to cause spontaneous features of autoimmunity on a mixed C57BL/6J-129/Sv mouse background [81].

Cell-type specific contributions of PTPN22 to disease

Since PTPN22 is expressed in all leukocyte lineages, it is plausible that PTPN22*W620 contributes to the pathogenesis of different rheumatological conditions through a mix of effects on different immune cell lineages, but perhaps with a different weight of each lineage in each disease. We extrapolate this assumption from the varying roles that different immune cell lineages are thought to play in the pathogenesis of each disease. For example, in diseases where autoantibodies are recognized to be particularly important (*e.g.*, SLE), dysfunction of PTPN22*W620-expressing B cells is likely to play a larger role. Similarly, in diseases where a primary dysfunction of neutrophils is considered instrumental for pathogenesis (*e.g.* AAV or RA), PTPN22*W620 is more likely to contribute to pathogenesis through neutrophils. However, in AAV, anti-neutrophil autoantibodies are also important, suggesting that PTPN22*W620 may also contribute to this disease through B cell dysfunction. As we learn more about the effects of PTPN22*W620 in other immune cells, such as myeloid or plasmacytoid dendritic cells, macrophages, monocytes, or eosinophils,

we will be able to hypothesize how dysfunction of these cell lineages may contribute to diseases where they are critically involved in the pathogenesis. These concepts will require lineage-specific knockout or knock-in mice for a deeper mechanistic analysis.

How PTPN22*W620 may corrupt myeloid cells in rheumatological diseases

Macrophages, dendritic cells, and neutrophils are emerging as key players in many autoimmune conditions, for example in disposition of apoptotic or necrotic cells and immune complexes in SLE [82], protein citrullination in RA, autoantigen exposure through neutrophil extracellular traps (NETs) [83], nucleic acid sensing and type I interferon production [84]. All of these cells express PTPN22, but there are relatively few papers addressing its role in these cells.

PTPN22 selectively promotes type I interferon responses after activation of myeloid-cell pattern-recognition receptors. In contrast to TCR signaling, this function of PTPN22 is not mediated by PTPN22 catalytic activity; rather PTPN22 binds to the E3 ubiquitin ligase TRAF3 and selectively promotes its Lys63-linked autoubiquitination in myeloid cells after engagement of toll-like receptors (TLRs). This leads to production of type I interferon without an effect on expression of proinflammatory cytokines, such as IL-1 β and TNF. PTPN22*W620 displays reduced binding to TRAF3, and myeloid cells carrying this variant display deficient type I interferon production following TLR stimulation. Other studies carried out in mice suggest that macrophages carrying PTPN22*W620 have hyperreactive phagocytic and pro-inflammatory abilities and/or skewed polarization [85, 86].

In neutrophils, PTPN22*W620 appears to play a strikingly different role than in T cells. Vermeren and co-workers [87] found that loss of PTPN22 impaired (rather than augmented!) Fc γ RII signaling. They measured receptor-triggered Ca²⁺ mobilization, the oxidative burst, and NETosis, all of which were reduced in PTPN22^{-/-} neutrophils. Bayley and co-workers [88] went a bit further and isolated neutrophils from genotyped RA patients or healthy volunteers and measured neutrophil activation in heterozygous (*W/*R) and homozygous (*R/*R) individuals; there was only one homozygous carrier of the disease-predisposing allele (*W/*W) in the control group and 2 in the RA group, precluding much experimentation with neutrophils of this genotype. They found that PTPN22*W620 enhanced neutrophil activation, oxidative burst, and NETosis in RA donors [88]. In contrast, Cao et al [89] reported that leukocytes (PBMC) from AAV patients with *W620 had reduced Erk activity and *IL10* transcription. However, they observed elevated activity of p38 kinase [89]. It should be noted that many experiments in this paper used mixed leukocytes – hence a difference between neutrophils and lymphocytes may have gone unnoticed.

Perhaps the rheumatological condition with the most likely manifestation of neutrophil dysfunction potentially caused by PTPN22*W620 is AAV. It is clear that ANCA play a key role in driving disease by activating neutrophils to degranulate [90], produce reactive oxygen species (ROS) [90], and extrude NETs [91]. In patients [92], vasculitis begins with local accumulation and activation of neutrophils, which rapidly undergo NETosis, apoptosis, or necrosis while driving a necrotizing inflammation that results in endothelial cell death, vascular leakage, fibrin deposition, and a subsequent monocyte and macrophage recruitment

[39]. This phase eventually evolves into a fibrin and collagen-rich lesion, which may resolve if the initial inflammation was limited, or become permanent scar tissue with lingering chronic mononuclear cell infiltrates with B and T cells in ectopic germinal center-like structures. In these instances, the inflamed artery may be permanently occluded. The events leading to the formation of a non-vascular granuloma are less understood but appear to be similar. The margins of a granuloma consist of monocytes and epithelioid macrophages that wall off a center of necrotic neutrophil-derived and fibrinous debris.

PTPN22 is involved in several steps of this pathogenesis and may influence: 1) ANCA-mediated neutrophil activation via regulation of Fc γ RIIa signaling; 2) neutrophil priming by IL-6 via TRAF3 association; 3) NET extrusion via regulation of PAD4; and 4) inflammasome-mediated production of IL-1 β , IL-18, and gasdermin D activation, leading to neutrophil cell death by pyroptosis. All of these possible points of influence may synergize with each other and with the increased numbers of autoreactive T and B cells that produce ANCA in a vicious circle of disease propagation.

Remaining key questions

While it is intellectually gratifying that a risk allele such as that of *PTPN22* is associated with so many different autoimmune diseases, it also is thought-provoking that the risk it confers varies from strong (second only to MHC) to weak or non-existent between different diseases. What can we learn from this? Are there patterns of disease manifestations that segregate the *PTPN22*-associated diseases from those that are not associated? Why do subjects who carry one or two risk alleles come down with a very specific autoimmune disease instead of another one? Clearly, other genetic and external factors must play a role, some of them in concert with *PTPN22*, some independently.

By examining the spectrum of diseases on a scale of their magnitude of association (*e.g.*, by odds ratio) (Fig. 1), one can draw a few tentative conclusions: 1) strongly associated diseases tend to have autoantibodies, the presence or titer of which correlate with the presence of the 1858T allele (*e.g.*, RA, T1D, AAV); 2) strongly associated diseases tend to have a prominent role of autoreactive T and B cells (RA, SLE, AAV); 3) diseases with a central role of neutrophils tend to associate strongly (RA, AAV); 4) diseases with a key role of Th17 cells, but little involvement of autoantibodies, tend to associate poorly (AS, PsO); 5) perhaps related to the previous point, diseases of mucosal sites tend to associate poorly, or even be protected by the 1858T allele.

Another curious observation is that arthritis is strongly associated with the 1858T allele in two diseases, RA and PsA, but not in ankylosing spondylitis. The association is weaker in sero-negative RA, suggesting that it is not the manifestation of joint disease *per se* that correlates with *PTPN22*, but the underlying immune dysfunction that can be seen as autoantibodies against immunoglobulins.

Therapeutic implications?

If indeed the degree of *PTPN22* association with a disease, or a subset of patients with the disease, tells us more about the critical mechanisms of pathogenesis, then these insights

should be helpful for the selection of new drug targets, perhaps even PTPN22 itself. One can envision using PTPN22 expression or genetic variation as a biomarker for disease predisposition or responsiveness to specific therapeutic agents. Therapeutic targeting of PTPN22 might also be useful in prevention or control of rheumatic diseases. For example, “molecular glue” compounds that re-establish the interaction between CSK and PTPN22 W620 might be able to rescue most of the immune abnormalities induced by the PTPN22 risk allele. A simpler approach using small-molecule inhibitors of PTPN22 might be sufficient to correct key pathogenic mechanisms and still exert sufficient preventative or therapeutic action. For example, inhibition of PTPN22 activity with the small-molecule compound LTV-1 was effective at rescuing B cell selection and preventing the development of autoreactive W620 B cells in a humanized mouse model [79]. Considering that in a mouse model of RA, PTPN22 promoted Th17 cell differentiation, a PTPN22 inhibitor might also be useful in treatment of the large spectrum of diseases characterized by enhanced Th17 presence/activation.

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Fig. 1. The spectrum of PTPN22 1858T-associated diseases by magnitude of the risk.

The x-axis indicates odds ratio, 1.0 being no association and <1 meaning protection. The diseases are placed above the approximate average odds ratio for heterozygous carriers from all published papers and meta-analyses.

Fig. 2. Structure, interactors, and substrates of PTPN22.

PTPN22 (green box) contains a catalytic PTP domain, a linker (thicker black line) and 4 proline rich regions (P1 – P4). The location of the R620W (C1858T) missense mutation in the P1 motif is indicated. Protein domains of interacting proteins are: protein arginine deiminase (PAD), protein tyrosine phosphatase (PTP), Src homology 2 domain (SH2), Src homology 3 domain (SH3), really interesting new gene zinc finger domain (RING), TNF receptor-associated factor domain (TRAF), Spindle pole body component 1, C-terminal homology (BBP1_c), Spindle pole component 29 homology (Spc29), Fes-CIP homology domain (FCH), and Wiscott-Aldrich protein (WASP).

Fig. 3. Effects of the *PTPN22* risk allele on the function of important immune cells. Effector T cells (Teff), regulatory T cells (Treg), B cells (B), plasma cells (PC), macrophages (Mac), and neutrophils (PMN, polymorphonuclear cells). N22*W denotes the disease-associated *PTPN22**W620 variant.