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Lymphoid tyrosine phosphatase and autoimmunity: human genetics rediscovers tyrosine phosphatases

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Abstract

A relatively large number of protein tyrosine phosphatases (PTPs) are known to regulate signaling through the T cell receptor (TCR). Recent human genetics studies have shown that several of these PTPs are encoded by major autoimmunity genes. Here, we will focus on the lymphoid tyrosine phosphatase (LYP), a critical negative modulator of TCR signaling encoded by the *PTPN22* gene. The functional analysis of autoimmune-associated *PTPN22* genetic variants suggests that genetic variability of TCR signal transduction contributes to the pathogenesis of autoimmunity in humans.

Keywords

PTPN22; LYP; Pep; Csk; Lck; TCR signaling; Tyrosine phosphatase; Autoimmunity

Tyrosine phosphatases: from TCR signaling to human autoimmunity

A relatively large number of protein tyrosine phosphatases (PTPs) are able to either upregulate or downregulate signaling through the T cell receptor (TCR). For the current classification of PTPs and an overview of all the PTPs involved in T cell activation, we refer the reader to the following reviews [1–3]. There is well-established evidence that alteration of the expression/activity of PTPs involved in TCR signaling regulation causes immunopathology in mice. One of the first examples reported was the SH2-containing PTP SHP-1, which is encoded by the gene *Ptpn6* and is a negative regulator of signaling through the TCR and other immune receptors. Functional inactivation of SHP-1 in mice gives rise to the *motheaten* phenotype, characterized by immune-deficiency, autoimmunity, and lymphoproliferation [4,5]. Another well-known example is the receptor PTP CD45, encoded by the *Ptprc* gene, which is a positive regulator of TCR signaling. CD45 is currently considered a drug target for inflammatory diseases and autoimmunity, based upon several lines of in vivo evidence, including the fact that CD45 knockout (KO) mice show severe immunodeficiency [6], while mice carrying a gain-of-function E613R mutation develop autoimmune-like disease [7].

Studies on PTPs in human immunopathology have somehow lagged behind until recently, when genetic studies have shown that PTPs make up a significant fraction of the autoimmunity genes in humans. Initial studies using the candidate-gene approach and more recent genome-wide association (GWA) studies have shown that at least six major (i.e., showing genome-wide signal in association studies) autoimmunity genes encode known PTPs (*PTPN22*, *PTPN2*, *PTPRC*, *UBASH3A*, *PTPN11*, and *PTPRT*) [8–14]. Most of these enzymes are known regulators of T cell activation [3,15]. Among the PTPs encoded by autoimmunity genes, only CD45 (encoded by *PTPRC*) has an established role in mouse autoimmunity, and excellent reviews have been published on the biochemistry and immunology of this enzyme [16,17]. Little is known about the other PTPs and/or their mechanism of action in human autoimmunity. In this review, we will focus on the PTP encoded by *PTPN22*, which is known as lymphoid tyrosine phosphatase (LYP) and is a potent modulator of TCR signaling. The results of functional genetics studies of autoimmune-predisposing *PTPN22* variants support the idea that genetic variability of TCR signaling predisposes a subset of individuals to development of autoimmune diseases. These same studies also suggest that inhibition of LYP might be beneficial in autoimmunity. If confirmed by further validation data, this will make LYP one of the first cases of a novel drug target emerging from human genetic studies.

LYP is a critical negative regulator of TCR signaling

LYP is a Class 1 cytosolic PTP [2], with expression restricted to hematopoietic cells. It belongs to a subfamily of “PEST-enriched PTPs” (corresponding to the NT4 subtype of classical PTPs according to another classification system [18]), which includes two additional enzymes: PTP-PEST (encoded by the *PTPN12* gene) and BDP1 (encoded by the *PTPN18* gene).

LYP and its mouse homolog pest-enriched phosphatase (Pep) are ~105 kD proteins characterized by a ~300-aa N-terminal tyrosine phosphatase domain and a ~200-aa C-terminal domain which includes four putative polyproline (PEST-enriched) motifs (termed P1-P4) [19,20]. The catalytic domain and the C-terminal domain are separated by a ~300-aa region called “the interdomain.” A second shorter isoform of LYP called LYP2 has been identified in resting T cells [20]. Little is known about the expression/function of LYP2 or the possible existence of additional isoforms of LYP or Pep. However, by western blotting of lysates of resting or TCR-stimulated human T cells, we observed that full-length LYP is by far the predominant isoform in these cells and that LYP2 expression levels are much lower than full-length LYP both at the mRNA and protein levels (our unpublished observation).

In T cells, LYP and Pep are potent negative regulators of TCR signaling [21–26] through dephosphorylation of several key mediators of early TCR signal transduction [25,27]. The activatory pTyr residues in the catalytic domain of the Src kinases Lck (Tyr394) and FynT (Tyr417) and of the Syk family kinase Zap70 (Tyr493) are considered to be physiological substrates of Pep and LYP. In addition to these kinases, TCRzeta, CD3epsilon, Vav, and Vcp were also identified in substrate-trapping experiments and are additional putative substrates of the phosphatase [27]. Importantly, in T cells, and presumably in other immune cells, Pep and LYP form a complex with the tyrosine kinase Csk, also a negative regulator of TCR signaling [8,21,22,25]. The complex between the phosphatase and the kinase is dependent on the interaction between the most N-terminal P1 motif of Pep/LYP and the SH3 domain of Csk [21]. The molecular basis of the Pep/ Csk interaction has been elucidated by alanine scanning of the P1 domain [28] and by crystallography [29]. In T cells, the high stoichiometry of the complex (around 50% Pep co-precipitates with Csk [25]) points to an important physiological function. Early experiments carried out in mouse cell lines overexpressing Pep mutants [25] and in Jurkat cells transfected with Pep and/or Csk [26] suggested that the interaction between Pep and Csk leads to synergistic inhibition of TCR signaling. However, as discussed below, recent data emerging from the functional characterization of human genetic variants of LYP

suggest that this model might not be universally valid and/or exhaustive. More work is needed in order to clarify the function of the LYP–Csk complex in TCR signaling. The recent finding that the phosphatase is excluded from lipid rafts in mouse T cells [30] adds complexity to the problem, since it is hard to reconcile with the high stoichiometry of the Pep–Csk complex and the main action of the phosphatase on Lck and Zap70. Also, there might be additional physiological interactors of the P1 or other domains of LYP/Pep beside Csk, and additional proteins might be recruited to the LYP/ Csk complex.

The regulation of LYP/Pep is currently an active area of research. Recently, the Zhang group showed that LYP can be phosphorylated on Ser35 by PKC, with consequent inhibition of the catalytic activity [31]. LYP and Pep contain multiple additional putative sites for Ser/Thr kinases. As mentioned below, we also recently observed phosphorylation of LYP on Tyr residues, which might contribute to regulate its activity. Additional interesting aspects of LYP/ Pep regulation are emerging from molecular and structural studies. By studying truncation mutants of the recombinant phosphatase, we recently demonstrated that the activity of LYP is modulated by an intramolecular interaction between the proximal interdomain and the catalytic domain [32]. Crystallization of the catalytic domain of the phosphatase in our hands also showed that the enzyme might be regulated by a reversible oxidation mechanism involving a back-door Cys residue [33].

Relatively little is known about the role of LYP/Pep in the immune system in vivo. Andrew Chan's group published in early 2004 the phenotype of a global *Ptpn22* KO mouse [34]. Deletion of the phosphatase caused expansion of the T cell memory compartment and increased TCR signaling in effector T cells. At the thymic level, there was a phenotype of increased positive selection [34]. The phenotype of the mouse supports the idea (originally proposed by Andre Veillette [21]) that Pep is a key negative regulator of TCR signaling. The prominent effector/memory T cell phenotype is in line with the high expression of the phosphatase in these cells ([35] and our unpublished observation). Pep is highly expressed in thymocytes as well ([35] and our unpublished observation), and its role in thymic selection might help explain the effect of the phosphatase in human autoimmunity.

An open area of discussion is whether LYP and Pep play any role in regulation of B cell activation. The KO mouse shows no alterations of signaling through the B cell receptor (BCR) [34], and low expression levels of Pep have been found in mouse B cells [35]. Expansion of B cells in germinal centers occurs in aging mice, but the phenotype has been attributed to increased T cell help [34]. However, a recent study suggested that LYP might affect signaling through the BCR in primary human B cells ([36] and see below). Thus, it is possible that the KO mouse is a less faithful model of LYP function in human B cell physiology due to compensation phenomena or perhaps to real functional differences between the human and the mouse phosphatase. Besides T cells and B cells, little is known about the role of LYP/Pep in other immune cell subpopulations. For example, a simple search of the BioGPS database [37](<http://biogps.gnf.org>) suggests that dendritic cells (DC) and natural killer (NK) cells carry high mRNA levels of LYP/Pep. More immunological studies in the available KO mouse model are warranted. However, in order to fully understand the role of LYP/Pep in the immune system, we will also need to generate additional knockout and transgenic models, engineered in order to enable deletion/overexpression of the phosphatase in selected immune cell subpopulations.

Association of *PTPN22* with human autoimmunity

Three reports in 2004 documented the association between a missense C1858T (R620W) single nucleotide polymorphism (SNP) in *PTPN22* and type 1 diabetes (T1D) [8], rheumatoid arthritis (RA) [22], and systemic lupus erythematosus (SLE) [38]. The association between *PTPN22* and T1D, RA, and SLE was subsequently widely replicated by us and others (for example, see

[39–41]) and extended to many additional autoimmune diseases, including Graves' disease [39,42,43], Addison's disease [44,45], vitiligo [46,47], myasthenia gravis [48–50], and systemic sclerosis [51]. *PTPN22* *T1858 behaves as a dominant variant, conferring increased risk of disease already when present in single copy [52,53]. The risk conferred by *PTPN22* is variable among diseases, but it is substantial in T1D and RA, with average reported odds ratios of 1.7–2.0 per single allele copy. Recent GWA studies detected a major signal on *PTPN22* for T1D and RA, and *PTPN22* currently ranks in third and second position, respectively, for single-gene contribution to the risk of T1D and RA in Caucasian populations [10]. In SLE [54] and T1D [55], the effect of *PTPN22* seems to be even more prominent in the subgroup of patients who have familiarity for autoimmunity.

As mentioned, the association of *PTPN22* C1858T with autoimmune diseases has been replicated across different populations. For example, the association with T1D has been replicated in the American [56,57], Italian [58], German [59], Spanish [60], English [39], Estonian [61], and Ukrainian [62] populations. These studies also showed that there are significant differences in the frequency of the *T1858 allele among populations. The *T1858 allele is more frequent (around 12.5%) in Northern than in Southern Europeans, while it is almost absent in African-American and Asian populations [63–66]. Possible explanations for such dramatic geographic differences in allele frequency are that the *T1858 allele appeared recently during evolution and/or its frequency is severely affected by selection. By analyzing extended haplotype homozygosity, McPartland et al. showed evidence of positive selection at the *PTPN22* locus [67]. One intriguing hypothesis is that the *T1858 allele confers protection toward some highly prevalent infectious disease. Only a few studies have been carried out on *PTPN22* in infectious diseases so far. Chapman et al. found that the *T1858 allele might increase risk of complication in patients affected by common pneumococcal infections [68], while another study on immuno-compromised transplant recipients found an opposite protective effect of the *T1858 allele against infections [69]. In tuberculosis (TB), we found some evidence that the *T1858 allele might play a protective role [70,71]. This is an interesting finding considering that TB might have been a powerful selective force in Northern Europe. However, these data need to be replicated and backed by more mechanistic studies before any conclusions can be drawn about the possible role of TB in shaping selection at the *PTPN22* locus.

PTPN22 C1858T belongs to a growing family of “shared autoimmunity loci,” which are associated with multiple autoimmune diseases. Together with a subset of these genes, *PTPN22* also has been shown to contribute to the recurrence of multiple different autoimmune diseases in certain families [72]. The identification and functional dissection of shared autoimmunity loci could potentially unravel major pathogenic mechanisms of autoimmunity. Association with certain but not other autoimmune diseases also can give important hints on the mechanism of action of shared autoimmunity loci. For *PTPN22*, some of the negative findings might be due to variable combinations of small effect, low frequency of the allele, and sometime low statistical power of the study. However, well-powered studies found no association with multiple sclerosis and celiac disease [73–76]. The *T1858 allele was reported to have negligible effect on the risk of inflammatory bowel disease (for example, see [77] and [78]), but a recent large study suggests that in Crohn's disease, it might be a protective factor [79]. A similar protective effect has been reported in Behcet's disease [80]. Interestingly, *PTPN22* *T1858 is associated with psoriatic arthritis [81,82] but not with psoriasis. However, a psoriasis locus might be located in close proximity to *PTPN22* [83,84], suggesting that *PTPN22* might lay within an autoimmunity hot spot on chromosome 1. The reason why *PTPN22* associates with some but not other major autoimmune diseases is unclear at the moment. It has been suggested that the *PTPN22* C1858T polymorphism preferentially associates with diseases characterized by a strong autoantibody (auto-Ab) component [85]. In favor of this hypothesis, *PTPN22* associates with diseases which are exquisitely auto-Ab-

mediated, like myasthenia gravis; also, it has been reported by some groups that the association between *PTPN22* and RA is restricted to the anti-cyclic citrullinated peptide Ab positive subgroup [86]. However, it is unclear whether the association of *PTPN22* with auto-Ab is a causal one, and some observations do not fit well with this theory, for example, *PTPN22* does not associate with celiac disease, a disease characterized by auto-Ab production.

Genetic dissection and linkage studies in RA and T1D have determined that *PTPN22* C1858T is a primary disease locus [87–91]. Studies are ongoing to clarify whether there are additional predisposition/protection loci within or close to *PTPN22*. We reported a rare missense variation R263Q within the catalytic domain, which is functional (see below) and segregates on different haplotypes than the R620W variant [92]. A recent comprehensive analysis of the T1D Genetic Consortium (T1DGC) collection has confirmed the primary association between T1D and C1858T and found evidence for an independent protective haplotype (Steck et al., manuscript in press). Also, there is some evidence that a variation G-1123C in the promoter region of *PTPN22* associates with autoimmunity [93]. The data on this SNP have been difficult to interpret due to the strict linkage disequilibrium (LD) between the G-1123C and the C1858T SNPs in European populations [94]. In the Sardinian population, where LD between the two variants is lower, we could detect a strong signal at the C1858T locus only, suggesting that in the presence of C1858T, the effect of G-1123C might be a minor one [90]. However, the G-1123C polymorphism might be a significant risk factor in Asian populations, and more work is needed in order to establish the association of this SNP with autoimmunity and its functional effect.

Other important areas of genetic research concern possible interactions between *PTPN22* and other genetic or environmental factors, and whether *PTPN22* associates with prognosis and disease variables other than incidence. Some groups reported that the risk conferred by *PTPN22* depends on HLA genotypes [95], while no *PTPN22*-HLA interaction has been found in other studies [60,96,97]. Few studies reported interactions with environmental factors, for example, smoking in RA [97,98] and early exposure to cow milk in T1D [99]. In some populations, the association between *PTPN22* and autoimmunity seems to depend on gender [59,100]; however, this finding has not been universally confirmed, and it is of difficult interpretation at the moment. As for the clinical variability of disease, beside the mentioned data on the association with auto-Ab-positive subsets of RA, there are sporadic reports about a possible effect of *PTPN22* on age of onset [56,60]. The possible value of *PTPN22* in early diagnosis/prognosis has been assessed in prospective studies in T1D and RA. An association with radiographic progression of disease has been reported in RA [101]. The data in T1D are less homogeneous, and association with progression to disease has been found in some studies [102] but not in others [103], including a notable one, which reported exclusive association with development of persistent auto-Abs [104].

Functional genetics of the *PTPN22* C1858T polymorphism

Understanding the effect of the R620W polymorphism on the function of LYP/Pep is obviously of critical importance. Several functional genetics studies have focused on possible differences in signal transduction through the TCR in cells from carriers of the W620 variant of LYP when compared to subjects carrying exclusively the R620 variant. We reported that primary T cells from T1D patients carrying the W620 allele exhibited reduced IL-2 response to TCR engagement. These findings were replicated by Aarnisalo et al. in T1D [105]. The Buckner group reported decreased TCR-induced phosphorylation of early signaling intermediates and Ca^{++} mobilization in T cells from *T1858 homozygous RA patients [36]. Importantly, the same group also extended their studies to B cells and reported that BCR signaling in primary B cells from carriers of the *T1858 allele is also reduced [36]. Thus, the vast majority of reports points to decreased TCR-mediated T cell activation in primary T cells from carriers of the

LYP-W620 variant. The only exception so far is a single report on myasthenia gravis, where the R620W polymorphism associated with increased TCR-induced IL-2 production [106]; however, this finding has not been replicated by another group [50]. Further functional genetics studies on large samples of primary T cells from healthy controls are ongoing in several laboratories and hopefully will help solidify even further our view of the effect of the polymorphism on T cell activation.

Despite most studies have focused so far on T cells and on readouts of TCR signaling, as mentioned, the polymorphism seems to affect signaling through the BCR as well [36]. It is currently unknown whether the polymorphism affects the function of other cell types which are critical for autoimmunity, for example, DC and NK/NKT cells.

Few studies have looked so far at possible effects of the polymorphism on the phenotype of primary T and B cells from genotyped patients and controls. For example, a study suggested that *T1858 carriers have increased numbers of memory T cells, and that T cells from these individuals might secrete less of the immunosuppressive IL-10 cytokine [36]. Much progress is expected in this area in the near future, which will shed light on the mechanism of action of the polymorphism in autoimmunity.

At the molecular level, the *PTPN22* C1858T polymorphism leads to a substitution of a Trp for an Arg at position 620. This is a nonconservative variation of a residue within the P1 motif, which had been previously shown to be critical for the Pep-Csk binding. As a consequence, the autoimmune-associated LYP-W620 variant exhibits reduced interaction with Csk [8,22]. Besides its effect on the complex between the kinase and the phosphatase, the mechanism of action of the polymorphism at the biochemical and molecular level is still poorly understood. By studying T cells overexpressing LYP-W620 or LYP-R620, we found that LYP-W620 expression induces a gain-of-function decrease of TCR-induced phosphorylation of early key signaling players and decreased TCR-induced Ca^{++} mobilization [23]. In our hands, also the autoimmune-associated LYP-W620 variant showed increased phosphatase activity when compared to LYP-R620 [23]. We concluded that gain-of-function inhibition of TCR signaling by LYP-W620, mediated at least in part by increased phosphatase activity, is responsible for the decreased T cell activation observed in carriers of the pathogenic phosphatase variant. These conclusions have been recently challenged by a report from Zikherman et al., claiming that the W620 mutant of LYP (and the homolog W619 mutant of Pep) is a hypomorph variant, and the gain-of-function phenotype is an artifact which arises when the phosphatase is overexpressed without parallel overexpression of Csk [35]. However, it is unclear whether the system used by Zikherman et al. (based on co-transfection of cells with LYP/Pep, Csk, and GFP) is more respectful of the physiological stoichiometry of the interaction between the phosphatase and the kinase. It also remains to be explained how an hypomorph allele of *PTPN22* would give rise to the anomalies of T cell activation reported in primary T cells from LYP-W620 carriers. More studies in multiple systems including cells from mice carrying knock-in mutations of LYP/Pep (which are in preparation in several laboratories in the world) are needed in order to better define the effect of the mutation on cell signaling.

We and others are also actively investigating how the mutation affects the function of LYP at the molecular level. LYP mRNA levels seem to be unaffected by the polymorphism, suggesting that the mutation acts mainly at the protein level [107]. We recently found that LYP undergoes Csk-dependent phosphorylation on at least one tyrosine, which results in inhibition of the phosphatase activity. We suggest that anomalies in Csk-dependent posttranslational modification(s) of LYP mediate at least in part the molecular mechanism of the R620W variation (Fiorillo et al., manuscript submitted). Csk-independent mechanisms are also possible, including impaired binding to additional interactors and/or recruitment of LYP-W620 to an unknown protein through its P1-W620 motif. One of the challenges of the current studies

at the molecular level is to reconcile the gain-of-function phenotype of LYP-W620 with previous results suggesting a model of synergistic inhibition of signaling by the complex between the kinase and the phosphatase [25,26]. A possible explanation is that the regulation of LYP and Pep is not entirely conserved: indeed, the two phosphatases share relatively low (<60%) identity in the interdomain, which might be important for regulation.

(Putative) mechanisms of action of PTPN22 in autoimmunity

Our current working model is that gain-of-function inhibition of signaling in T cells (and perhaps other cell types) mediates the pathogenic action of the polymorphism and the increased risk of autoimmunity of carriers of LYP-W620. It might sound a little counter-intuitive that decreased immune cell activation leads to autoimmunity; however, our model is in line with the current view that decreased TCR signaling increases risk of at least a subset of autoimmune diseases. Decreased TCR signaling has been reported in T cells from NOD mice [108] and in peripheral T cells from T1D patients [109]. Mechanistic evidence of a link between decreased TCR signaling and autoimmunity was also provided by the description of the SKG mouse by Sakaguchi et al., in 2003 [110]. In this mouse, a loss-of-function mutation of Zap70 (one of the physiological substrates of LYP) causes a spontaneous autoimmune disease which is remarkably similar to human RA. Similar findings of autoimmune-like disease in mice carrying loss-of-function of Zap70 have been subsequently reported by two additional groups [111, 112]. These studies also are showing that decreased TCR signaling impinges on RA through multiple mechanisms [111]. In the case of *PTPN22*, we could also speculate that some mechanisms might be prominent over others in different diseases, or even in different subjects affected by the same disease.

One of the favored models is that gain-of-function inhibition of TCR signaling at the thymic level leads to decreased negative selection and elimination of potentially autoreactive T cells and/or decreased production of natural regulatory T cells (Treg). The observations that (1) Pep is highly expressed in the thymus, (2) the *Ptpn22* KO mouse shows anomalies of thymic selection, and (3) normalization of TCR signaling in the thymus is able to rescue the phenotype of the SKG mouse [110] provide additional support to the “thymic selection” theory. In addition or alternative to thymic selection anomalies, other mechanisms have been envisioned. For example, an anomalous increase in the activity of LYP in effector T cells might negatively impact the activity/expansion of peripheral Treg in carriers of LYP-W620 [113]. Decreased TCR-induced production of IL-2 by effector T cells is known to impair expansion of Treg in mouse T1D, and neutralization of IL-2 in vivo induces autoimmunity in mice through a Treg-mediated mechanism [114–116]. Marson et al. also recently identified *PTPN22* among a group of genes that are highly occupied by FoxP3 in Treg. The same study also showed that Treg carry lower levels of the phosphatase compared to effector T cells [113], suggesting a direct mechanism by which gain-of-function of LYP can affect Treg function. Since TCR signaling intensity is an important regulator of naïve T cell differentiation, it is also possible that decreased TCR signaling affects polarization of naïve T cells into specialized T helper populations, for example, favoring the appearance of diabetogenic interferon- γ -producing Th1 cells, in carriers of LYP-W620. The observation that peripheral T cells from LYP-W620 carriers have a different cytokine secretion pattern characterized by reduced production of IL-10 is in line with this hypothesis. Other mechanisms are possible and, considering the association between *PTPN22* and the presence of auto-Ab, we cannot exclude that LYP-W620 also affects B cell differentiation and/or tolerization directly.

LYP as a possible drug target for autoimmunity

Several academic laboratories have begun developing small molecule inhibitors of LYP [31, 117,118]. Given the increased activity of LYP-W620, it has been hypothesized that a selective

inhibitor of LYP could revert the negative effects of the W620 variant on TCR signaling, and thus constitute an effective etiological therapy of autoimmunity in carriers of the autoimmune-predisposing variant. Because *PTPN22* is implicated in many prevalent autoimmune diseases (and perhaps even in transplant rejection [119]), an anti-LYP drug could be of broader value for the treatment of multiple human conditions. Also, the phenotype of the KO mouse suggests that a specific inhibitor of *PTPN22* is likely to have limited side effects.

Although it remains to be proven that the mechanism of action of LYP in autoimmunity is reversible, the success of trials targeting T1D with monoclonal antibodies against CD3 supports the idea that positive modulation of the TCR helps re-establishing tolerance in at least a subset of autoimmune patients [120,121]. In support of the above-mentioned hypothesis, we also recently found a rare loss-of-function LYP-R263Q genetic variation, which segregates on haplotypes different from the R620W one and plays a protective role in SLE [92].

Further studies in animal models are needed in order to validate LYP as a drug target for autoimmunity. Importantly, therapeutic inhibition of LYP in autoimmunity might also carry some risks. For example, excessive inhibition of LYP activity might lead to parallel counterproductive increase in TCR signaling in effector T cells. Although the *Ptpn22* KO mutation on the B6 background fails to induce autoimmunity [34], Zikherman et al. recently showed that crossing of the *Ptpn22* KO mouse with the CD45 E613R (“wedge”) model led to more severe autoimmunity [35]. Since spontaneous autoimmunity on B6 background in the CD45 wedge model is driven by increased TCR [122] and BCR signaling [123,124], the results of Zikherman et al. suggest that inhibition of LYP might be counterproductive in diseases or subsets of diseases with a strong component of TCR or BCR hyperactivity (which has been observed in large subsets of lupus patients [125–127]) and thus not easily extended to noncarriers of gain-of-function LYP mutation(s).

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