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Protein tyrosine phosphatases in multiple myeloma

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ABSTRACT

Many cell signaling pathways are activated or deactivated by protein tyrosine phosphorylation and dephosphorylation, catalyzed by protein tyrosine kinases (PTKs) and protein tyrosine phosphatases (PTPs), respectively. Even though PTPs are as important as PTKs in this process, their role has been neglected for a long time. Multiple myeloma (MM) is a cancer of plasma cells, which is characterized by production of monoclonal immunoglobulin, anemia and destruction of bone. MM is still incurable with high relapse frequency after treatment. In this review, we highlight the PTPs that were previously described in MM or have a role that can be relevant in a myeloma context. Our purpose is to show that despite the importance of PTPs in MM pathogenesis, many unanswered questions in this field need to be addressed. This might help to detect novel treatment strategies for MM patients.

1. Introduction

The roles of protein tyrosine kinases (PTKs) in oncogenic processes have been extensively investigated during the last decades. Interestingly, their counterparts, the protein tyrosine phosphatases (PTPs), have largely been neglected for a long time. This might be due to the false notion that PTPs were enzymes whose function was only to counteract PTKs in a linear manner from receptor to target genes. However, it is now known that phosphorylation/dephosphorylation networks are tightly regulated through a complex combination of negative and positive feedback loops, and both PTPs and PTKs are equally important in regulating these processes [1]. In addition, PTPs have long been regarded as "undruggable" due to their highly conserved structure and their preference for recognizing negatively charged molecules. However, during the last years it has been clarified that these enzymes can be considered feasible drug targets by demonstrating the reactivation of tumor suppressor phosphatases or inhibition of oncogenic phosphatases [2]. Allosteric activation or inhibition of the catalytic domain or regulatory domains are promising possibilities to modulate PTP activity. For instance, many receptor-like PTPs are inactivated by dimerization. Therefore, inhibitors that target the extracellular domains of these phosphatases and induce their dimerization could be used to block downstream signaling [3].

Multiple myeloma (MM) is a cancer of plasma cells (PCs), which is characterized by the production of monoclonal immunoglobulin, anemia, and the destruction of bone. Introduction of proteasome inhibitors, immuno-modulators (IMiDs), and monoclonal antibodies against cluster of differentiation (CD)38 (a glycoprotein on the surface of myeloma cells) have resulted in significant improvements in survival for patients with MM. Despite these advances in treatment in recent years, MM is still considered a fatal disease. A specific trait of MM is its particular location to the bone marrow (BM) and the cells' dependency on signals from this environment such as cytokines. External signals activate crucial intracellular oncogenic signaling pathways such as mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase (ERK), Janus kinase (JAK)/signal transducer and activator of transcription (STAT) and SRC [4,5]. A deeper understanding of mechanisms involved in perturbation of these signaling pathways could help to improve therapy outcome. Even though expression of many tyrosine phosphatases is shown to be dysregulated in various cancers, their role is not well studied in MM. A literature search on MM and kinases and phosphatases in Pubmed demonstrated a large discrepancy between the two enzyme classes. For this, we used the terms "MM" and "phosphatase or kinase" as keywords with no restriction on the year of publication.

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While 2609 studies analyzed the role of kinases in MM, only 670 studies could be found on the role of phosphatases in MM.

PTPs can be divided into three separate superfamilies depending on recent structure-sequence-based phosphatase classification: Class I (105 genes), II (1 gene) and III (3 genes) [6,7]. The phosphatases discussed in this review belong to class I, with the exception of cell division cycle (CDC)25A, -B and -C, which constitute class III. A literature search of the 109 known PTPs (by gene or protein name) and MM revealed that only 19 (17.4%) of them have been investigated in MM, and few of them in detail. In this review, we highlight the PTPs that have been previously described in MM or have a role that can be relevant in a myeloma context. In addition, we show the expression level of these PTPs and investigate their clinical significance in MM patients. The aim of this review is to emphasize that despite the importance of PTPs in MM pathogenesis, their role has not been well investigated.

2. Protein tyrosine phosphatases in multiple myeloma

2.1. CD45 phosphatase

CD45 (encoded by the gene *PTPRC*) is a receptor PTP that was originally known as leukocyte common antigen since its presence distinguishes leukocytes from erythrocytes and non-hematopoietic cells [8]. CD45 plays a critical role in regulating antigen receptor signaling, which is essential for lymphocyte development, survival, and function [9]. CD45 contains a single transmembrane domain. Its cytoplasmic portion consists of tandem PTPase domains and a C-terminal tail and utilizes the same chemical mechanism for catalysis of substrate as other PTPs [10]. Progression of MM is associated with a decline in CD45 on the MM cells, as in normal plasma cell differentiation [11,12].

Clinical significance [13,14] of CD45 subsets in MM is a matter of debate. However, analysis of RNA seq data on purified MM cells from 767 diagnostic patient samples in the online database MM research foundation (MMRF) CoMMpass IA13 (https://research.themmrf.org/) supports studies showing that patients with lower CD45 expression have longer overall and progression-free survival (Fig. 1A). There is also an inconsistency in the description of the proliferative capability of MM cells expressing CD45 [15–19]. One of the models reported is that MM has various stages of progression. Immature $CD45^+$ PCs predominate at the initial stage of progression. Immature $CD45^+$ MM cells have high capacity of homing in co-culture with bone marrow stromal cells (BMSC) due to high levels of homing receptors and proteases [20,21]. In addition, these immature MM cells are the subpopulation that can grow in response to interleukin (IL)-6, the most important growth factor for myeloma cells [22]. Upon IL-6 stimulation, STAT3 and MAPK are activated in both $CD45^+$ and $CD45^-$ cells [23,24]. However, IL-6-induced proliferation of myeloma cells is not dependent only on activation of these molecules but requires also activation of LCK/YES1 novel tyrosine kinase (LYN) (a member of the SRC family of PTKs) associated with CD45 [12,23,24]. Moreover, IL-6 causes elevation of myeloid cell leukemia (MCL)1, an anti-apoptotic protein, in $CD45^+$ U266 cells but not in $CD45^-$ U266 cells [22]. These features of $CD45^+$ MM cells allow them to be the predominant BM homing clone in MM [25].

Even though CD45 expression is an advantage for MM cells when responding to IL-6, it also results in apoptosis of $CD45^+$ myeloma cells dependent upon circumstantial stimuli. In a study of MM cell lines, it was indicated that the $CD45^+$ population activated LYN in response to cell stress. In this context, active LYN leads to activation of phospholipase C gamma (PLCG), followed by high Ca^{2+} influx and induction of apoptosis [26–29]. This finding supports the notion that $CD45^+$

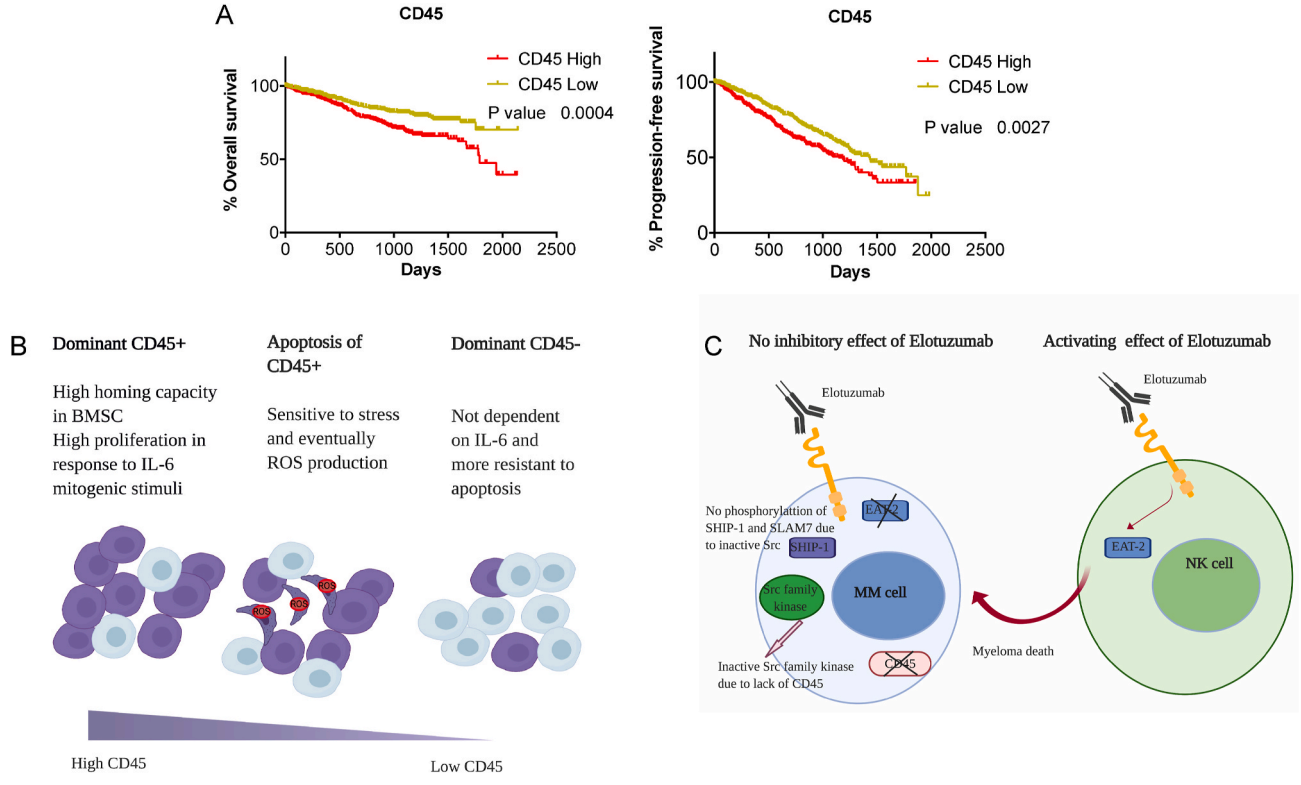

Fig. 1. The phosphatase CD45 (*PTPRC*) in MM. A) Kaplan-Meier curves showing overall and progression-free survival in MM patients dichotomized in two equal groups with high and low CD45 expression, derived from MMRF CoMMpass IA13. The survival curves were compared with the log-rank test. The statistical analysis was performed in Graphpad Prism (version 5.03).
B) Model showing decline in CD45 during the progression of MM.
C) Schematic figure showing how and why elotuzumab activates natural killer (NK) cells but has no inhibitory effect on multiple myeloma (MM) despite of the lack of Ewing's sarcoma-associated transcript (EAT)-2. Figures B and C were created with BioRender.

immature myeloma cells are growing but are mortal, depending on the environment, whereas CD45^{-} cells are resting but relatively resistant to apoptosis [22]. Moreover, even though IL-6 is a growth factor only for CD45^{+} human MM cell lines (HMCLs), other growth factors such as insulin-like growth factor 1 (IGF1), fibroblast growth factor (FGF), hepatocyte growth factor (HGF) and epidermal growth factor (EGF) are growth promoting only for CD45^{-} HMCLs [30]. It should be noted that the amount of IL-6 is limited in the BM of MM patients [22]. Therefore, relatively low levels of IL-6 in the BM promote CD45^{+} cell apoptosis under physiological conditions or lead to their differentiation into CD45^{-} MM cells [22,25]. Consequently, at the end, the balance between the CD45^{+} and CD45^{-} compartments is inverted in MM ([16,28] and Fig. 1B).

Interestingly, expression of CD45 influences how MM cells respond to various drugs, which can be beneficial for the choice of treatment. For instance, CD45 negatively regulates the phosphoinositide 3-kinase (PI3K) pathway [28,31]. Therefore, CD45^{-} MM cells are more responsive to inhibitors that target this pathway [28,32,33]. Contrary to CD45^{-} MM cell subpopulations with an active PI3K pathway, CD45^{+} subpopulations have an active JAK/STAT pathway and are more sensitive to JAK inhibitors than CD45^{-} cells [34].

The expression of CD45 in myeloma cells also affects to what extent the cells are responsive to signaling lymphocytic activation molecule (SLAMF)7 antibodies. SLAM family receptors are hematopoietic-cell-specific receptors playing critical roles in immune regulation. High expression of SLAMF7 in MM led to the introduction of a monoclonal antibody against SLAM7, elotuzumab, as treatment for MM. In natural killer (NK) cells, SLAMF7 is usually a positive regulator of NK cell activation. Elotuzumab binding to SLAM7 on the surface of NK cells recruits the adaptor protein Ewing's sarcoma-associated transcript 2 (EAT-2). EAT-2 signaling leads to NK cell activation and enhances cytotoxicity toward the tumor cell. Therefore, EAT-2 is required for SLAMF7 to activate NK cells. In the absence of EAT-2, SLAMF7 mediates inhibitory effects. Many MM cells, even though they express SLAMF7 and lack EAT-2, are not inhibited by elotuzumab *in vitro*. Using NK cells lacking EAT-2, it has been found that SLAMF7 mediates its inhibitory effect through SLAMF7 phosphorylation, which further phosphorylates the SH-2 containing inositol 5′ polyphosphatase (SHIP)1. Phosphorylation of SLAM7 and SHIP1 is triggered through SRC family kinases including SRC, LYN and FYN. As most mature MM cells are negative for CD45 and have inactive SRC family kinases, they are not inhibited by elotuzumab. This explains why elotuzumab has no direct effect on MM cells *in vitro* but rather eliminates these cells by activating normal immune cells, such as NK cells ([35,36] and Fig. 1C).

2.2. Mitogen-activated protein kinase phosphatases (MKPs)

MKPs represent a subfamily within a larger group of dual-specificity PTPs (DUSP), which can dephosphorylate serine, threonine as well as tyrosine residues. MKPs play an important role in determining the magnitude and duration of MAPK signaling by dephosphorylating and deactivating MAPK [37]. MKPs form a family with 10 members including DUSP1, DUSP2, DUSP4, DUSP5, DUSP6, DUSP7, DUSP8, DUSP9, DUSP10, and DUSP16. Our analysis of the MMRF CoMMpass IA13 database indicated that *DUSP1* and *DUSP5* are highly expressed on the mRNA level in MM PCs with transcripts per million (TPM) values that reach above 1000 (Fig. 2A). In addition, analyzing gene expression data obtained from the public database Oncomine (Agnelli Myeloma 3, Zhan myeloma 3 and Zhan myeloma datasets) (https://www.oncomine.org/), we found that *DSUP1* and *DUSP5* are significantly higher expressed in PCs from MM and monoclonal gammopathy of undetermined significance (MGUS) patients than in normal PC samples ([38] and Table 1). This supports possible importance of these phosphatases in MM. A study by Walker et al. identified *DUSP2* and protein tyrosine phosphatase non-receptor (*PTPN)11* as mutated driver genes in some newly diagnosed MM patients [39]. *DUSP2* was expressed higher in PCs from 12 smoldering MM patients than in 22 normal BM control cells (Table 1).

Previous gene expression analysis of MM cells with clinical information identified *DUSP6* to be induced in MM cells harboring a constitutively active mutant NRAS gene [40] and *DUSP6* and *DUSP10* as genes that were associated with poor prognosis (Fig. 3 and [41,42]). Interestingly, *DUSP6* was also among the genes that were expressed higher in MM PCs than in normal control PCs in Agnelli Myeloma 3, Zhan myeloma 3 and Zhan myeloma datasets (Table 1). Higher expression of *DUSP10* was only found in Angeli Myeloma 3 dataset, which is a comparison of BM PCs from 133 MM patients with PCs from 5 healthy controls (Table 1). The chromosomal translocation t(4; 14) is seen in about 10–20% of the cases of MM and is associated with a poor prognosis. This translocation is associated with upregulated expression

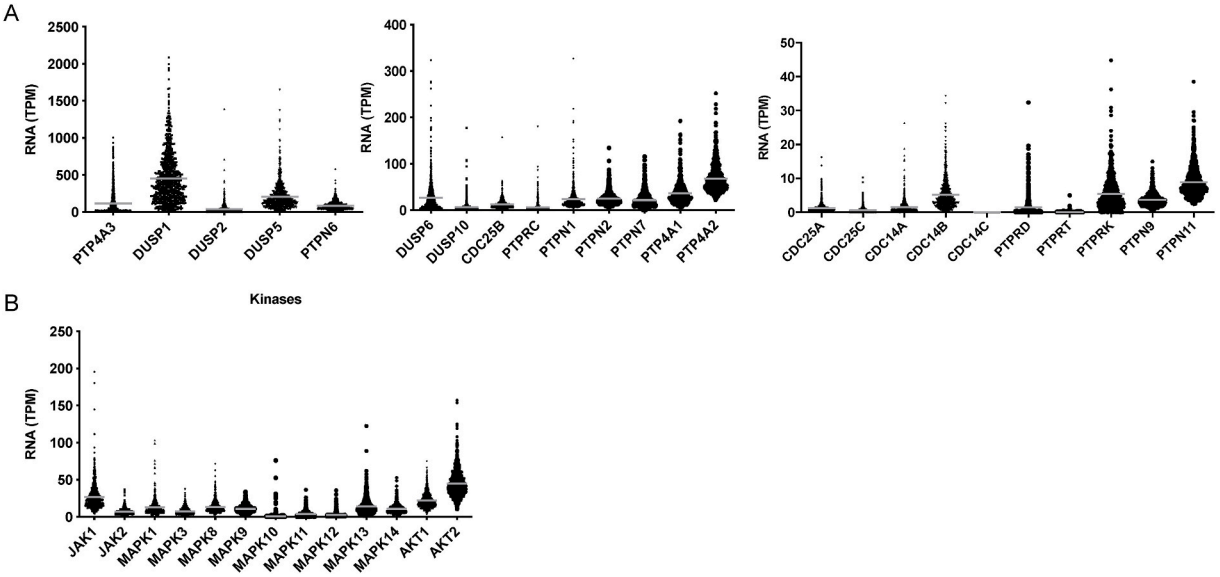

Fig. 2. RNA-seq data showing expression of A) protein tyrosine phosphatases described in this review paper and B) some important protein tyrosine kinases in 767 newly diagnosed MM patients derived from MMRF CoMMpass IA13. Note the large differences in Y axis scale between plots. TPM: Transcripts per million. The grey line shows the mean expression.

Table 1
Microarray gene expression analyses of the list of the protein tyrosine phosphatases in myeloma and MGUS patients from 3 different datasets.

	Angeli Myeloma 3				Zhan myeloma 3				Zhan myeloma			
	MGUS (11) vs. normal (5) PC		MM (133) vs. normal (5) PC		MGUS (44) vs. normal (22) PC		SMM (12) vs. normal (22) PC		MGUS (5) vs. normal (37) PC and tonsil BC (7)		MM (74) vs. normal (37) PC and tonsil BC (7)	
	Fold change	pvalue	Fold change	pvalue	Fold change	pvalue	Fold change	pvalue	Fold change	pvalue	Fold change	pvalue
DUSP1	**1.73**	**0.049**	**1.83**	**0.03**			**1.52**	**0.03**			**1.54**	**0.01**
DUSP2							**2.63**	**0.01**				
DUSP5	**2.99**	**0.006**	**3.98**	**0.003**	**1.48**	**0.011**	**2.59**	**1.84E-04**	**1.71**	**0.042**	**2.84**	**1.46E-07**
DUSP6			**1.64**	**1.33E-05**	**1.68**	**0.004**	**2.86**	**0.005**			**1.50**	**3.84E-06**
DUSP10	**1.35**	**0.022**	**1.52**	**0.004**								
PTP4A1			**1.57**	**0.02**			**1.76**	**3.96E-04**			**1.41**	**1.04E-07**
PTP4A2					**1.35**	**9.44E-04**	**1.64**	**5.20E-04**				
PTP4A3	**1.66**	**0.045**	**3.09**	**3.45E-04**	**3.19**	**2.03E-04**	**10.75**	**1.2E-04**				
CDC25A			**1.38**	**0.002**								
CDC25B							**1.80**	**0.02**				
CDC25C									**1.51**	**0.02**		
CDC14B					**1.55**	**3.49E-05**	**2.22**	**0.001**				
PTPN11					**1.37**	**6.29E-04**	**2.07**	**6.81E-06**				
PTPN6							**1.44**	**0.03**				
PTPN1	**1.53**	**0.04**			**1.59**	**0.023**	**1.31**	**0.03**				
PTPN2							**1.48**	**1.25E-04**				
PTPN7					**1.44**	**9.85E-04**						
PTPRD	**1.38**	**8.79E-04**							**1.60**	**0.021**		
PTPRK			**1.79**	**0.02**	**2.66**	**9.48E-10**	**3.79**	**2.49E-04**	**2.39**	**0.052**	**4.29**	**1.48E-14**

Data is derived from Oncomine (http://www.oncomine.org). Samples compared in each dataset are indicated in the table. Numbers in parentheses represent the number of samples in each clinical group. Only the described PTPs with fold change ≥1.3 and p-value ≤0.05 are listed in the table. DUSP10, PTP4A3, CDC14B, PTPN6 probes were not detected in Zhan myeloma. In other case, the blank means fold change is lower or P value higher than the described threshold. *t*-Test was used to calculate the P value. MM: Multiple Myeloma, MGUS: Monoclonal gammopathy of undetermined significance, SMM: Smoldering Multiple Myeloma, PC: Plasma cell, BC: B cell.

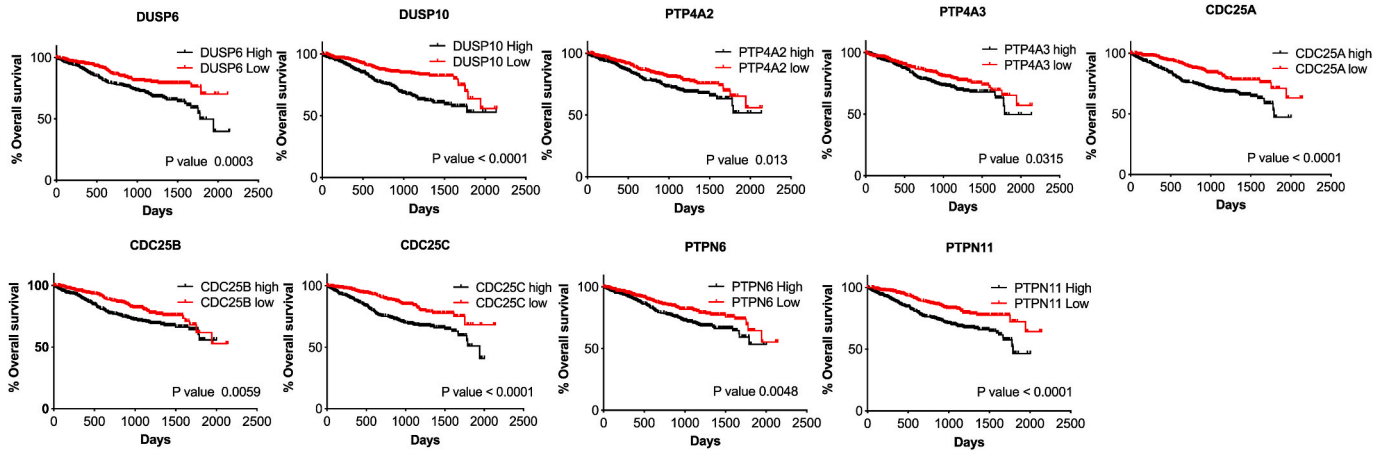

Fig. 3. Kaplan-Meier curves showing association between expression level of some protein tyrosine phosphatases (PTPs) and overall survival of patients with MM. Data derived from MMRF CoMMpass IA13. 767 patients were divided in two groups of equal size. We did analysis on all the PTPs shown in Fig. 2A and in this figure, we only include the ones that were statistically significant. The survival curves were compared with the log-rank test. The statistical analysis was performed in Graphpad Prism (version 5.03).

of fibroblast growth factor receptor (FGFR)3 and myeloma SET domain protein (MMSET). Gene expression analysis defined *DUSP10* to be more highly expressed in t(4; 14) MM cells than in t(4; 14)-negative tumors [43]. Knocking down FGFR3 in a MM cell line led to downregulation of DUSP6 [44] and DUSP2 [45] implicating DUSP family members in FGFR3 signaling. Moreover, a study by Shi et al. indicated that DUSP1 plays a role in resistance to proteasome inhibitors for MM patients. p38 MAPK was activated upon proteasome inhibitor treatment. This

activation resulted in induction of anti-apoptotic DUSP1, in association with suppressed activation of the pro-apoptotic c-Jun-N-terminal kinase (JNK) [46]. It is clear from the limited literature and data available that DUSPs might have important roles in MM pathogenesis, but more detailed studies are necessary to clarify their function.

2.3. Protein tyrosine phosphatase 4A (PTP4A) family

Phosphatases of regenerating liver (PRL) constitute a family of small proteins of approximately 20 kDa that consists of three members, PRL-1, -2 and -3 (encoded by *PTP4A1, -2* and *-3*). There is evidence for upregulation of the three PRL family members in various human cancers. In contrast to PRL-1 and PRL-2, which are ubiquitously expressed in various tissues, expression of PRL-3 is restricted to a few specific organs and cancer cells, which makes it an attractive target for cancer treatment [47–49]. While all three PTP4As are expressed on the mRNA level in MM PCs, PTP4A3 stands out as more highly expressed than the other two PRL members, with TPM values reaching 1000 in some patients (Fig. 2A). Nevertheless, analysis of datasets derived from Oncomine showed higher expression of all *PTP4As* in MM and/or MGUS PCs than in healthy PCs (Table 1). In addition, *PRL-2* and *PRL-3* expression was associated with poor prognosis in MM patients (Fig. 3). This emphasizes the possible importance of these phosphatases in MM. However, no studies have been performed until now on biological roles of PRL-1 and PRL-2 in MM progression.

Several studies have been carried out on PRL-3's role in MM. *PTP4A3* is shown to be consistently highly expressed in MM and MGUS PCs compared to PCs from healthy donors ([50] and Table 1). A study of 320 newly diagnosed MM patients by Broyl et al. defined 3 novel subgroups of MM. One of these novel clusters composed of 9 patients (2.8%) and showed upregulation of PTPs PRL-3 and PTPRZ1 as well as suppressor of cytokine signaling (SOCS)3 [51]. Moreover, PRL-3 is proposed as a biomarker in MM to identify high-risk patients upon treatment with proteasome inhibitors and IMiDs [52]. Fagerli et al. introduced PRL-3 as an effector protein downstream of IL-6 [50]. Later studies showed that forced expression of PRL-3 enhances MM cell survival in the absence of or in suboptimal concentrations of IL-6. This implies that ectopic PRL-3 expression makes the cells less dependent on IL-6 for their viability. This is possibly due to activation of STAT3, STAT1, AKT, ERK1/2 and SRC family kinase members by PRL-3 [4,52,53]. Subsequently, the expression of MYC and anti-apoptotic genes will be enhanced, which leads to MM cells being resistant to bortezomib. Chong et al. suggested that activation of STAT3 happened through direct deactivation of SRC homology region 2 (SH-2) domain-containing phosphatase (SHP)2 by PRL-3, thus blocking the GP130 (Tyr 759)-mediated repression of STAT3 activity. The study of five independent cohorts confirmed that the STAT3 activation signature was significantly enriched in patients with high PRL-3 expression [52].

2.4. Cell division cycle 14 (CDC14) phosphatases

Among the large family of DUSPs the CDC14 family is one of the most extensively studied, mainly because of the essential role of these phosphatases in regulating late mitotic events and mitotic exit [54]. In vertebrates, three homologs of yeast CDC14 have been characterized (CDC14A, CDC14B and CDC14C). While *CDC14C* does not seem to be expressed in PCs from MM patients (Average TPM below 1), *CDC14B* and to lesser extent *CDC14A* are both expressed on the mRNA level (Fig. 2A). Zhan Myeloma 3 dataset in Oncomine indicates differential expression of *CDC14B* in 12 smoldering MM and 44 MGUS PCs compared to 22 normal PC samples (Table 1). Chromosome 1 abnormalities are among the most common cytogenetic findings in MM [55] and associated with poor prognosis [56]. Marzin et al. and Walker et al. both reported that 23–27% of MM cases had 1p deletions in the region between 1p12–1p21 [57,58]. Using gene expression profiling, Shaughnessy et al. showed that 50% of the downregulated genes in high-risk MM were located on chromosome 1p, suggesting that loss of certain tumor suppressor gene (s) within the 1p region may contribute to the aggressiveness of MM [59]. Later, Chang et al. identified *CDC14A* as the candidate tumor suppressor gene in this region. MM patients with 1p21 deletions had a significantly shorter progression-free and overall survival than patients without 1p21 deletions [56].

2.5. Cell division cycle 25 (CDC25) phosphatases

CDC25 phosphatases regulate transitions between cell cycle phases during normal cell division and are key targets of the checkpoint machinery activated in response to DNA damage to ensure genetic stability. In mammalian cells, three isoforms have been identified: CDC25A, CDC25B and CDC25C. Fig. 2A shows the expression of all three isoforms of CDC25 on the mRNA level in MM PCs. In addition, CDC25 overexpression has been reported in various types of human malignancies including MM (Table 1) and has been correlated with tumor aggressiveness and poor prognosis (Fig. 3 and [60,61]). Checkpoint responses are initiated by ataxia telangiectasia mutated (ATM) and ataxia telangiectasia and Rad3-related (ATR), which induce checkpoint kinases (CHEK1 and CHEK2) and subsequently lead to phosphorylation and degradation of CDC25. CDC25 degradation further halts the cells at S phase of the cell cycle. ATM and ATR alterations (mutations and deletions) occur in a small subset of MM patients, 4.3% and 1.5% of newly diagnosed patients, respectively, resulting in cell cycle progression in the presence of DNA damage and eventually genomic instability of MM cells [62]. Gene expression analysis showed that so-called side population cells, which are cells with tumor-initiating characteristics, from five MM cell lines express higher levels of genes involved in the cell cycle and mitosis including *CDC25C,* than non-side population cells [63].

Various compounds such as arsenic trioxide (As_2O_3) [64] and pterostilbene [65] have been reported to induce cell cycle arrest and apoptosis in MM cells through downregulation or inhibition of CDC25. Pterostilbene, a natural dimethylated analog of resveratrol, downregulates CDC25, and is an efficient agent in treating MM cells resistant to bortezomib [65]. Therefore, CDC25 may be an important future target in MM treatment.

2.6. Protein tyrosine phosphatase non-receptor type 6 and 11 (PTPN6 and PTPN11)

SHP2, encoded by the *PTPN11* gene, is an oncogene and its overexpression and mutation are common in various types of carcinomas [66]. However, some tumor-suppressive roles of SHP2 are also reported, which will be discussed later here.

SHP2 has been shown to positively regulate the ability of several receptor tyrosine kinases to activate the MAPK/ERK and PI3K/AKT signaling cascades [67,68]. Agazie et al. found that SHP2 was required for the transformation of mouse fibroblast cells expressing oncogenic receptor tyrosine kinase FGFR3. Given that mutations activating FGFR3 are relatively frequent in MM patients, these observations may indicate that SHP2 also plays an oncogenic role in MM cells [69,70]. Even though the exact mechanisms of how SHP2 mediates activation of signaling pathways downstream of receptor tyrosine kinases are still under study, it is known that both the PTP activity of SHP2 and its tyrosyl phosphorylation might play a role in mediating the actions of this phosphatase [71]. In the latter case, SHP2 functions as a scaffold protein [72,73]. Furthermore, it has been shown that SHP2 is needed for the growth of mutant KRAS-driven cancers [74]. These studies were not done in MM, but it is well known that RAS mutations are detectable in up to 50% of newly diagnosed MM patients. Consequently, SHP2 inhibition can be relevant in the context of MM [75]. Importantly, Zhou et al., by using a tissue-specific gene knockout approach, found a key regulatory role of SHP2 in osteoclastogenesis. SHP2 is required for receptor activator of nuclear factor kappa-B ligand (RANKL)-induced formation of osteoclasts. Thus, SHP2 can possibly serve as a target for treatment of

myeloma patients who suffer from bone fragility due to high osteoclast activity [76].

In addition, SHP2 is an important regulator of programmed cell death protein (PD)-1/PD-ligand 1 (PD-L1) signaling, which also makes it an interesting target for cancer therapy. PD-1 is an immune checkpoint molecule and reduces the T cell function. Many cancer cells evade death by becoming invisible to the host's immune system when they start to express ligands of checkpoint receptors (such as PD-L1) [77]. Upon binding of tumor-derived PD-L1 on T cells, PD-1 is phosphorylated and recruits SHP2, which antagonizes T cell activation [78]. Overexpression of PD-L1 on primary MM cells and plasma dendritic cells in MM patients has been demonstrated [77]. Therefore, PD-1/PD-L1 axis blockade in MM is a hot topic, despite the observation of serious side effects in clinical trials combining PD-1/PD-L1 inhibitor with IMiDs [77]. The role of SHP2 as a regulator of the PD-1/PD-L1 pathway adds another rationale for targeting SHP2 in MM.

The oncogenic role of SHP2 might be the reason for the inverse correlation between SHP2 expression and degree of MM response to treatment with dexamethasone/thalidomide [79–81].

SHP1 encoded by *PTPN6* is another PTP, which, despite sharing homologous structure and sequence with SHP2, is known as a putative tumor suppressor [66]. In addition, while *PTPN6* is primarily expressed in hematopoietic cells, *PTPN11* is more ubiquitously expressed ([82] and Fig. 2A). As for SHP1, studies have revealed that SHP2 also shows some tumor-suppressive capabilities through direct or indirect inactivation of JAK/STAT [82,83]. Gene expression profiling of *PTPN6*, *PTPN11* and *SOCS1* in PCs freshly isolated from the BM of MM patients and from healthy donors demonstrated significantly lower level of *PTPN6* and *PTPN11* gene expression in patient PCs [79]. This can be explained by hypermethylation of these phosphatase genes in myeloma samples during active disease [82,84,85]. Moreover, a study of phospho-STAT3 status in patients' BM specimens by immunohistochemistry showed a negative correlation between the sustained activation of the JAK/STAT3 pathway and the gene expression of *PTPN6*, *PTPN11* and *SOCS1* in patient PCs [79]. Various drugs such as icariside II and capillarisin are reported to inhibit STAT3 by induction/phosphorylation of SHP1 and/or SHP2 expression [86,87].

Surprisingly, when we analyzed SHP1 and SHP2 expression in Oncomine, we observed that both PTPs are more highly expressed in smoldering myeloma PCs compared to normal healthy controls in Zhan myeloma 3 datasets (Table 1). In addition, high expression of both PTPs is associated with poor prognosis (Fig. 3). The conflicting results on oncogenic or tumor-suppressive roles of both SHP1 and SHP2 indicate that more detailed investigations for instance by knock out/down studies in MM should be performed to explain these apparently contrary roles.

2.7. Other protein tyrosine phosphatases

Various other PTPs are reported to play a key role in regulating phosphotyrosyl protein homeostasis in MM cells. Among these are *PTPN7* [88], which is shown to be overexpressed in MM [89] and MGUS

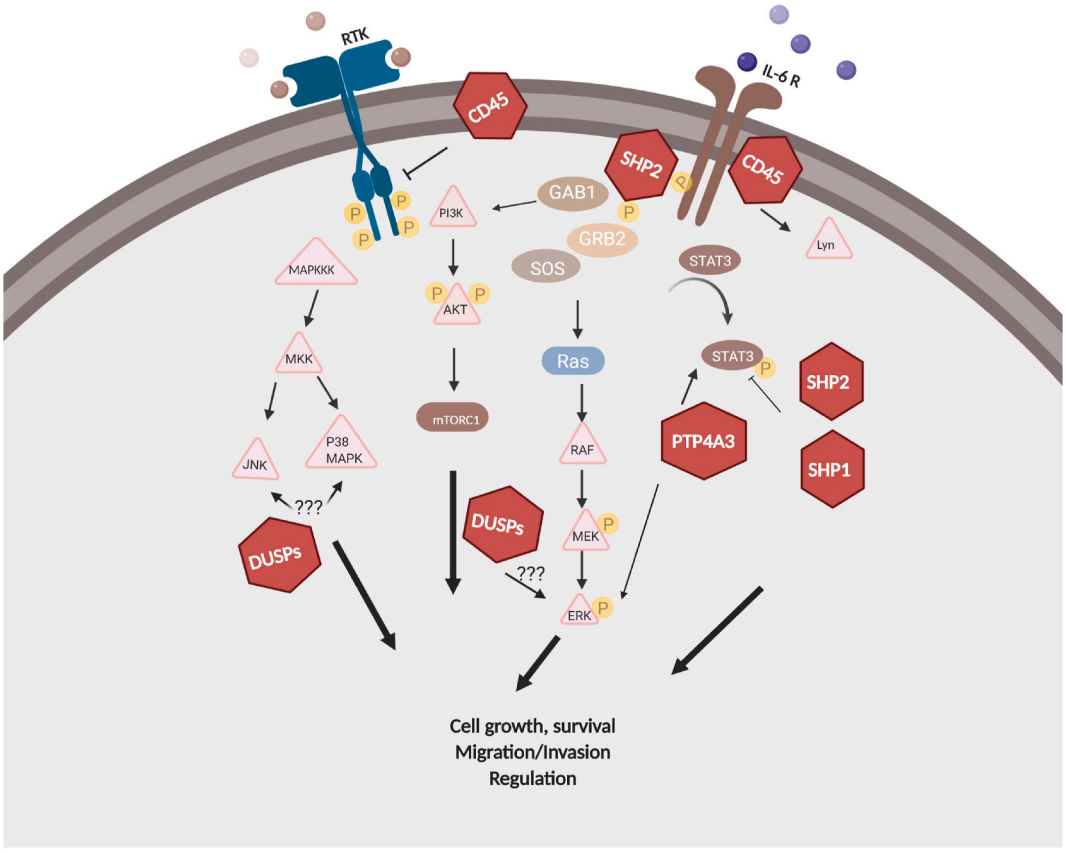

Fig. 4. Overview of signaling pathways regulated by some protein tyrosine phosphatases discussed in this review. Protein tyrosine phosphatases (Red hexagons) together with protein kinases (Pink triangles) regulate crucial biological functions in the cell such as growth, survival, migration and invasion. Protein tyrosine phosphatases shown in the figure are: CD45, DUSP, SHP2, SHP1, PTP4A3. Protein tyrosine kinases shown in the figure are: Raf, MEK, ERK, MAPKKK, MKK, P38 MAPK, JNK, LYN, AKT, PI3K.

Abbreviations: CD45 (Cluster of differentiation 45), DUSP (Dual-specificity phosphatase), SHP1 and SHP2: (SRC Homology Phosphatase 1 and 2), PTP4A3 (Protein tyrosine phosphatase type IVA 3), ERK (Extracellular signal-regulated kinases), P38 MAPK (Mitogen activated protein kinase), JNK (c- Jun N-terminal kinases), MAPKKK (MAPK kinase kinase), MKK and MEK (MAPK kinase), PI3K (Phosphoinositide 3-kinases), RTK (Receptor tyrosine kinase), IL-6R (Interleukin-6 receptor). The figure was created with BioRender. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

patients (Table 1), and *PTPN1* and *PTPN2,* which are suggested to be key negative regulators of FGFR3 [88]. These phosphatases seem to be expressed in myeloma cells (Fig. 2A). In addition to *PTPN6* and *PTPN11,* which were mentioned earlier, a series of other phosphatases such as *PTPRD, PTPRT, PTPRK, PTPN9,* and *PTPN2* are described to play a role in STAT3 inactivation. However, these studies did not include MM [83]. As IL-6/STAT3 signaling is a crucial pathway regulating MM growth and proliferation, study of these phosphatases in MM can be of great interest. Except for *PTPRT*, which does not seem to be expressed in MM (Average TPM below 1), the others are expressed on the mRNA level, but with relatively low TPM values (Fig. 2A). Interestingly, in contrast to the possible role of PTPRK as tumor suppressor by inhibiting STAT3, gene expression analysis derived from Angela Myeloma 3, Zhan Myeloma 3 and Zhan Myeloma datasets in Oncomine indicated that *PTPRK* was consistently upregulated in MM and MGUS PCs compared to normal PCs (Table 1). Therefore, further investigations are necessary to decipher the role of these phosphatases in MM.

2.8. Protein kinases vs. protein tyrosine phosphatases

Fig. 4 shows an overview of some PTPs discussed here and their possible roles in MM pathogenesis. As indicated in this figure, most of the phosphatases we reported here were described in the context of 3 crucial pathways: JAK/STAT, PI3K and MAPK pathway. Therefore, we chose the best-known kinases in these pathways and compared their expression pattern in MM plasma cells to phosphatases that affect these pathways. These kinases are: JNK (MAPK8, MAPK9, MAPK10)/P38 MAPK (MAPK11, MAPK12, MAPK13, MAPK14)/MAPK1 and MAPK3/AKT (AKT1, AKT2)/JAK (JAK1, JAK2). While the expression of the selected kinases has the value of 0–200 TPM (Fig. 2B), this value was up to 2000 (Fig. 2A) for some of the phosphatases that might regulate the same pathways. Even though gene expression (TPM value) does not necessarily represent the protein expression, this comparison still points to the equal importance of these two groups of proteins with counteracting functions.

3. Concluding remarks

Protein phosphorylation/dephosphorylation controls many aspects of cell biology and is often dysregulated in pathological conditions. It is now clear that even though kinases and phosphatases may work in opposition, they also work together to regulate signaling pathways. Therefore, phosphatases as kinases are critical components of signal transduction and their dysregulation supports the development of various tumors such as MM. Based on literature review and analysis of public databases, there are many candidate phosphatases that are clearly worthy to be studied in more detail in MM. For instance, *DUSP1*, *DUSP5* and *PTP4A3* are the top three PTPs with the highest TPM value compared to the other PTPs in MM. Even though the mRNA level does not necessarily correlate with the protein level, the high mRNA level encourages the study of these phosphatases in more detail. In addition, some of the PTPs such as the CDC25 family, PRL-2, PRL-3, SHP2, SHP1, DUSP6 and DUSP10 have clinical significance for MM patients and/or are differentially expressed in MM/MGUS compared to normal plasma cells. This indicates that expression of these PTPs can be used as a tool to evaluate dysregulation of normal plasma cells and emphasizes their importance in MM pathogenesis. However, the research on these phosphatases in general is very limited and further studies are necessary to unravel mechanisms by which PTPs may contribute to MM progression. This might subsequently lead to development of targeted drugs to be used either alone or in combination with proteasome inhibitors, IMiDs or other drugs in MM treatment.

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CRediT authorship contribution statement

Pegah Abdollahi: conceptualized the project, searched relevant literature and wrote the paper. **Maja Köhn:** reviewed, gave feedback and helped writing the paper. **Magne Børset:** reviewed, gave feedback and helped writing the paper.

Declaration of competing interest

The authors have no conflicts of interest to declare.

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