[Frontiers in Bioscience 3, d1060-1096, November 1, 1998]

LYMPHOCYTE ACTIVATION: THE COMING OF THE PROTEIN TYROSINE PHOSPHATASES

T. Mustelin, J. Brockdorff, A. Gjörloff-Wingren, P. Tailor, S. Han, X. Wang & M. Saxena

Division of Cell Biology, La Jolla Institute for Allergy and Immunology, 10355 Science Center Drive, San Diego, CA 92121, USA

Received 9/10/98 Accepted 9/15/98

TABLE OF CONTENTS

1. ABSTRACT

The molecular mechanisms of signal transduction have been at the focus of intense scientific research world-wide. As a result, our understanding of protein tyrosine kinase-mediated signaling has advanced at an unprecedented pace during the past decade. In contrast, the study of protein tyrosine phosphatases is in its infancy, but is currently gathering momentum and is predicted to become a “hot topic” in the field within the next few years. This review summarizes the current state-of-the art in our understanding of the structure, regulation and role of protein tyrosine phosphatases in lymphocyte activation.

2. INTRODUCTION

Phosphorylation of proteins on tyrosyl residues is an important mechanism for many signal transduction pathways controlling cell growth, differentiation and development (1-3). Although the phosphotyrosine (PTyr) content of cellular proteins is the net result of the opposing effects of protein tyrosine kinases (PTKs) and protein tyrosine phosphatases (PTPases), most investigators have concentrated on the PTKs, many of which were cloned and sequenced nearly two decades ago. The first PTPase was not cloned until 1990 and most PTPases have been known for less than five to seven years. Although our progress has been remarkable, and clearly is accelerating, very little is still known about most of these enzymes. It is also likely that many more PTPases remain to be discovered. Presently some 50 mammalian PTPases have been described and a recent estimate puts the total number of PTPase genes in the human genome at 500 (4). This number should be compared to the predicted number of recognized genes for protein kinases: 1,000-3,000 (2), of which roughly half are thought to be specific for tyrosine. Despite this estimated ratio of PTKs to PTPases, the level of PTyr in normal cells is only 0.1-0.01% of acid-stable protein-bound phosphate,

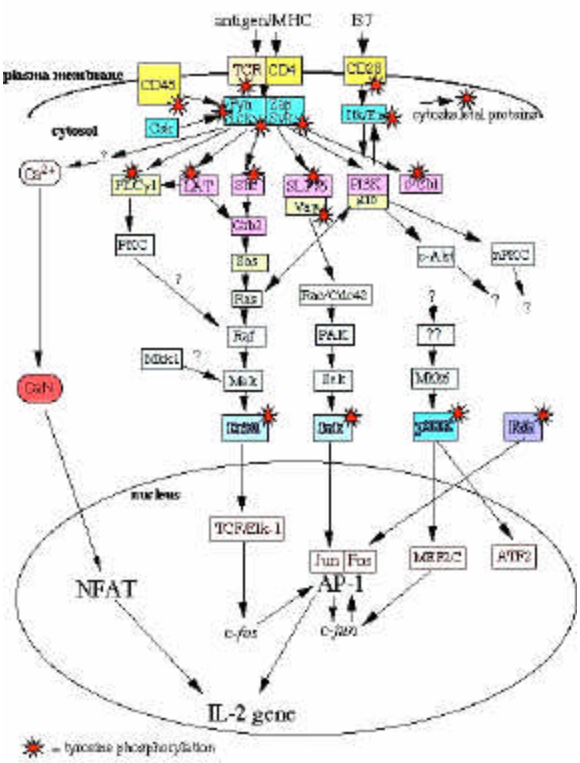

Figure 1. Schematic overview of main signaling pathways in T lymphocyte activation. The most important co-receptors are shown in yellow, the PTKs are dark blue, the secondary signaling molecules are adapters (pink) or enzymes (pale green), small GTPases are even paler green, the downstream Ser/Thr protein kinases are pale blue, and transcription factors are flesh colored, calcineurin (CaN) is red. Tyrosine phosphorylated proteins, which are substrates for PTPases, are indicated with a red star.

or 3-4 orders of magnitude lower than the level of phosphoserine (PSer) and phosphothreonine (PThr), suggesting that the cellular PTPases readily counteract the PTKs in normal cells. Whether this is due to a high number of expressed PTPases, high expression levels of some PTPases, or high specific activity, is not known. Importantly, even a small increase in steady-state tyrosine phosphorylation caused by deregulation or overexpression of some PTKs, notably members of the Src family (5), can induce acute malignant transformation and uncontrolled proliferation of cells. Also physiological processes mediated by tyrosine phosphorylation (e.g. signal transduction) are accompanied by relatively small and transient increases in cellular PTyr. Thus, it seems clear that PTPases play an important role in the maintenance of normal cell physiology by counteracting substrate phosphorylation by the PTKs. To complicate matters, we and others have found that some PTPases directly regulate the PTKs, either negatively or positively (5-10), by dephosphorylating specific regulatory tyrosine phosphorylation sites in these PTKs. At the same time, some PTPases are also phosphorylated by the PTKs (11-20), indicating that PTK - PTPase interactions can be rather complex. There are already examples of PTPases that are regulated by phosphorylation on tyrosine, threonine or serine residues and therefore also must be dephosphorylated by themselves ('autodephosphorylation') or by other protein phosphatases, perhaps forming 'phosphatase cascades' analogous to the kinase cascades involved in many signal transduction processes.

Like most normal cells, resting lymphocytes contain very low levels of PTyr, presumably reflecting the finding that overall PTPase activity is several orders of magnitude higher than overall PTK activity (6). This conclusion is in agreement with the truly dramatic increase in intracellular tyrosine phosphorylation that follows a brief treatment of T cells with membrane-permeable PTPase inhibitors, such as phenylarsine oxide (21) or pervanadate (22,23). The increase in PTyr-content after addition of these pharmacological agents is detectable within seconds and quickly reaches levels that far exceed the response to any physiological stimuli. These experiments underscore the importance of PTPases in the maintenance of the resting levels of tyrosine phosphorylation. Since these inhibitors also cause many functional events of T cell activation (22,23) and prevent reversion of activated T blasts to a resting state (24), it seems that PTPases play a crucial part in maintenance of the resting phenotype of lymphocytes.

Lymphocyte activation is a convenient and popular model for studying signal transduction and mitogenesis. Consequently, the molecular mechanisms of antigen receptor-mediated signaling are relatively well understood (although many questions do remain unresolved). When lymphocytes are activated by ligation of their receptors for antigen or other mitogens together with appropriate co-receptors or accessory molecules, there is a very rapid, but transient, increase in PTyr in a number of cellular proteins (25-27, reviewed in 28,29). Our observation (30) that inhibition of this response by pharmacological means blocks lymphocyte activation completely gave rise to the current dogma that the first event triggered by receptor ligation is the activation of one or several PTKs (5,30,31). Several PTKs are currently known to participate in the initiation of lymphocyte activation. Using homologous recombination, transgenic mice, and mutant cell lines, it has been demonstrated that two members of the Src family of PTKs, Lck and Fyn, are important (31-39) in T cells, although their relative contribution and redundancy remains unclear. In B cells, the corresponding Src family PTKs are Lyn, Blk and Fyn, while natural killer (NK) cells also utilize c-Fgr (5). The two Syk family PTKs ZAP-70 and Syk are also activated within the first minute (28,40) and lack of a functional *zap* gene is known to cause a severe immunodeficiency in humans (41). TCR crosslinking also transiently activates the Csk kinase (42), which negatively regulates Lck and Fyn (43). Finally, the Tec family PTKs Btk and Itk/Emt (44,45) are activated in B cells and T cells, respectively. The importance of these PTKs is also demonstrated by the transforming capacity of some of them (5) and the observed changes in amount or function of them in malignancies, *e.g.* in T cell lymphomas (46-48), and in T cell anergy (5).

The molecular mechanisms of signal transduction and lymphocyte activation have been intensely studied during past few years (5,49-51). The major signaling pathways are delineated schematically in figure 1. It has been firmly established which PTKs carry the main responsibility for initial signal transmission and these enzymes, their physiological importance, regulation, and substrates have been thoroughly studied. In contrast, it is far from clear which PTPases are involved in lymphocyte activation, how they are regulated or what substrates they act on. In fact, it is likely that the most important PTPases have not yet been found. Although the main focus of most researchers has been on the PTKs, it is generally acknowledged that PTPases are likely to be equally important in the propagation and coordination of the signaling cascades (52-56). We predict that there will be a sharply increasing interest in PTPases within the next few years, accompanied by many significant breakthroughs in our understanding of these enzymes and their roles in physiological processes. They will also become the focus of targeted drug discovery for the treatment of human diseases. This review will present all the PTPases that are known or suspected to be expressed in lymphocytes. We will summarize and discuss their known, suspected or potential roles in lymphocyte physiology.

2. 1. PTPases present in lymphocytes

The purification to homogeneity in 1988 of the first PTPase, PTP1B from human placenta (57,58), and the subsequent isolation of its cDNA in 1990 (59), provided the required basis for a search for related genes using a number of molecular biology techniques. The sequence of PTP1B also revealed that a well-known molecule, the leukocyte common antigen CD45, was a PTPase with two catalytic domains in tandem in its cytoplasmic tail (60). Thus it became clear from the very start that PTPases can be transmembrane molecules or entirely intracellular enzymes, and that they can have more than one PTPase domain. During the early part of the 90s, a number of PTPases related to PTP1B and CD45 were discovered in eukaryotic cells from yeast to man (52-56). All these enzymes share several regions of homology, including a well-conserved signature sequence motif (HCXXGXXR). PTP1B was recently crystallized and its three-dimensional structure solved (61). The structure showed that the cysteine residue of the signature sequence resides at the bottom of a deep hydrophobic catalytic pocket and is a crucial component of the catalytic machinery (62). Specificity for phosphotyrosine is, at least partly, determined by the depth of the pocket (63). During catalysis the phosphate moiety is transferred from the substrate to the cysteine to form an enzyme-phosphocysteine intermediate, which is regenerated through the formation of free phosphate with the help of a water molecule (64).

The ”classical” PTPases comprises the largest family of PTPases and contains all currently known transmembrane enzymes, as well as PTP1B, and several related intracellular enzymes, all with a ~250 amino-acid catalytic domain with a relatively high degree of similarity. All intracellular members of this family have one copy of the catalytic domain, which can be located anywhere in the molecules. In contrast, many transmembrane PTPases have two PTPase domains in tandem in their intracellular C-terminal part. In many cases, the second domain appears to be enzymatically inactive and its function remains speculative. The classical PTPases can be further subdivided in subfamilies or groups based on overall structure and the presence of other domains (figure 2). For example, the group consisting of SHP1 and SHP2 is characterized by two SH2 domains in the N-terminal half of the molecule and a PTPase domain in the C-terminal half. Another group, often referred to as the “cytoskeletal” PTPases, is characterized by an N-terminal region of homology to band 4.1 and other cytoskeletal proteins (termed the ERM domain), a central region often with at least one PDZ domain, and a C-terminal PTPase domain. The PEST group consists of enzymes with an N-terminal PTPase domain and C-terminal region rich in proline, glutamic acid, serine and threonine. These enzymes will all be discussed in detail below.

In addition to the “classical” family of PTPases with a high degree of similarity to PTP1B and CD45, another family of enzymes that not only dephosphorylate PTyr, but also PSer and PThr, was discovered by K. Guan and J. Dixon (65). The founding member of this family of dual-specific protein phosphatases was the VH1 protein from Vaccinia virus (65). A closely related enzyme was subsequently found in mammalian cells and termed VHR for VH1-related (66). The majority of the members of the dual-specificity phosphatase group specifically dephosphorylate PThr and PTyr in one or several kinases that belong to the MAP kinase family (reviewed in 67-69). Interestingly, there are currently 9 known dual-specificity phosphatases (often collectively termed MKPs), but only 7 known MAP kinases: Erk1, Erk2, Erk5, Jnk1, Jnk2, p38, and p38beta. One reason for this excess of phosphatases might be that some of them have restricted expression profiles, while the MAP kinases are expressed in all tissues and cell types. Thus, only a few MKPs might be present in any one cell. The structure of these enzymes is presented in figure 3.

Finally, a number of much more distantly related proteins have been identified, which may be specific for PTyr, but in some cases are dual-specific or have an unclear specificity in intact cells. These enzymes share the CXXXXXXR motif with the classical PTPases, and include the cell cycle regulators CDC25 (70) and KAP (71), and the low Mr PTPases LMPTP (72), PRL-1 (73), PRL-2 (74), PRL-3 (74). Finally, two enzymes that have the PTPase signature sequence, PTEN (75,76) and CEL-1 (77), were recently discovered to be specific for non-protein substrates: PTEN dephosphorylates inositol phospholipids (78) and the *C. elegans* protein CEL-1 dephosphorylates RNA as part of the mRNA capping process (77). Thus, the “PTPase signature sequence” is not unique to enzymes hydrolyzing phosphoesters in protein substrates. Rather it seems that the PTPases have evolved from several different ancestral cysteine-based hydrolases specific for many other types of substrates. These primordial enzymes apparently provided a starting point for the evolution of PTPases in parallel with the appearance of dual-specific protein

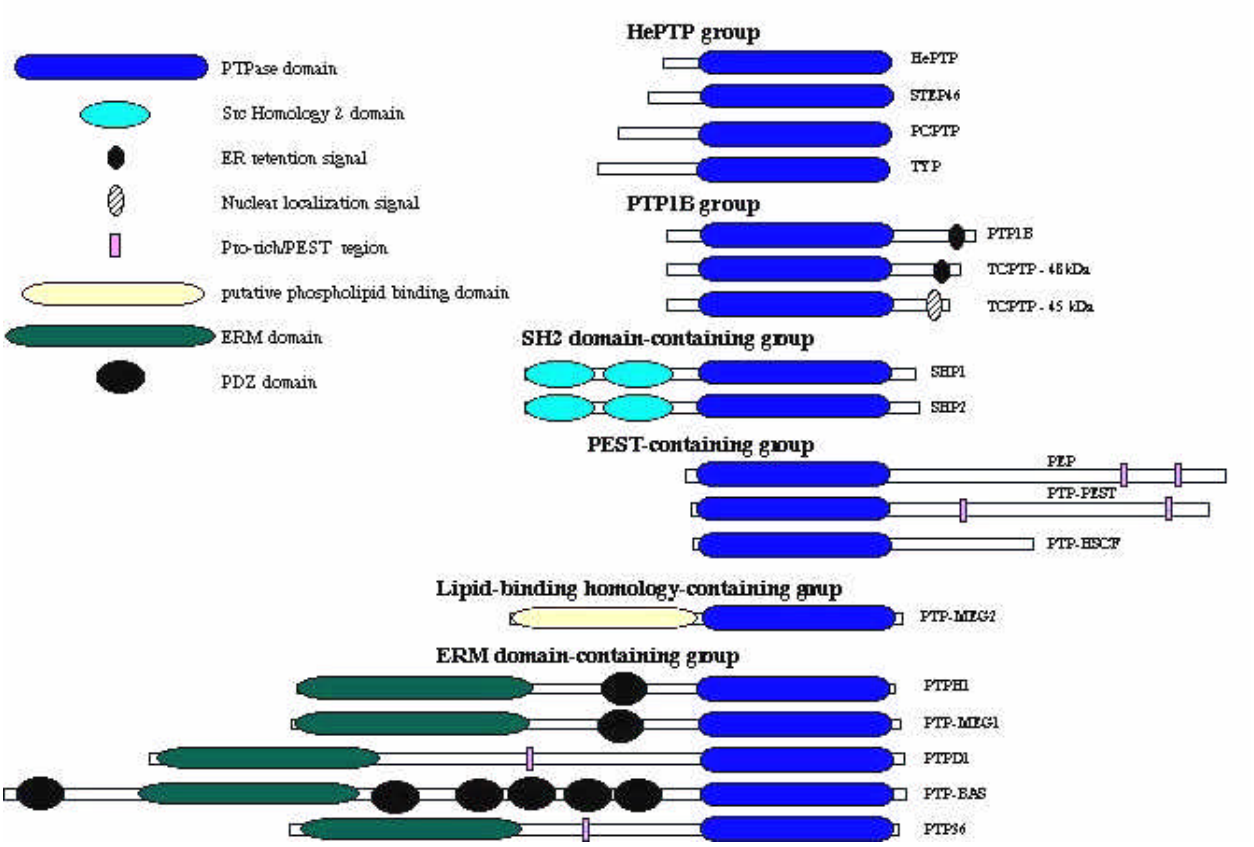

Figure 2. Structure of the intracellular classical PTPases. The enzymes are aligned for their ~260-amino acid PTPase domain and the location of different domains (key in upper left had corner) indicated. All PTPases are shown in the same scale, except PTP-BAS, which is shown shorter than its actual relative size. CAAX, isoprenylation/farnesylation signal.

kinases (e.g. Mek) and PTKs during the transition from unicellular to multicellular organisms some 570-600 million years ago.

Lymphocytes express many, but not all, of the known PTPases (table 1). The leukocyte common antigen, CD45, seems to be the predominant transmembrane PTPase on most leukocytes, and it is expressed at very high levels in lymphocytes. Very little is known about other transmembrane PTPases in lymphocytes. Therefore, we have decided to ignore them in this review. Table 1 contains all currently known intracellular PTPases, including their numerous synonyms. For many, the information on their tissue distribution has not been published and it remains unclear if they are present in lymphocytes.

2. 2. The targets and specificity of PTPases in lymphocyte activation

Many molecules that regulate lymphocyte activation become transiently tyrosine phosphorylated following receptor ligation (figure 1). As a general rule, these molecules are phosphorylated on multiple sites with each site potentially having its own specific impact on the function of the molecule. Each site may be phosphorylated by a different PTK (43,131), even if target sites for individual PTKs often are clustered. Naturally, all these proteins must also be substrates for cellular PTPases. It remains unknown, however, how many PTPases are required. Are PTPases very specific for their substrates? How many substrates does each PTPase have? The case of the MAP kinase-specific phosphatases suggests that the number of phosphatases may even exceed the number of their targets.

Recent findings indicate that many PTPases display a high degree of substrate specificity. As in the case of the PTKs, PTPases are often remarkably selective when tested *in vitro* towards phosphorylated peptides and proteins, and it is widely held that they are even more selective in intact cells. Some PTPases seem to prefer PTyr residues preceded and followed by specific amino acid residues (132,133). For example, PTP1B strongly prefers acidic residues N-terminal of the target phosphotyrosine and a methionine or glycine immediately C-terminal of it (132). In intact cells, this intrinsic substrate specificity is combined with a selective targeting of the enzyme to specific subcellular compartments or to multisubunit protein complexes by the presence of protein-protein interaction domains or "zip codes" (134). Examples include the binding of SHP1 and SHP2 via their SH2 domains to certain tyrosine phosphorylated sites on other proteins, the association of the non-catalytic C-termini of TCPTP with substrate proteins or regulators, the binding of proteins

Table 1. Currently known mammalian cytoplasmic PTPases

PHOSPHATASE (SYNONYMS)	CHR. LOC.	PROTEIN Mr	IN	T	REF[a)]
I. CLASSICAL PTPases					
HePTP group					
HePTP (LCPTP)	1q32.1	38-40 kDa	Yes		79,80
STEP	11p15.2-p15.1	20[b)], 38[b)], 46, 61	No		81
PCPTP (=PTPBR7, PC12-PTP1)		42, 65 kDa	No		82, 83, 84
TypPTP		40, 45 kDa	No		85
PTP1B group					
PTP1B	20q13.1-13.2	50 kDa	No		59
TCPTP (=MPTP, PTP-S)	18p11.2-11.3	45, 48 kDa	Yes		86
SH2 domain-containing group					
SHP1 (=PTP1C, SH-PTP1, HCP, PTPN6)	12p12-13	67 kDa	Yes		87-90
SHP2 (=SH-PTP2, Syp, PTP1D, PTP2C, SH-PTP3,	12q24.1	70 kDa	Yes		91-94
PEST-containing group					
PEP		110 kDa	Yes		87
PTP-PEST (=PTP-P19, PTPG1)	7q11.23	89/97 kDa	Yes		95-97
PTP-HSCF		50 kDa	No		98-102
Lipid-binding homology-containing group					
PTP-MEG2		68 kDa	Yes		103
ERM domain-containing group					
PTPH1		104 kDa	Yes		104
PTP-MEG1		106 kDa	Yes		105
PTPD1 (=PTP2E, PTP-RL10)		130 kDa	No		106-108
PTPD2		unknown	No		106
BA14		290 kDa	No		109
PTP-BAS (=FAP-1, PTP1E, RIP, PTPL1, PTP-BL,	4q21.3	275 kDa	Yes		110-113
PTP36 (=PEZ)	1q32.2-41	130 kDa	Yes		114,115
II. DUAL-SPECIFIC PHOSPHATASES					
VH1-like, MAP kinase-specific group					
VHR	17q21	21 kDa	Yes		66
Pac-1 (=DUSP2)	2q11.2-q11	32 kDa	Yes		116
MKP-1 (=CL100, 3CH134, erp,hVH1)	5q34-35	39 kDa	Yes		117-119
MKP-2 (=TYP1, hVH2, DUSP4)	8p11-p12	43 kDa	Yes		120,121
MKP-3 (=Pyst1, rVH6, DUSP6)	12q22-q23	42 kDa	No		122,123
MKP-4	Xq28	42 kDa	?		124
MKP-X (=Pyst2, B59, DUSP7)	3p21	39 kDa	Yes		122,125,126
B23 (=hVH3)	10q25	44 kDa	?		127
hVH4	10q11	?	?		128
M3/6 (=hVH5, HB5)	11p15.5	69 kDa	?		129,130
Cell cycle regulators					
CDC25A	3p21	52-72kDa	Yes		70
CDC25B	20p13	52-72kDa	Yes		70
CDC25C		52-72kDa	Yes		70
KAP		24 kDa	?		71
Tumor suppressor					
PTEN (=MMAC1, TEP1)	10q23.3	45 kDa	Yes		75,76
III. SMALL, UNRELATED ENZYMES					
LMPTP(low MrPTP,AcP,BHPTP)	2p25	18 kDa	Yes		72
PRL-1	6q12	20 kDa	Yes		73
OV-1 (PRL-2, PTP4A)	17q12-21	20 kDa	Yes		74
PRL-3		20 kDa	No		74

[a)] Original cloning papers
[b)] Isoforms devoid of PTPase domain

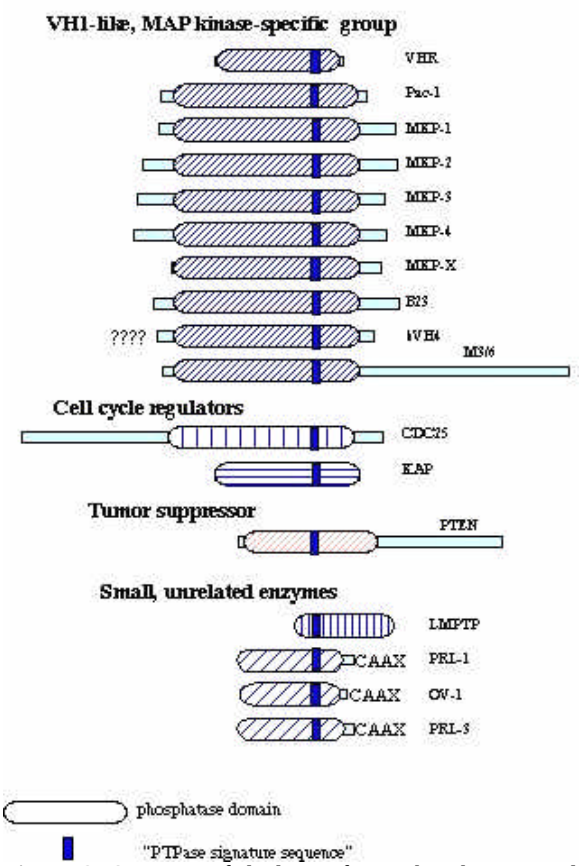

Figure 3. Structure of dual-specificity phosphatases and low-molecular weight PTPases. The enzymes are aligned for their "PTPase signature sequence". The extent and exact placement of the phosphatase domain is uncertain in many. We have included the CH2 domain in the phosphatase domain. A low degree of amino acid similarity to other enzymes is indicated by a different shading of the domain. In PTEN, the phosphatase domain overlaps with a tensin homology region (in pink).

with SH3 domains to the proline-rich regions of PTP-PEST and PEP, and the potential association of some PTPases with transmembrane proteins or cytoskeletal elements via ERM and PDZ domains. These will all be discussed in detail below.

An important group of PTPase substrates are the PTKs involved in lymphocyte signal transduction. With the probable exception of Csk, these enzymes are all negatively and positively regulated by phosphorylation of multiple tyrosine residues (5-9,43,44,131,135-138). The CD45 PTPase is known to positively regulate the Src family PTKs by dephosphorylating their C-terminal negative regulatory site (discussed below). Other PTPases may also act on this site (139). Several other PTPases are very likely to participate in the regulation of the PTKs, particularly by dephosphorylating the sites that CD45 does not act on. We have observed that the autophosphorylation site of Lck, Tyr-394, and the site in the SH2 domain, Tyr-192, both become rapidly phosphorylated in cells treated with PTPase inhibitors (131,140), suggesting that they are normally efficiently dephosphorylated by one or several PTPases. Likewise, both Syk (141) and Zap (142) become hyperphosphorylated within seconds after the addition of pervanadate. This response is also seen in CD45-negative cells (our unpublished observation). Taken together, these observations suggest that these PTKs are under very efficient control by PTPases, most likely several of them.

A large number of substrates for the PTKs have been identified, although it remains largely unknown which PTK phosphorylates these substrates under physiological conditions. It is even less clear which PTPases that dephosphorylate these proteins. These signaling molecules include components of many known pathways and in some instances their phosphorylation has been shown to switch on the pathway. For example, phosphorylation of phospholipase Cgamma1 at Tyr-783 leads to its activation (143-147) and subsequent hydrolysis of membrane inositol phospholipids, calcium mobilization mediated by inositol trisphosphate and activation of protein kinase C through diacylglycerol formation (148). Another mechanism by which tyrosine phosphorylation regulates signaling events is by inducing physical association of proteins. For example, phosphorylation of the LAT (149) and Shc (150) proteins, causes them to bind the Grb2 adapter molecule, which, in turn, associates with Sos, a guanine nucleotide exchange factor for the small membrane-associated G protein Ras (151,152). Activated GTP-bound Ras then recruits the cytosolic inactive form of the Ser/Thr protein kinase c-Raf, causing its membrane translocation and activation (153,154). Raf, in turn, activates a cascade of Ser/Thr kinases, including Mek (155,156), which activates the mitogen-activated protein (MAP) kinases Erk1 and, in T cells particularly, Erk2 (157,158). Erk1 and 2 then phosphorylate additional kinases and the cascade culminates in the phosphorylation of transcription factors and cell cycle regulators (159,160). An important downstream target of Erk is the Elk-1 transcription factor, which participates in the transcriptional control of the c-*fos* protooncogene. Erk is known to be important in many events of lymphocyte physiology, such as development (161), cytokine production (162), proliferation (163) and anergy (164).

A parallel, but distinct, kinase cascade is initiated by tyrosine phosphorylation of Vav (165), an important (166,167), 95-kDa multidomain protein, which is a guanine nucleotide exchange factor for the small G protein Rac (168). GTP-bound Rac subsequently activates one or several protein kinases, which in turn activate Mkk4 (also called Sek), a dual-specificity protein kinase, which specifically activates the MAP kinases Jnk1 and Jnk2 (169,170). These two kinases are often referred to as stress-activated protein (SAP) kinases as this pathway is particularly efficiently switched on by stimuli such as heat shock, UV light, pro-inflammatory cytokines, etc. A main target for Jnk1 and 2 is the c-Jun protooncogene product (169), which together with the Fos proteins form the AP-1 dimer, an important transcription factor that cooperates with NFAT, NF-kappaB and Oct proteins in activation of cytokine genes in activated lymphocytes (171-174). A third kinase cascade includes Mkk3 and 6, which activate the

p38 MAP kinase (175). There is at least one more, poorly understood, kinase cascade that leads to activation of the 80-kDa Erk5 MAP kinase.

Other cellular proteins that become tyrosine phosphorylated in triggered T cells include the protooncogene product c-Cbl (176), a 120-kDa protein with multiple potential tyrosine phosphorylation sites and proline-rich regions for binding of SH2 and SH3 domains, *e.g.* of phosphatidylinositol 3-kinase p85, Grb2 (177), and Zap-70 (178). The 76-kDa SLP-76 (179), which also has an SH2 domain, associates with the SH3 and SH2 domains of Vav and the SH3 domains of Grb2 (179). It was recently shown that SLP-76 is important in T cell development (180) and in TCR signaling for coupling the receptor to phospholipase Cgamma1 (181). The 36-38-kDa LAT protein (149) is also somehow involved in linking the TCR to phospholipase Cgamma1 (182), and it may serve as the main mechanism for tyrosine phosphorylation-dependent recruitment of phosphatidylinositol 3-kinase to the plasma membrane (183,184).

Finally, an interesting group of PTPase substrates is the PTPases themselves. Several PTPases have been reported to be phosphorylated on tyrosine residues (11-20). However, the significance of this modification is in many cases still unclear. Often the stoichiometry is very low and PTyr is only detected in the PTPase after treatment of the cells with potent PTPase inhibitors, such as phenylarsine oxide or pervanadate. On the other hand, in some cases a catalytically inactive mutant of the PTPase becomes much more phosphorylated than the active enzyme, suggesting that it normally is able to autodephosphorylate. This would explain why strong pharmacological inhibition is required to preserve the phosphorylation through the immunoprecipitation procedure. It could also be argued that even a very low stoichiometry phosphorylation could be highly significant in intact cells, for example if the phosphorylated form specifically interacts with other proteins. The relevance of tyrosine phosphorylation of PTPases can only be tested by mapping the site(s), changing these tyrosine residues to phenylalanines by site-directed mutagenesis, and using these mutants in functional experiments.

3. CLASSICAL PTPases

3. 1. CD45 - a positive regulator of T cell activation

The first PTPase whose function in TCR-initiated T cell activation was elucidated is the transmembrane receptor-like CD45 PTPase, which is abundantly expressed on the surface of all nucleated hematopoietic cells (185,186). The enzyme has a long and slender extracellular domain, which is variable due to alternative splicing of exons 4, 5, and 6 during processing of the primary RNA transcript. As a result the mature mRNA encodes a protein that contains all, some, or none of the sequences encoded by these three exons. The smallest CD45 isoform, termed CD45-R0, lacks these sequences and has a relative molecular weight of 180 kDa, while the largest, CD45-RABC, contains them all and has a Mr of 220-240 kDa. The extracellular domain of CD45 is also heavily glycosylated being rich in sialic acid and galactose amine (187). These carbohydrates make CD45 a good ligand for some lectins, including animal galectins (188). Different leukocyte populations and subtypes have different expression patterns of CD45 isoforms, each individual cell usually expressing several isoforms. It seems likely that the different isoforms have somewhat different physiological functions, perhaps through differences in interaction with other surface proteins resulting in enhanced or reduced juxtaposition with other signaling molecules (e.g. CD4-Lck). Our understanding of the alternative splicing of CD45 and its role in lymphocyte physiology is still rudimentary. Nevertheless, it seems that much of the initial enthusiasm sparked by the discovery that it is a PTPase (60), now has dissipated and that only a few laboratories still focus on this molecule and its role in leukocyte physiology. Consequently, our understanding of CD45 has progressed relatively little in the last few years. As recent reviews (e.g. 186) contain essentially all current knowledge, we will summarize the state-of-the-art quite briefly.

T lymphocytes lacking CD45 fail to respond to stimulation by antigen or mitogenic antibodies (189). Responsiveness is restored upon reexpression of wild-type CD45 (190), or by expression of chimeric molecules containing the intracellular domain of CD45 fused to transmembrane and extracellular parts from heterologous proteins (191,192) or by the intracellular domain of CD45 alone (193) targeted to the plasma membrane by addition of the myristoylation signal contained within the first N-terminal amino acids of c-Src, the "SH4 domain" (5). Under physiological conditions, however, it is likely that the alternatively spliced extracellular domain of CD45 also plays an important role (194), perhaps by regulating the interaction with other surface proteins. The requirement for CD45 in T cell activation seems to reside at a very early stage in the signal transduction cascade, since, in the absence of CD45, the rapid receptor-triggered tyrosine phosphorylation of cellular proteins is severely reduced (195), resulting in impaired activation of phospholipase C (196) and disturbed calcium homeostasis (197). Experiments with B lymphocytes and other leukocytes have largely confirmed the central role of CD45 in signaling through receptors that primarily use Src family PTKs for signal transmission. Other receptor systems, *e.g.* for cytokines or growth factors, are not perturbed by the lack of CD45. The role of CD45 in T cell signaling is also seen as a failure in thymic development in mice with CD45-negative thymocytes lacking exon 6 of the CD45 gene (198).

It seems that the main mechanism by which CD45 influences TCR-induced tyrosine phosphorylation is by positively regulating the Src-family PTKs Lck and Fyn (5-10, 199-202) in T cells, and other members of the Src family in other cell types. Dephosphorylation of these kinases occurs at their C-terminal negative regulatory site (reviewed in 5), and correlates with responsiveness of the T cells to TCR/CD3 stimulation (202). Consequently, we

have hypothesized (9) that the main physiological role of CD45 is to counteract the suppressive effect of the Csk kinase, which rephosphorylates the C-terminal tail of Src family PTKs (reviewed in 5), and thereby to keep a sufficiently large fraction of the cellular pool of Src family PTKs active and able to participate in signal transmission. This function of CD45 seems to be constitutive and not significantly modified by receptor ligation. On the other hand, there is evidence that CD45 does not treat all Src family members equally. In T cells, for example, CD45 does not seem to have the same affinity for Fyn as for Lck. Although some skewing may arise from differences in expression levels or subcellular location, there is data to support the notion that the N-terminus of Lck allows the kinase to increase its interaction with CD45 compared to other Src-like kinases (203). This physical interaction of Lck with CD45 can be visualized by co-capping and is strong enough for co-immunoprecipitation .

The expression of CD45 has also been found to affect the phosphorylation state of Zap (142) and Syk (our unpublished observation) in one pair of $CD45^+$ and $CD45^-$ cells, the murine YAC-1 T lymphoma. A physical association of Zap with CD45 was seen by co-immunoprecipitation and by co-capping experiments and Zap was constitutively tyrosine phosphorylated in the $CD45^-$ YAC-1.N1 clone (142). Although a direct action of CD45 on Zap or Syk has not been excluded, it appears more likely that the effects of CD45 on Syk and Zap are indirect. Instead, there is evidence suggesting that TCR-zeta is a physiological substrate for CD45 (204). Since dephosphorylation of TCR-zeta would prevent the association of Zap and its subsequent activation by Lck, it seems that CD45 can have a negative influence on signaling, which is opposite to its positive effects of Lck and Fyn. This may explain the contradictory results obtained with anti-CD45 mAbs, which can be either stimulatory or inhibitory for T cell activation. It may also be important to note that results obtained in $CD45^-$ variants of several transformed T cell lines are partly contradictory. For example, while Lck is hyperphosphorylated only at Tyr-505 and has a low catalytic activity in most T cells lacking CD45, it also becomes hyperphosphorylated at the positive regulatory site, Tyr-394, and is catalytically activated in the YAC1.N1 (10). Although this effect is reversed by re-expression of CD45 (193), it is clear that CD45 is not the main PTPase responsible for Tyr-394 dephosphorylation as the authors propose. In other T cells lacking CD45, Tyr-394 of Lck is not phosphorylated, but phosphate does accumulate at this site if the cells are treated with a PTPase inhibitor (our unpublished observation). The YAC-1 cell line might be deficient in some other PTPase. PTPase inhibitors also induce hyperphosphorylation of Syk and Zap in T cells lacking CD45, suggesting that a PTPase distinct from CD45 dephosphorylates these PTKs as well.

The physical size of CD45 has puzzled scientists. The extracellular domain of CD45 forms a long rod, which exceeds the TCR and its co-receptors several fold in length, and thereby would prevent interaction of the TCR with MHC molecules on the surface of another cell. There is recent insight into the mechanics of T cell contact with antigen-presenting cells that overcomes this dilemma. By immunofluorescence staining and computer-enhanced confocal microscopy, A. Kupfer's laboratory has found that CD45 leaves the small area that forms the contact with the antigen-presenting cell (205,206). At the same time, the TCR and its co-receptors accumulate in this area, as do Lck and other signaling molecules on the cytoplasmic face of the contact area. These results suggest that signaling from the TCR proceeds without being counteracted by the PTPase domains of CD45 as long as the contact with the antigen-presenting cell is maintained. As CD45 might be the PTPase that dephosphorylates the ITAMs of the TCR-zeta, the exclusion of CD45 would strongly promote the phosphorylation of these sites. On the other hand, the absence of CD45 in the contact area will also prevent dephosphorylation of the negative regulatory sites in Lck and Fyn, causing their inactivation. We have measured the turnover of phosphate at this site of these PTKs (140) and found it to be relatively slow. Thus, the activity of Lck and Fyn molecules that are out of CD45's reach in the contact area will remain active for sufficiently long periods of time. This new findings underscore the importance of studying PTPases not only on a biochemical level, but also as components in a highly organized, three-dimensional context within living cells.

3. 2. HePTP - a cytosolic leukocyte-specific PTPase

The hematopoietic protein tyrosine phosphatase (HePTP) was originally cloned from human T lymphocytes (79,80). The gene is expressed exclusively in thymus and at lower levels in spleen, and in most leukemic cell lines examined, including the Jurkat T leukemia cells (our observation), HL-60 (promyelocytic leukemia), NALM-6 (pre-B cell line), Tall-1 (T cell leukemia cell line), PEER (T cell leukemia line) and RPM18226 (myeloma cell line). HePTP is not detected in non-hematopoietic tissues (79,80,207) or cell lines. HePTP belongs to a group of PTPases with currently 3 other members, STEP (for striatum-enriched phosphatase; ref. 81), PCPTP1 (82-84), and Typ (85). Interestingly, at least the two former come in many different isoforms due to alternative mRNA splicing (208-210) or translational initiation (82). The four genes of this family are all expressed in different tissues; STEP mainly in brain, particularly, striatum (81) and PCPTP1 in lung, heart and brain, particularly in cerebellum, but not in striatum (82), and Typ only in spermatocytes (85). Thus, hematopoietic cells express only HePTP and none of the other family members.

The exon/intron structure of the HePTP gene has been determined (207). It is located on chromosome 1q32.1 (211) and is organized into 11 exons, including the 5'-noncoding first exon and the 3'-noncoding exon. The exon/intron structure is very similar to that of the phosphatase domains of human CD45 (212). Particularly the splicing sites for exons 4 to 10, which encode the conserved catalytic PTP domain, arise at the same position as in the CD45 gene. Interestingly, the CD45 gene is located on human chromosome 1 at q31-q32, quite close to HePTP at 1q32.1. Together with their common restriction to hematopoietic cells and the relatively high (53.8%)

degree of amino acid identity between their catalytic domains, it seems likely that they arose by gene duplication of a primordial gene. In contrast to CD45, however, HePTP consists of only a single PTPase domain, which occupies the C-terminal 3/4 of the enzyme and is preceded by a ~80-amino acid non-catalytic N-terminus (figure 2).

There is some controversy regarding the first N-terminal amino acids of HePTP. Brent Zanke's group (79) cloned the cDNA for HePTP from human peripheral T lymphocytes and found the open reading frame to encode a protein of 339 amino acids (38 kDa). Simultaneously, Adachi's team (80) isolated a cDNA clone from a human T cell PEER cDNA library, which encoded a protein of 360 amino acids, which they termed LCPTP for Leukocyte PTP. Comparison of the two cDNAs indicates that they correspond to the same gene. However, they differ in the presence of a single nucleotide in LCPTP (missing in HePTP) that results in a frame-shift and 21 extra amino acid residues in the N-terminus of LCPTP. However, from Met-22 of LC-PTP, the two proteins are nearly identical. A few single base differences that result in amino acid changes are present at positions 235 (His in HePTP versus Gln in LCPTP), 236 (Val in HePTP versus Leu in LCPTP) and 337 (Ala in HePTP and Asp in LCPTP). These substitutions are probably insignificant and they could represent allelic variation or be due to mutations in the transformed PEER leukemia cells from which LCPTP was cloned. A third group (213) isolated the cDNA encoding the rat equivalent of the human HePTP from a rat basophilic leukemia mast cell cDNA library. The rat and human sequences share 77 and 91 % identity at the nucleotide and amino acid levels, respectively. The protein expressed in the mast cells was of a size (~40kDa) and PI (6.9) predicted from the deduced amino acid sequences, which agrees in the extreme N-terminus with LCPTP.

The lack of putative transmembrane sequences or recognizable signal motifs in HePTP for subcellular targeting suggests that the enzyme might be soluble in the cytosol. Indeed, immunofluorescence microscopy indicates that HePTP is localized only to discrete globular compartments within the cytoplasm of mast cells and not in the nucleus or associated with the cell surface membrane (213). In T cells, the immunofluorescence is quite evenly distributed throughout the cytosol (our unpublished observation).

Recent experiments have begun to shed some light on the biological function of HePTP. Ectopic expression of HePTP in NIH3T3 cells resulted in altered cell morphology, disorganized growth, anchorage independent colony formation and subtle differences in the pattern of tyrosine phosphoproteins compared to control cell lines (211). In hematopoietic cells, the first indication of a role of HePTP in cell proliferation or differentiation came from the finding that the HePTP gene is located on the long arm of chromosome 1, which is often found in extra copies (trisomy) in bone marrow cells from patients with myelodysplastic syndrome (214,215), which is characterized by reduced hematopoiesis and increased risk of acute leukemia. Indeed, amplification and overexpression of HePTP has been reported in a case of myelogenous leukemia (211). Deletions of 1q32 have also been reported in non-Hodgkin lymphomas and chronic lymphoproliferative disorders (216). Together, these findings suggest that excess HePTP may correlate with reduced proliferation (in myelodysplasia) and loss of HePTP with increased cell proliferation and/or survival. A connection with proliferation is also supported by the finding that the HePTP gene is transcriptionally activated in T cells treated with interleukin-2 (180). Although mRNA levels also increased several fold upon stimulation of normal mouse lymphocytes with phytohemagglutinin, lipopolysaccharide, Concanavalin A or anti-CD3 (79), the HePTP protein was present in resting cells and its amount increased only moderately. HePTP has also been reported to become phosphorylated on tyrosine in RBL-2H3 mast cells stimulated through their Fc-epsilonRI (213).

We have found that transient expression of HePTP in T cells causes a clear reduction in antigen receptor-induced transcriptional activation of a reporter gene driven by a NFAT/AP-1 element taken from the interleukin-2 gene promoter (217). In contrast, a catalytically inactive C270S mutant of HePTP had no effect, suggesting that the PTPase activity of HePTP was required for inhibition (217). HePTP also reduced TCR-induced activation of the mitogen-activated protein (MAP) kinase Erk2, but not of the N-terminal c-Jun kinase (Jnk). HePTP also did not affect the activity or phosphorylation of MEK, the upstream activator of Erk, and all examined tyrosine phosphorylation events upstream of MEK appeared intact. Furthermore, we found that HePTP binds specifically to Erk2 and p38 kinase in intact T cells and dephosphorylates the critical PTyr in their activation loop (218,219). This reaction causes rapid inactivation of the bound Erk or p38. The region of HePTP responsible for the specific binding to Erk and p38 was mapped to the non-catalytic N-terminus of HePTP, which also is phosphorylated by Erk and p38 at Thr-45 and Ser-72. We propose that HePTP is a negative regulator of T cell activation, and acts by specifically reducing the activation of the Erk and p38 MAP kinase pathways. We speculate that this function of HePTP can be regulated through modulation of its expression levels and through post-translational modifications, such as phosphorylation on serine, threonine and tyrosine. The relation to dual-specific MAP kinase phosphatases is discussed below under these enzymes.

3. 3. TCPTP - a PTPase of the endoplasmic reticulum

The T cell PTPase, TCPTP, is an intracellular enzyme with a single catalytic domain, which is located in its N-terminus (figure 2). Its cDNA was originally isolated in 1989 by Deborah Cool and co-workers from a human peripheral T-cell cDNA library (86), and it encodes a 48-kDa protein (86,220) with 65% sequence identity to the first cloned PTPase, PTP1B (59). In 1992, Mosinger and co-workers (221) described a cDNA encoding the mouse homologue of TCPTP (termed MPTP), which predicted a protein of 383 amino acids with Mr~44,640. The similarity between MPTP and human TCPTP is 88.8% at the nucleic acid level and 93.2% at the amino acid. However, the

human and murine open reading frames differed markedly at their 3' ends. This puzzle was solved by the realization that there is a splice donor site (AGGT) present in the human TCPTP cDNA at the position where the sequence diverges from the murine cDNA, suggesting the primary transcript undergoes an alternative splicing event that results in two isoforms differing in their C-termini. This has been confirmed. The larger protein is approximately 48 kDa and its C-terminus contains a hydrophobic and basic endoplasmic reticulum-retention signal, which is lacking in the smaller, 45-kDa isoform (221,222). Instead the smaller protein contains a nuclear localization signal, Arg-Lys-Arg-Lys-Arg, which immediately precedes the splice junction (223). Accordingly, the 45-kDa isoform is nuclear. The rat homologue of TCPTP (termed PTP-S for protein tyrosine phosphatase of spleen) has also been cloned (224) and it is 95% identical to the human protein within the catalytic domain. There is also evidence for alternative splicing in the rat, perhaps giving rise to more than two isoforms (225).

Although TCPTP was isolated from T cells (86) and from spleen (221,224), it is not restricted to lymphoid cells, but is found in a variety of cell types and tissues. The expression is low in embryonic stem cells and increases during later stages of mouse development (221). Highest expression of the major RNA transcript of 1.9kb was observed in the ovaries, testes, thymus and kidneys. A second RNA transcript of ~1.3kb, was detected exclusively in the testes. The TCPTP gene was found to be located on chromosome 18p11.2-11.3 (226).

Mice with a $TCPTP^{null}$ mutation were recently generated in M. Tremblay's laboratory (227). The three genotypes (+/+, +/-, and -/-) showed the normal Mendelian 1:2:1 segregation at birth demonstrating that the absence of TCPTP was not lethal in utero. However, all $TCPTP^{-/-}$ mice grew poorly and died by 3-5 weeks of age, having enlarged spleens and lymph nodes. These mice also exhibited specific defects in their bone marrow, in B cell lymphopoiesis, and in their erythropoiesis, as well as impaired T and B cell functions. However, myeloid and macrophage development in the bone marrow and T cell development in the thymus were not significantly affected. Furthermore, bone marrow transplantation experiment showed that the lymphoid problems in $TCPTP^{-/-}$ animals were not due to defects in the hematopoietic stem cells, but rather to a stromal cell deficiency. Although these findings do not exclude the possibility that TCPTP plays an important role in lymphocytes, they indicate that TCPTP is not an indispensable component of the lymphocyte development or activation machinery.

Despite the generation of knock-out mice, the physiological function and substrates of TCPTP remain poorly understood. The high degree of sequence similarity between TCPTP and PTP1B, with as high as 85% sequence similarity within the catalytic domain, predicted that they may have similar physiological functions and modes of regulation. This prediction has been partly fulfilled, but there are also important differences between the two proteins. Both enzymes are targeted to the endoplasmic reticulum through their carboxy-terminal segments (220,228-232). The C-termini also suppress the catalytic activity of the native enzymes (228), suggesting the existence of an intramolecular regulatory mechanism. Accordingly, truncation of the C-terminus of TCPTP results in a constitutively active cytosolic protein (228). Expression of such a 37-kDa C-terminally deleted form of TCPTP caused BHK cells to become multinucleated and it suppressed v-*fms*-induced transformation of rat-2 cells (233,234). However, correct subcellular localization is likely to be crucial for targeting TCPTP to its physiological substrates, and overexpression of wild-type TCPTP has little effect on the morphology or growth of cells.

Recently, a number of associated proteins and putative substrates for TCPTP have been described. Tiganis and co-workers (235) isolated three proteins, p97, p116 and p120, that interacted with the alternative C-termini of TCPTP. p120 interacted with the longer C-terminus, while p116 and the nuclear import factor p97 bound to the basic residues of the TCPTP bipartite nuclear localization signal, which targets the 45-kDa TCPTP isoform to the nucleus. These findings are consistent with the notion that the alternative C-terminal segments of the TCPTP isoforms target the enzyme to defined intracellular locations through specific interactions with regulatory proteins.

Lammers and co-workers (236) reported that both PTP1B and the 48-kDa isoform of TCPTP preferentially dephosphorylated the precursor forms of several receptor tyrosine kinases during their synthesis in the endoplasmic reticulum. This feature was not shared by two other intracellular PTPases, PTPH1 and SHP-1. Substrates included the epidermal growth factor receptor and the adapter protein Shc (237). It seems therefore that PTP1B and TCPTP counteract the autophosphorylation of receptor tyrosine kinases during their synthesis and posttranslational processing. We have found that expression of TCPTP in T cells, even at 10-100 fold above endogenous levels, has no effects on TCR signaling as measured by many different parameters from early tyrosine phosphorylation events to the transcriptional activation of the interleukin-2 gene. However, TCPTP does reduce the basal tyrosine phosphorylation of several PTKs if they, too, are overexpressed at sufficiently high levels, presumably being abundant also in the endoplasmic reticulum. In agreement with the notion that the 48-kDa TCPTP has a localized housekeeping function, we have found that this enzyme is quite promiscuous *in vitro* compared to other PTPases.

The role of the smaller form of TCPTP is less clear. A substrate-trapping mutant (D182A) of the 45-kDa TCPTP isoform transiently overexpressed in COS cells underwent a change in localization, exiting the nucleus and accumulating in the cytoplasm in response to epidermal growth factor (235). It bound PTyr-containing proteins of approximately 50, 57, 64, and 180 kDa. Of these, the 57- and 180-kDa proteins were identified as Shc and the epidermal growth factor receptor, respectively. No effects were seen on epidermal growth factor-induced MAP kinase activation, but the association of Shc with Grb2 was reduced. Whether the endogenous 45-kDa TCPTP remains

Table 2. ITIM containing receptors

RECEPTOR	LIGAND	EXPRESSION PATTERN	REFERENCE
I. Type I transmembrane molecules with Ig-like domains			
Fc-gamma-RIIB (human and mouse)	Fc of IgG	many lymphoid/myeloid cells	255
CD22 (human and mouse)		B cells	256,257
p58 (KIR, human)	MHC	NK cells, small subset of T cells	258,259
p70 (KIR, human)	MHC	NK cells, small subset of T cells	260,261
LAIR-1 (human)	?	NK cells, B cells, T cells, monocytes	262
LIR-1 (human)	?	B cells, monocytes	263
ILT-2 (human)	?	many leukocytes	264,265
ILT-3 (human)	?	myeloid cells, antigen presenting cells	266
ILT-4 (human)	?	myelomonocytic cells	265
ILT-5 (human)	?	myelomonocytic cells	265
gp49B1 (mouse)	?	mast cells, basophils, NK cells	267,268
p91/PIR-B (mouse)	?	B cells, myeloid lineage cells	269
MAFA	?	mast cells	270
II. C-type lectin group			
CD72 (human and mouse)	carbohydrate	B cells	271
NKG2A/B (human)	MHC	NK cells, small subset of T cells	272,273
Ly-49 (mouse)	MHC	NK cells, small subset of T cells	274,275

in the nucleus at all times or cycles to the cytoplasm, remains to be clarified. A number of nuclear proteins contain PTyr, including MAP kinases, transcription factors and the Abl kinase and its substrates. The 45-kDa form of TCPTP may act on any of these, and could thereby have an important regulatory role in cell growth, differentiation or apoptosis.

3. 4. SHP1 - a negative regulator of signaling

The approximately 100-amino acid residue Src Homology 2 (SH2) domain is a hemispherical protein-protein interaction domain that specifically binds to phosphotyrosine-containing peptide sequences in other cellular proteins. Two PTPases are currently known that have SH2 domains, namely SHP1 (previously PTP1C, SHP, HCP, or SH-PTP1) and SHP2 (also known as PTP1D, PTP2C, SH-PTP2, or Syp). These two PTPases are similar in overall structure; both have two SH2 domains in the N-termini and a catalytic PTPase domain in the C-termini followed by a short C-terminal tail with two tyrosine phosphorylation sites. SHP1 is expressed at highest levels in cells of hematopoietic origin, while SHP2 is ubiquitous. Lymphocytes contain easily detectable levels of both. An alternative splicing of a 39-amino acid fragment in the C-terminal SH2 domain of SHP1 (238-240) creates some heterogeneity in the apparent molecular size of SHP1. There are also two naturally occurring point-mutations in the *shp1* gene in the two mouse strains *motheaten* (*me*) and *viable motheaten* (*me^v*) (241), in the former leading to premature termination of the protein, and in the latter strain causing the expression of functionally deficient SHP1 protein (238-241). These two mouse strains have been tremendously valuable in the search for the function and importance of SHP1. The majority of data indicate that SHP1 acts as an important negative regulator of many signaling systems in hematopoietic cells.

The posttranslational regulation of the catalytic activity of SHP1 and SHP2 proteins is at least partly clear. The role of the two SH2 domains seems to be twofold: regulation of the catalytic activity of the enzyme and physical localization of the protein to its physiological sites of action. The first task is accomplished by a physical association of the N-terminal SH2 domain with the catalytic domain resulting in a strong suppression of the phosphatase domain (242,243). This interaction, which occurs in a PTyr-independent manner, is disrupted by binding of a PTyr-containing peptide ligand to the SH2 domain. As a consequence of SH2 domain engagement, the catalytic domain is liberated and activated up to 100-fold (242,244). As predicted by this intramolecular suppression, investigators have found that removal of the SH2 domains increases the enzymatic activity (242,244-247, and own observations). The second SH2 domain does not seem to participate in regulation of catalytic activity and only serves as a recruiting domain (242,243). Its importance lies in its participation in the synergistic binding of SHP1 to doubly phosphorylated ligands (248,249). Thus, the ligand specificity of the SH2 domains of SHP1 are largely responsible for juxtaposing SHP1 to certain phosphorylated cellular proteins that are, or associate with, the physiological substrates for the PTPase. At the same time, SHP1 is activated at the site of binding. On the other hand, studies where the tandem SH2 domains were exchanged between SHP1 and SHP2 indicated that substantial specificity also resides in the catalytic domain (250,251).

The ligand specificity of the SH2 domains of SHP1 has been determined. The preferred sequence is now referred to as the immunoreceptor tyrosine-based inhibition motif (ITIM), Val/Ile-Xaa-PTyr-Xaa-Xaa-Leu/Val (where Xaa represents any amino acid) (252-254). This motif is found in many different proteins, many of which are transmembrane receptors for inhibitory ligands (table 2).

Another potential mode of regulation is the phosphorylation of SHP1 at Tyr-538 (Tyr-536 in mouse SHP1) upon various extracellular stimuli (276-277), and also at Tyr-566 (Tyr-564 in mouse SHP1) in the Lck-overexpressing thymoma cell line LSTRA and in T cells (278). In vitro, Lck readily phosphorylates both these sites (our unpublished observation). Phosphorylation of these tyrosines does not seem to affect the enzymatic activity of SHP1, but both are in an optimal sequence for binding to the SH2 domain of the Grb2 adaptor protein (279). Indeed, association of SHP1 with Grb2 has been reported in P815 mastocytoma cells and in bone marrow derived macrophages but not in T cells (280,281).

3. 4. 1 Role of SHP1 in B cells

B lymphocyte activation is accomplished by binding of soluble multivalent antigen to the B cell antigen receptor (BCR) (282-284), which consists of a transmembrane immunoglobulin D or M molecule, having two heavy chains and two light chains, and at least two invariant glycoproteins MB-1 (Ig-alpha) and B29 (Ig-beta). Recognition of antigen is mediated by the variable portion of the Ig chains, and must lead to crosslinking or oligomerization of BCRs to cause signals to be transmitted into the cell. While the Ig heavy chains have very short cytoplasmic tails (the light chains are solely extracellular), the MB-1 and B29 polypeptides have long intracellular tails and are thought to be mainly responsible for signal transmission. A number of other transmembrane glycoproteins also participate as co-receptors, accessory molecules, or alternative routes of activation. These include CD19, TAPA-1, Leu13, the CR2 complement receptor (CD21) and CD40.

B cell activation is inhibited by co-ligation of the BCR with the type IIB receptor for the Fc portion of immunoglobulin G, Fc-gammaRIIB (252,253). Under physiological conditions, this co-ligation and juxtaposition of the two receptors occurs when there are circulating antigen-antibody complexes that bind and co-cluster the receptors. Under these circumstances, there is less need for more antibodies and, accordingly, B cell activation will be suppressed. The molecular mechanisms of this inhibition of BCR signaling by a juxtaposed Fc-gammaRIIB has been partly clarified. A key event is the phosphorylation of Fc-gammaRIIB on tyrosine within its cytoplasmic ITIM sequence (253), followed by recruitment of SHP1 and another SH2 domain-containing molecule, SHIP, which is a inositol polyphosphate 5-phosphatase (253). Inhibition of BCR signaling then occurs through dephosphorylation of protein substrates by SHP1 and inositol-containing phospholipids and soluble inositol polyphosphate second messengers by SHIP. The exact targets for SHP1 in this system are not entirely clear. It seems that dephosphorylation of CD19 (252,285) is important, and the finding that signaling by Fc-gammaRIIB was deficient in *me/me* mice, confirms that SHP1 plays an important role (252,286). In contrast, two reports suggest that SHIP, but not SHP1, is required for Fc-gammaRIIB-mediated inhibitory signaling in B cells (287,288).

SHP1 also associates with the ITIM-containing CD22 molecule in B cells (289). CD22 also functions as a inhibitory signaling molecule. Results obtained with mice deficient in the B cell-specific Src family PTK Lyn, indicate that this kinase is required for the tyrosine phosphorylation of CD22, its association with SHP1, and the suppressive function of CD22 on BCR signaling (290). Recently, the ITIM containing paired Ig-like receptor B (PIR-B) on murine B cells was shown to associate with SHP1, SHP2, and SHIP *in vitro*, but only with SHP1 at detectable levels *in vivo* (291). Furthermore, when a chimera between the extracellular domain of Fc-gammaRIIB and the cytoplasmic domain of PIR-B was transfected into a Fc-gammaRIIB-negative mouse B cell lymphoma and co-crosslinked to the BCR, the intracellular free calcium release and NFAT activation was inhibited compared to stimulation by BCR crosslinking alone (292). The tyrosine phosphorylated chimera was able to bind SHP1 and SHP2, but not SHIP, and mutational studies showed that Tyr-771 and to some extent also Tyr-801 in the cytoplasmic domain of PIR-B were essential for maintaining the inhibitory capabilities of the chimera (292). Finally, as shown with a SHP1/SHP2 deficient chicken B cell line (individually deficient and in combination), both SHP1 and SHP2 are required for the inhibitory function of PIR-B (292).

3. 4. 2. The function of SHP1 in Natural Killer Cells

Natural Killer (NK) cells are large granular lymphocytes that are devoid of T of B cell antigen receptors and that express unique lineage-specific receptors, including CD56, CD16 and a number of killer cell inhibitory receptors (KIRs). The role of NK cells is to recognize defective cells, e.g. tumor cells or virus-infected cells, and lyse them (293). Recognition is mediated by the KIRs (253,254,294), which bind to specific MHC class I molecules and suppress the killer instinct of the NK cell. Conversely, in the absence of normal (e.g. missing, altered or foreign) class I molecules, the suppression does not occur and the NK cell eliminates the target. NK cells also recognize antibody-coated target cells via their CD16 molecule, which is a transmembrane splice form of the type III Fc receptor for IgG (Fc-gammaRIIIA) (295-297). This 50-70 kDa highly glycosylated protein has only 25 cytoplasmic residues, but associates with a homodimer of the zeta-chain (of the TCR) (298-300), or a heterodimer consisting of the TCR-zeta and the gamma chain of the high affinity Fc receptor for IgE (Fc-epsilonRI) (301). CD16 transmits a positive signal that induces killing of the target cells, termed antibody-dependent cytotoxicity, ADCC.

SHP1 is thought to be the key signaling molecule in the function of the KIRs (287,288,302) and of the functionally, but not structurally, related NKG2A and B receptors (303). The cytoplasmic domain of the KIRs contain one or two ITIM sequences. SHP1 was reported to associate with the human p58KIR in a NK cell line, and introduction of an inactive SHP1 mutant in the same cell line reduced the inhibitory function of p58 in target cell lysis (302). The involvement of SHP1, but not SHIP, in

KIR-mediated inhibition of target cell lysis has been supported by other investigations (287,288).

Subsets of T and NK lymphocytes express the CD94-NKG2A/B heterodimer, which recognizes the MHC class I molecule. Anti-CD16 induced specific cell lysis by a interleukin-2 dependent NK cell line was inhibited when anti-NKG2A or anti-CD94 was crosslinked at the same time, and the same pattern was observed with anti-CD3-induced specific cell lysis by a melanoma specific cytotoxic T lymphocyte (CTL) clone (303). NKG2A contains two intracytoplasmic ITIM like sequences and when tyrosine phosphorylated, both of them can associate with the SH2 domains of SHP1 and 2 *in vitro* (but not with SHIP), suggesting that SHP1/2 are involved in the CD94/NKG2A mediated inhibition of both antigen induced T cell response and antibody induced NK cell cytotoxicity (303).

3. 4. 3. SHP1 in T cell signaling

In contrast to the well established role of SHP1 in B lymphocytes and NK cells, it is less clear how important SHP1 is for T cell development and function. This is partly due to the absence of well-studied ITIM-containing inhibitory receptors on T cells. The recent cloned LAIR-1 might be such a molecule as it is expressed in most T cells (263), but its function is only now beginning to be investigated.

Studies with motheaten mice suggest that SHP1 may play a negative role in the T cell receptor (TCR) signaling. Thymocytes from these mice show enhanced and prolonged tyrosine phosphorylation of TCR-zeta and CD3 as well as prolonged MAP kinase activation upon TCR stimulation (304). It was also reported (305) that thymocytes from *me/me* mice incorporated 3- to 5-fold more [^{3}H]-thymidine in response to TCR-stimulation than thymocytes from normal mice. The response to interleukin-2 response was unchanged (305). This paper also showed increased tyrosyl phosphorylation of several cellular substrates, correlating with increased kinase activity of the Src-family kinases Lck and Fyn, suggesting that SHP1 is involved in the inactivation of Lck and Fyn (305). Interestingly, the catalytic activity of c-Src in thymocytes from *me/me* mice was substantially lower than in normal thymocytes, but could be enhanced by *in vitro* exposure to SHP1 (306). Furthermore, SHP1 preferentially dephosphorylated c-Src isolated from Jurkat T cells at its inhibitory site of tyrosine phosphorylation, Tyr-527, indicating that SHP1 is involved in the activation of this kinase (306). This is apparently not true for other related kinases (e.g. Lck and Fyn), and it seems not to have any significant effect on T cell activation. In Jurkat T cells, expression of a chimera between the extracellular and transmembrane domain of the HLA-A2 molecule and SHP1 was unable to rescue TCR-mediated signal transduction in the CD45-deficient J45.01 variant of Jurkat (307). However, expression of the chimera in normal Jurkat cells diminished the inositol phosphate production as well as NFAT/AP-1 promotor activity, confirming that SHP1 can regulate the TCR response. Finally, the direct regulation of ZAP-70 by SHP-1 in T cells has also been suggested (308). Other investigations based on *in vitro* studies or transfection of heterologous cells also show that SHP1 has many potential substrates, e.g. co-expression of SHP1 with ZAP-70, Lck, and TCR-zeta chain in Sf21 insect cells show that SHP1 can dephosphorylate all of them *in vivo* (309).

Despite the finding that the response to interleukin-2 is unaltered in thymocytes from *motheaten* mice, Migone and coworkers (310) showed that interleukin-2 induced association of SHP1 to the interleukin-2 receptor complex of T cells, and that SHP1 was able to decrease the tyrosine phosphorylation level of the 75-kDa beta subunit of the interleukin-2 receptor and the associated tyrosine kinases JAK1 and JAK3 (310). Interestingly, SHP1 expression is decreased or undetectable in many interleukin-2 independent HTLV-I transformed T cell lines that exhibit constitutive JAK/STAT activation, indicating that SHP1 downregulates the interleukin-2 induced signaling response in T cells (310).

3. 4. 4. Role of SHP1 in other hematopoietic receptor systems

SHP1 also plays a negative regulatory role in signaling through the erythropoietin receptor (EpoR) (311,312), growth hormone receptor (313,314), the stem cell factor receptor, c-Kit (247,248,213), colony-stimulating factor-1 receptor, CSF-1R (281,318), the receptor for interleukin 3 (319,320), and the receptors for interferon alpha and beta (321,322). These receptors are either PTKs themselves (c-Kit and CSF-1R), or use Jak family PTKs for signaling. Generally, SHP1 binds directly to these receptors via its SH2 domains and subsequently dephosphorylates either the receptor, the associated PTKs, or their substrates. For example, in the case of the EpoR, receptor ligation induces recruitment of Jak2, which phosphorylates itself, the receptor, and other proteins, thereby initiating a signaling cascade that leads to growth and/or differentiation. Following phosphorylation of EpoR at Tyr-429, SHP1 binds to this site via its SH2 domains and subsequently dephosphorylates Jak2 leading to termination of the proliferative signals (311,312). SHP1 also binds to c-Kit via its SH2 domains, and observations made in *motheaten* mice suggest that SHP1 directly dephosphorylates and regulates c-Kit (320). The preferred binding site of SHP1 on c-Kit is Tyr-569, and Tyr-567 might contribute to this interaction (316). When Tyr-569 was mutated to phenylalanine and the construct transfected into Ba/F3 cells, the association was disrupted and the cells hyperproliferated in response to stem cell factor. Macrophages from *me/me* mice also proliferate more in response to CSF-1 than control cells and their CSF-1R is hyperphosphorylated, indicating that SHP1 also is a critical negative regulator of CSF-1R signaling (281). The negative feedback role of SHP1 in all these receptor systems probably explain the multiple and severe abnormalities in the development and function of the hematopoietic cells in the *motheaten* mice (238,239,241).

In conclusion, it is becoming clear that SHP1 is an important negative regulator of most hematopoietic-specific signaling systems. In contrast, expression of SHP1 in non-hematopoietic cells, does not affect, or even

augments, signaling from receptors for epidermal growth factor, platelet-derived growth factor, insulin or interferon-gamma (323-326). Although the mechanisms for SHP1 recruitment have been elucidated in great detail, the exact substrates for SHP1 in most receptor systems remain unclear.

3. 5. SHP2 - a positive regulator of signaling?

Despite their structural similarity (figure 2), SHP1 and SHP2 differ substantially in their physiological functions. In many systems, SHP2 seems to behave mainly as a positive regulator of signals leading to activation of the MAP kinase pathway. The mechanism of this positive role remains unclear. Initial reports suggested that tyrosine phosphorylation of SHP2 in its C-terminal tail was responsible for enhanced recruitment of Grb2 to the membrane and thereby translocation of Sos and activation of Ras (327,328). Although this mechanism may operate under some circumstances, there is also evidence that the PTPase activity of SHP2 is important for the enhancement of MAP kinase activation (our unpublished observation).

3. 5. 1. SHP2 in lymphocytes

In T lymphocytes, SHP2 has been reported to become phosphorylated on tyrosine upon TCR triggering (16) [although negative results have also been published (329)] as well as after addition of interleukin-2 (330). Studies of a murine hematopoietic cell BAF-B03 transfectant clone expressing interleukin-2 receptors showed that the tyrosine phosphorylation of SHP2 required both the serine-rich as well as the acidic region within the beta chain of the receptor (330). The acidic region interacts with Src-family protein tyrosine kinases and co-expression in COS cells showed that Lck is capable of tyrosine phosphorylating SHP2 (330). It was also recently shown that expression of SHP2 augments TCR-induced MAP kinase activation (331) albeit to a relatively small extent. An earlier report from the same group found a 110-120 kDa protein that was tyrosine phosphorylated upon TCR stimulation and co-immunoprecipitated with SHP2 from Jurkat cells (329). These authors conclude that the 110-kDa protein is a homologue of the Dos (Daughter-of-Sevenless) protein, and that its dephosphorylation by SHP2 is involved in regulation of the MAP kinase pathway (330). A negative function for SHP2 in T cells was suggested by the finding that SHP2 associates with the inhibitory CTLA-4 receptor in mice (332). This report has not yet been confirmed by others.

A function of SHP2 in adhesion was suggested by the finding that SHP2 associated through its SH2 domains with the tyrosine phosphorylated form of the adhesion molecule PECAM-1 (CD31), which is involved in migration of hematopoietic cells across the endothelium (333). In B cells, integrin activation leads to tyrosine phosphorylation of the 130-kDa docking molecule Cas, followed by recruitment of Fyn and SHP2, indicating a modulator role of Cas signaling complexes by SHP2 and Fyn (334).

SHP2 has been reported to bind to many of the receptors that also bind SHP1 and it is unclear if the function of SHP2 in these cases overlaps that of SHP1. For example, a few investigators report that SHP2 binds to some of the KIR family members; however, whether SHP2 *in vivo* plays any role in KIR signaling is still uncertain (335,336).

3. 5. 2. Function of SHP2 in other hematopoietic receptor systems

SHP2 also associates with a number of hematopoietic receptors for growth factors and cytokines. These include the stem cell factor receptor c-Kit, in which binding was mapped to Tyr-567 (337). When Tyr-567 was mutated to phenylalanine and the receptor transfected into Ba/F3 cells, binding to SHP2 was abrogated compared to c-Kit wild-type transfected Ba/F3 cells, and the cells hyperproliferated indicating that SHP2 plays a negative role in the c-Kit signaling pathway (337). Erythropoietin, a growth factor for stem cells committed to the erythroid line, induces association of SHP2 to Tyr-401 on the erythropoietin receptor, followed by tyrosine phosphorylation of SHP2 and association with Grb2 (338-340). Granulocyte-macrophage colony-stimulating factor (GM-CSF) and macrophage colony-stimulating factor (M-CSF) also caused tyrosine phosphorylation of SHP2 (341-344).

Interleukin-3, a potent growth factor for many progenitor and myeloid cells, induced tyrosine phosphorylation and activation of SHP2 (345), and an association between SHP2 and Grb2, PI3K, SHIP, the beta subunit of the interleukin-3 receptor, as well as the unknown tyrosyl-phosphorylated proteins p100, p97, and p135 (345-350). Interleukin-4 and insulin, on the other hand, caused an association of SHP2 through its SH2 domains with insulin receptor substrate-2 in a murine myeloid cell line (351).

Interleukin-5, a regulator of the growth and function of eosinophils, induced rapid tyrosine phosphorylation of SHP2 and association to Grb2 and interleukin-5 receptor beta (352). SHP2 antisense oligonucleotides inhibited tyrosine phosphorylation of microtubule-associated protein kinase and reverse the eosinophil survival advantage provided by interleukin-5, suggesting a positive role for SHP2 in interleukin-5 signaling (352).

Interleukin-6 stimulation induced association of SHP2 to the signal transducing beta-subunit of the receptor (gp130), which is shared with the receptors for leukemia inhibitory factor, ciliary neurotrophic factor, interleukin-11, oncostatin M, and cardiotrophin-1, followed by tyrosine phosphorylation of SHP2 (possibly by a JAK kinase) and association to Grb2 (353-356).

3. 5. 3. SHP2 in nonhematopoietic receptor systems

Growth hormone (GH) receptor stimulation results in tyrosine phosphorylation of IRS-2 and the association of IRS-2 to SHP2 (357). Recent investigations indicate that SHP2 plays a positive role in the GH signaling, and that GH stimulation induced association of SHP2 with JAK2 and SIRPalpha (358,359).

Growth factor receptors that recruit SHP2 include the alpha and beta isoforms of the platelet-derived growth factor receptor (93,327,328,360,361), and the receptors for epidermal growth factor (93,362), insulin (363-365), insulin-like growth factor-1 (364), fibroblast growth factor (366) and nerve growth factor (367).

Cells expressing the chronic myelogenous leukemia-associated p210 Bcr-Abl or p190 Bcr-Abl oncogene show constitutive tyrosine phosphorylation of SHP2 and a complex formation between Bcr-Abl, SHP2, and Grb2 (368,369). In Bcr-Abl transfected BaF3 cells, SHP2 was shown to co-immunoprecipitate with SHIP, Bcr-Abl, Cbl, and also two novel tyrosyl-phosphorylated proteins p97 and p135 (349,350). SHP2 binds Bcr-Abl via its N-terminal SH2 domain, and deletion of the N-terminal tetramerization domain of Bcr-Abl abolished this association as well as the tyrosine phosphorylation of SHP2 (368-370).

A putative SHP2 binding protein and/or substrate called SHPS-1 (for SHP substrate 1) from rat and its human equivalent, SIRPalpha1, were recently described (371-373). Overexpression of this molecule in NIH3T3 cells resulted in decreased MAP kinase activation and proliferation upon stimulation of the cells with insulin, epidermal growth factor, or platelet-derived growth factor (372). Expression of dominant negative SHP2 constructs or a SIRP 1 construct with point-mutations in the four potential SHP2 binding sites indicated that the inhibitory effect correlated with association between SHP2 to SIRPalpha1. This effect could be mediated by sequestering SHP2 away from activated receptor tyrosine kinases (372). Studies with SHPS-1, however, concluded that overexpressed SHPS-1 had no major effect on the epidermal growth factor-induced MAP kinase activation (374).

Taken together, all the findings summarized above (as well as a large number of additional papers) indicate that SHP2 may carry out its function through dual physical association with activated transmembrane receptors together with a set of downstream signaling molecules. Some of these associations are mediated by the SH2 domains of SHP2, leading to the activation of the enzyme, while other interactions are mediated by Grb2 binding to the phosphorylated C-terminal tyrosines of SHP2. Although some of the substrates for SHP2 have been characterized, it is unclear which category of binding molecules are the principal substrates of SHP2 and whether any of the identified ones mediate the observed biological effects of SHP2. The binding of Grb2 to tyrosine phosphorylated SHP2 may result in enhanced activation of the Ras/MAP kinase signaling pathway if the bound Grb2 is complexed to the Sos guanine nucleotide exchange factor. This remains unclear. It is also plausible that the bound Grb2 binds any of a number of other recognized ligands for its SH3 domains, such as SLP-76 (179), Vav (16,375), c-Cbl (177), or phosphatidylinositol 3-kinase p85 (16,177). These molecules, or additional proteins bound to them, may serve as substrates for SHP2. This would provide a mechanism for a targeted dephosphorylation of selected substrates in a SHP2 tyrosine phosphorylation-dependent manner.

3. 6. PTPases of the PEST-containing group

Three PTPases, PEP (87), PTP-PEST (95-97), and PTP-HSCF (for hematopoietic stem cell factor (98), also known as PTP-K1 (99), PTP20 (100), FLP1 (for fetal liver phosphatase 1, ref. 101), or PTP-BDP1 (for brain derived phosphatase, ref. 102), are currently members of the group of enzymes with sequences enriched in proline, glutamic acid, serine and threonine (PEST), which were earlier thought to be signature motifs for rapid degradation of cellular proteins by a non-lysosomal, ubiquitination- and ATP-dependent pathway (376). However, direct measurements indicate that the half-lives of PEST-containing PTPases are quite ordinary; suggesting that the PEST sequences do not target the proteins to accelerated proteolysis (377,378). Instead, these motifs seem to play other roles, such as association with Src Homology 3 (SH3) domains in other proteins.

PEP, PTP-PEST and PTP-HSCF share a common overall structure with an N-terminal catalytic domain and a non-catalytical C-terminal segment of about 500 amino acid residues, which contains the PEST-sequences (figure 2). The extreme C-termini contain a highly conserved 24-amino acid proline-rich region that was proposed to be involved in nuclear targeting at least in some members of the PEST-PTPases (377,101). However, it has been demonstrated that these enzymes are predominantly cytoplasmic (96,99,378,379).

The regulation of the catalytic activity of the PEST family PTPases is poorly understood. PTP-PEST has been shown to be phosphorylated in vitro by both cyclic AMP-dependent protein kinase and protein kinase C (380), which are known to have overlapping substrate specificity. The major sites were identified as Ser-39 and Ser-435. Phosphorylation of the former causes a reduction in catalytic activity of PTP-PEST (380).

The physiological substrates for PEST family PTPases remain unknown, but a few recent papers have begun to explore this issue. The ubiquitously expressed PTP-PEST has been demonstrated to interact, directly or indirectly, with several different proteins including the adapter proteins Shc (381,382), Grb2 (383), Cas (384), Csk (385) and the focal adhesion-associated protein paxillin (386). In contrast to PTP-PEST, PEP is expressed only in hematopoietic cells (87), where it is reported to associate with Csk (379). Recently, PTP-HSCF, which is preferentially expressed in hematopoietic progenitor cells in the bone marrow (98,99), was shown to interact with a novel SH3-containing member of the actin-associated protein family termed PSTPIP (for proline, serine, threonine phosphatase interacting protein; ref. 387). This cytoskeletal protein is tyrosine phosphorylated in v-*src* transformed cells and is probably dephosphorylated by PTP-HSCF (387). PSTPIP is homologous to the *Schizosaccharomyces pombe* protein CDC15p, a phosphoprotein involved in formation of the cleavage furrow during cytokinesis (388). The SH3 domain of

PSTPIP is also most similar to that of a number of known cytoskeletal regulatory proteins including myosin, spectrin, fodrin, and hematopoietic specific protein (HSP) and cortactin (388). Interestingly, tyrosine phosphorylation of cortactin is enhanced in cells isolated from mice deficient in the Csk kinase (389). Thus, it seems that there might be a functional connection between this group of PTPases, Csk and the membrane cytoskeleton. This system may play a role in signal transduction or cell division.

Although the regulation of Csk function is still poorly understood, it is clear that it inactivates Src family kinases through phosphorylation of their inhibitory C-terminal tyrosine, Tyr-505 in Lck and Tyr-528 in Fyn (5,9,43,390). Csk has been shown to be mainly localized to the cytoplasm with a minor fraction in the plasma membrane (43), but also to focal adhesions in transfected HeLa cells (391,392). Both the SH2 and SH3 domains of Csk were responsible for the targeting to focal adhesions (391). Targeting of Csk to the plasma membrane by an added myristylation site increased the negative regulatory influence of Csk on Lck and Fyn in T cells and thereby reduced TCR-induced tyrosine phosphorylation and interleukin-2 production (393). PEP is mainly localized to cellular membranes and to some extent to the cytosol and nucleus (385). It is tempting to speculate that unbound PEP is a cytoplasmic protein, but becomes redistributed within the cell to close proximity to specific target molecules when associated with Csk. It is also tempting to speculate that the function of PEP (and PTP-PEST) is coupled to the function of Csk. In this case, PEP would be expected to dephosphorylate Src family kinases, e.g. at their positive regulatory site (Tyr-394 in Lck), or proteins in physical proximity of these kinases. This site is also the target for the SH2 domain of Csk (394), which may help juxtapose the PEP bound to the SH3 domain of Csk. We are currently addressing this hypothesis experimentally.

3. 7. PTP-MEG2 - a PTPase with a putative lipid-binding domain

PTP-MEG2 was cloned from a megakaryocytic cell line, MEG-01, and is expressed in many hematopoietic, epithelial, fibroblastic and other transformed cell lines (103). Currently, the 68 kDa PTP-MEG2 is the sole representative of a PTPase containing a 250 amino-acid N-terminus with 28% identity with cellular retinaldehyde-binding protein and 24% identity with SEC14p, a yeast protein with phosphatidylinositol transfer activity (figure 2). The presence of this region prompted P. Majerus and his group, who identified and cloned PTP-MEG2 (103), to suggest that the enzyme interacts with phospholipids, perhaps being regulated by them or being involved in the interaction between phospholipids and tyrosine phosphorylation.

3. 8. The band 4.1 homology (or ERM) domain-containing PTPases

This group of intracellular PTPases currently includes seven enzymes, PTPH1 (104), PTP-MEG1 (105), PTPD1 (106-108), the only partially known PTPD2 (106), BA14 (109), PTP36 (114; also known as PEZ (115) and a particularly large enzyme cloned by several groups and named FAP-1 (110), PTP-BAS, PTP1E, PTPL1, RIP, PTP-BL, the 4 first being the human gene, the two latter murine (111-113). This group of PTPases is characterized by an N-terminal region with relatively high homology to the cytoskeletal protein band 4.1, followed by a variable central segment, and a C-terminal PTPase domain. In some members, the central segment contains one (PTPH1, PTP-MEG1) or several (PTP-BAS) of the newly recognized protein-protein interaction domain termed the PDZ domain (figure 2). Although the physiological function of these enzymes is poorly understood, the presence of the band 4.1 homology and the PDZ domains suggest that these proteins may accumulate at the interface between the cytoskeleton and the plasma membrane. Furthermore, the PDZ domain in some members is likely to facilitate the identification of binding proteins and putative substrates. Indeed, FAP-1 has already been shown to associate with the Fas (CD95) receptor through the third and fifth PDZ domains binding to the extreme C-terminus of Fas (110).

The band 4.1 homology domain is an approximately 300-amino acid region found in several cytoskeletal proteins, such as in band 4.1, ezrin, talin, radixin, moesin, merlin (395) and this group of PTPases. The domain has also been termed the ERM domain (in reference to ezrin, radixin and moesin) and is thought to be an independently folded protein-protein interaction module. In the case of the band 4.1 protein in erythrocytes, the ERM domain is involved in binding to basic amino acid motifs in two membrane proteins, glycophorin and p55 (396-398). Likewise, other proteins with ERM domains are thought to localize to cytoskeleton-plasma membrane interfaces where they may play regulatory or structural roles. Whether the ERM-containing PTPases are also associated with the cytoskeleton and the plasma membrane, remains to be clarified.

In addition to a possible function in targeting the enzyme to the cytoskeleton and plasma membrane, the ERM domain of at least PTPH1 also serves a regulatory role for the PTPase itself. Removal of this region by limited trypsin cleavage stimulated the dephosphorylation of some in vitro substrates (399). PTPH1 was also recently found to associate with the 14-3-3 protein (400). The binding was abolished by pretreating PTPH1 with potato acid phosphatase and was greatly enhanced by treating PTPH1 with Cdc25C-associated protein kinase. Two motifs RSLSVE (residues 356-361) and RVDSEP (residues 832-837) in PTPH1 were identified as the binding sites in a serine phosphorylation-dependent manner (400). Thus, the action of PTPH1 on tyrosine phosphorylated targets may be regulated through serine phosphorylation of PTPH1.

The central segment of PTPH1, PTP-MEG1, and perhaps PTPD1 contain a single copy of the PDZ domain, while PTP-BAS contains a total of six PDZ domains, one in the extreme N-terminus and five between the ERM domain and the PTPase domain. The PDZ domain derives its acronym from three proteins that contain repeats of this domain: the mammalian postsynaptic density protein PSD-95; the *discs-large* tumor suppressor protein Dlg from *Drosophila*; and the mammalian tight junction protein ZO1

(401,402). Recently, the PDZ domain from PSD-95 was crystallized with a bound peptide ligand (403) and it is clear that the PDZ domain is a structural entity involved in protein-protein interactions. Different PDZ domains have distinct specificities, many binding specifically to the C-terminal tail of proteins with the sequence Thr/Ser-Xaa-Val-COOH (404). The PSD-95 PDZ domain, for example, binds to such sequences in the C-terminus of shaker-type potassium channels and of the NR2 modulatory subunit of the NMDA-type glutamate receptor (405,406). Another group of PDZ domains selected peptides with hydrophobic or aromatic side chains at the C-terminal three residues (404). It also seems that some PDZ domains can dimerize or bind internal (i.e. not C-terminal) peptide sequences in other proteins. Recently, the PDZ domain in PTP-BAS was found to bind to a protein termed RIL at an internal segment consisting of a LIM domain (for Lin-11, Isl-1, Mec-3 homology) (407). The structural basis and specificity of PDZ domains binding LIM motifs remains to be determined. Together all the new discoveries suggest that the PDZ domain(s) in the ERM-family PTPases are likely to serve in coordinating interactions with specific transmembrane membrane proteins, signaling molecules or substrates. In agreement with this notion, it has been found that PTP-BAS/FAP-1 interacts with the cytosolic domain of Fas/CD95. Fas is a cell surface receptor which is expressed on a variety of normal and neoplastic cells, while the ligand for Fas is expressed predominantly on cytolytic T cells (408). Ligation of Fas induces programmed cell death by apoptosis of cells, including of T cells in human immunodeficiency virus-infected individuals (409). The C-terminal 15 amino acids of Fas represent a negative regulatory domain, the deletion of which facilitates death signaling by the receptor (110,410). The extreme C-terminus is also the binding site for the third and fifth PDZ domain of PTP-BAS/FAP1, suggesting that this PTPase may play a negative regulatory role in FAS signaling (110,410). FAP-1 expression is highest in tissues and cell lines that are relatively resistant to Fas-mediated cytotoxicity.

Very few papers published to date deal with the expression and possible function of the ERM domain PTPases. The available information suggests that lymphocytes express at least PTP-MEG1, PTP36 and FAP-1, perhaps also some PTPH1, while PTPD1 and PTPD2 are not present in hematopoietic cells. Of these PTPases, FAP-1 may participate in Fas-mediated signaling as described above, while the 130-kDa PTP36 may play a role in thymic maturation of T cells as the gene is expressed predominantly in the immature $CD4^+8^+$ cells in the thymus (114). PTP36 does not contain a recognizable PDZ domain, but has a proline-rich region possibly serving as a binding site for an SH3 domain.

4. DUAL-SPECIFICITY PROTEIN PHOSPHATASES

The founding member of the group of enzymes that dephosphorylate not only PTyr, but also PSer and PThr is the Vaccinia virus protein VH1 (65). Additional dual-specificity protein-tyrosine phosphatases (table 1 and figure 3) were subsequently identified based on their sequence similarity to VH1 and their ability to hydrolyze PTyr, PSer, and PThr monoesters in protein substrates (67-70). This group of phosphatases have the PTPase signature sequence, including the catalytic cysteine residue. Outside this conserved active site, however, this group of enzymes share very limited amino acid sequence homology with other members of the PTPase family.

4. 1. VHR, a dual specificity phosphatase of unknown function

The first mammalian dual-specific PTPase to be recognized was the human VHR (for VH1-related) discovered by S. Aaronson's laboratory by an expression cloning approach (66). The 21-kDa VHR protein was found to dephosphorylate both PTyr in a number of growth factor receptors and PSer in myelin basic protein (66). Recently, VHR was crystallized and its three-dimensional structure solved (411). The structure revealed that the catalytic center of VHR is composed of the same structural elements as the catalytic domains of other PTPases (70), including the cysteine (C124) in the bottom of the catalytic cleft. Mutagenesis experiments and kinetic analyses has identified C124 (412) as crucial and D92 as the general acid in the first step of the reaction and its conjugate carboxylate as a general base in the breakdown of the phosphoenzyme intermediate (413,414). For VHR, phosphoenzyme formation appears to be the rate-limiting step in hydrolysis under most conditions since no burst is seen in rapid-reaction kinetic experiments. Ser-131 has been proposed to donate a proton to stabilize the thiolate leaving group; mutation of this residue to alanine decreases the rate of phosphoenzyme intermediate breakdown and results in a burst pattern of hydrolysis (415,416).

The VHR mRNA is approximately 4.2 kb and is expressed in most tissues with highest levels in breast, ovary, heart, brain and skeletal muscle. Lymphocytes contain easily detectable amounts of the VHR protein. The human VHR gene was localized to human chromosome 17q21 in a region thought to contain BRCA1, a locus that confers susceptibility to breast and ovarian cancer, but VHR was recently found to not be identical with the BRCA1 gene (417).

Despite being the first recognized dual-specific PTPase, the physiological function of VHR have remained obscure. In vitro, VHR can dephosphorylate both PTyr and PThr in synthetic phosphopeptides based on the MAP kinases (418,419), but its substrate(s) in intact cells are unknown.

4. 2. MAP kinase phosphatases

The majority of the VH1-related enzymes identified to date are specific for one or several members of the MAP kinase family and efficiently dephosphorylate the PTyr and PThr in their activation loops. These two residues (e.g. Thr-183 and Tyr-185 in Erk2) must both be phosphorylated for the kinase to be catalytically active. Thus, dephosphorylation of either or both is sufficient for a complete inactivation of the MAP kinase. Accordingly, the MAP kinase phosphatases (often called MKPs) play important roles in several cellular signaling processes in

Table 3. Currently known MAP kinase-specific phosphatases

PROTEIN (SYNONYMS)	SIZE	SPECIFICITY
VHR	21 kDa	?
Pac-1	32 kDa	Erk, p38
MKP-1 (=CL100, 3CH134, erp, hVH1)	39 kDa	Erk, Jnk
MKP-2 (=TYP1, hVH2, DUSP4)	43 kDa	Erk2=Jnk=p38
MKP-3 (=Pyst1, rVH6, DUSP6)	42 kDa	Erk1,2 only
MKP-4	42 kDa	Erk1,2>p38=Jnk
MKP-X (=Pyst2, B59, DUSP7)	39 kDa	Erk1,2
B23 (=hVH3)	44 kDa	Erk
hVH4	?	?
M3/6 (=hVH5, HB5)	69 kDa	Jnk=p38>>>>>Erk

response to environmental signals, such as mitogenesis, programmed cell death, differentiation and secretion of cytokines (67-69). The two first enzymes found to have specificity for MAP kinases were Pac-1 (116) and MKP-1 (Mitogen-activated protein kinase phosphatase), the latter a gene cloned by several groups under various names (117-119). Subsequently, a number of related proteins have been discovered, many having a restricted tissue distribution. While most of these enzymes can dephosphorylate all MAP kinase family members, they usually show a preference for one or a few MAP kinases (table 3). Nevertheless, their exact specificities in intact cells remain unclear.

Lymphocytes express primarily the Pac-1 protein (116), which is encoded by an immediate early gene. Accordingly, the protein is not present in resting lymphocytes, but its mRNA is induced by mitogens even in the presence of protein synthesis inhibitors. The Pac-1 protein becomes detectable in 30-60 min after cell stimulation and resides in the nucleus, where the majority of the activated and phosphorylated MAP kinases also are. Thus, Pac-1 is ideally suited for dephosphorylation of the activated Erk kinases and thereby resetting the MAP kinase pathway. It is worth noting, however, that the activation of Erk2 in lymphocytes peaks at around 5 min after stimulation and then returns to near basal levels by 10 – 15 min, at which time Pac-1 or other inducibly expressed dual-specificity phosphatases are still undetectable. In fibroblasts lacking MKP-1 (420), also encoded by an immediate early gene (421), the activation of MAP kinase also proceeds normally. In contrast, when MKP-1 is expressed in cells under a non-inducible promotor, it strongly blocks MAP kinase activation by active Ras (422) or by extracellular stimuli (118,119,421). Disruption of the *mkp*-1 gene does not affect the development of mice (420). The downregulation of MAP kinase activity that occurs before synthesis of Pac or MKP-1 protein in lymphocytes could be explained by the presence of other dual-specific phosphatases. For example, MKP-3, which is not expressed in lymphocytes (123), is not inducible, but present in resting cells. At present, however, no constitutively expressed dual-specific MAP kinase phosphatases are known in lymphocytes. Instead, we have found that the strictly phosphotyrosine-specific PTPase HePTP is involved in regulation of Erk and p38 MAP kinases in T cells (217,218). HePTP is expressed in resting T cells and forms a physical complex with Erk and p38 (218), in which it can dephosphorylate the bound MAP kinase and inactivate it. Upon activation of the MAP kinases by Mek or Mkk6, a fraction of the activated MAP kinase molecules dissociate from HePTP through a phosphorylation-dependent mechanism, and translocate to the nucleus (218). HePTP is exclusively cytosolic, and apparently does not follow the activated MAP kinases to the nucleus, where they can phosphorylate their targets unopposed by phosphatases until the dual-specific phosphatases are induced and synthesized.

Of all the presently cloned MAP kinase phosphatases, only a few are active against the p38 and Jnk kinases. The human VH5 (mouse M3/6) has a high preference for these kinases over Erk (129), while MKP-2 dephosphorylates both Erk and Jnk with comparable efficiency (120). Both these enzymes are nuclear, but MKP-2 is induced with much slower kinetics that MKP-1 (120).

In conclusion, the MKPs are a diverse group of mainly inducible, nuclear enzymes, although their transcriptional regulation varies, and some also reside in the cytosol. Their specificity is, at least partly, governed by physical association with one or several members of the MAP kinase family. For most MKPs, however, their specificity in intact cells remains unclear. The physiological function of the MKPs is apparently not the fine-tuning of MAP kinases, a role reserved for HePTP (and perhaps other related PTPases), but the termination of signals through these kinases.

4. 3. PTEN

PTEN (phosphatase and tensin homologue deleted on chromosome ten), a candidate tumor-suppressor gene identified on chromosome 10, also known as MMAC1 (mutated in multiple advanced cancers), shares homology (figure 3) with the PTP family, as well as with the cytoskeletal protein tensin (75,76,423). PTEN was isolated from chromosome 10q22-23 that is frequently deleted or mutated in ~45% of endometrial cancers, ~30% of glioblastomas, and at lesser frequencies in a wide range of other human cancers, such as prostate, human brain, breast

and kidney cancer (75,422). Abnormalities of 10q were found in lymphoproliferative diseases (424,425), and mutations of PTEN were found in leukemia cell lines (426,427). These findings suggested that disruption of PTEN is necessary for the development of specific forms of cancers. PTEN also functions during normal development. Germline mutations of PTEN are found in three related human autosomal dominant disorders, Cowden disease, Lhermitte-Duclos disease (428) and Bannayan-Zonana syndrome (429). All these disorders share similar pathological traits, such as the formation of multiple benign tumors (mostly hamartomas) and an increased incidence of malignant cancers (428,429).

PTEN encodes the catalytic "PTPase" signature motif in a context resembling the dual-specificity phosphatases (430). However, PTEN does not dephosphorylate PSer or PThr, and it prefers PTyr in extremely acidic substrates, exhibiting almost 50 times more activity toward poly-acidic substrates than towards more traditional substrates (430). The extreme selectivity of PTEN toward acidic substrates in vitro suggests that the physiological substrates also will be acidic. It is possible that the acidic character may be manifested by proteins that are phosphorylated on multiple sites (430). Recently Maehama and co-workers (78) found that overexpression of PTEN reduced insulin-induced phosphatidylinositol (3,4,5)-triphosphate production in human 293 cells without effecting insulin-induced phosphoinositide 3-kinase activation. PTEN catalyzed dephosphorylation of phosphatidylinositol (3,4,5)-triphosphate, specifically at position 3 on the inositol ring. PTEN also exhibited 3-phosphatase activity toward inositol (1,3,4,5)-tetrakisphosphate. These data suggested that PTEN may act in vivo as a regulator of phosphatidylinositol (3,4,5)-triphosphate, which produces a substrate that can be recycled by PI3-kinase (78). Thus, it now seems that PTEN is the enzyme that directly counteracts phosphatidylinositol 3-kinase, which often plays an important role in growth signaling and modulation of the cytoskeleton (431,432). This may well explain the function of PTEN as a tumor suppressor and its role in cytoskeletal organization. It remains to be determined how PTEN is regulated and whether it does also dephosphorylate protein substrates *in vivo*.

A number of point mutations of PTEN which have been found from tumor samples, tumor cell lines, and germ-line mutations shown disrupt PTEN phosphatase activity (75,423,428,429,433-436). The point mutations have been found in three major clusters in PTEN. One cluster surrounds the catalytic motif, which is predicted to disrupt enzymatic activity, either by disrupting the catalytic cysteine directly or by altering the orientation of this cysteine in the catalytic cleft (437,438). The second cluster surrounds the conserved aspartic acid residue required for the release of the product. The third cluster, near the last conserved structural feature of the PTP fold, an alpha-helix, also disrupts PTEN activity (437,438). These data indicated that the enzymatic activity of PTEN is necessary for its ability to act as a tumor suppressor (439), and suggested that PTEN may suppress tumor cell growth by opposing the action of protein kinases.

PTEN also exhibits extensive sequence homology along much of its length to the cytoskeletal protein tensin. Tensin is a Src homology 2 (SH2) domain containing protein which binds to actin and localizes to focal adhesions, where it is thought to play a role in the assembly of signaling complexes (440). Tamura and colleagues (441) found that integrin mediated cell spreading and the formation of focal adhesions were down-regulated by wild type PTEN but not by PTEN with an inactive phosphatase domain. PTEN interacted with the focal adhesion kinase FAK and reduced its tyrosine phosphorylation. Overexpression of FAK partially antagonized the effects of PTEN. PTEN phosphatase may function as a tumor suppressor by negatively regulating cell interactions with the extracellular matrix (441). PTEN may also act as a docking protein in the assembly of multi-protein signaling complexes. Alternatively, all observed effects could be due to the dephosphorylation of 3-phosphorylated inositol phospholipids. Identification of the physiological substrates for PTEN, whether they are only lipids or also phosphoproteins, will be required to reveal the biological function of PTEN and eventually may lead to the characterization of a novel signaling pathway.

4. 4. CDC25 and KAP

The eukaryotic cell cycle is regulated by a family of protein kinases, termed CDKs (for cyclin-dependent kinases), which control the progression through the cell cycle at critical transition points. The 34-kDa CDC2 kinase bound to cyclin B is crucial for the G2-M transition. The CDC25 family of dual-specificity phosphatases (70,442) play an important role in the control of CDC2 kinase/cyclin B by dephosphorylating residues Thr-14 and Tyr-15 in CDC2, thereby activating it (443). This activation serves as a trigger for entry into mitosis (444).

CDC25 contain the "PTPase" signature sequence (figure 3) and share some limited amino acid-similarity with the other dual-specificity phosphatases, notably a small sequence termed the CH2 domain. There are three genes for CDC25, termed A, B, and C (70), and the primary transcripts can undergo alternative splicing to produce additional variation in the proteins (445). CDC25 overexpression has been detected one third of primary breast cancers (446), adding this phosphatase to the list of oncogenes/anti-oncogenes within this class of enzymes. As CDC25 is not directly involved in lymphocyte activation, we refer to the many excellent reviews on this topic (70, 447).

The KAP phosphatase (71) is also very distantly related to other phosphatases (figure 3). It is a nuclear enzyme that binds CDC2 and CDK2, and probably participates in the control of the cell cycle (71).

5. LOW MOLECULAR WEIGHT PTPases

5. 1. LMPTP

The low molecular weight PTPase, LMPTP, was originally purified from liver by Heinrikson as an acid phosphatase (449) and was subsequently purified to homogeneity and its amino acid sequence determined (450, 451). Even before its cDNA was isolated (72,452), it was clear that several isoforms or related enzymes exist. It was

subsequently found that the primary transcript undergoes an alternative splicing event in which either exon 3 or exon 4 is excised (453). This results in two different isoforms: LMPTP-A, which contains exon 3 and moves a bit slower on SDS gels, and the faster moving LMPTP-B, which contains exon 4-encoded amino acids. We have also detected a third splice form, which lacks both exon 3 and exon 4 (454). This isoform, which we term LMPTP-C, is only 15-16 kDa and lacks catalytic activity *in vitro*. The corresponding mRNA can be detected in all tissues and cell lines examined, and is at least as abundant as the other isoforms. The LMPTP-C protein can also be visualized by Western blotting (454). The LMPTP gene is highly conserved through evolution from yeast to man. The homologues from budding yeast (*Saccharomyces cerevisisae*), Ltp1 (455), and fission yeast (*Schizosaccharomyces pombe*), Stp1 (456), are 39% and 42% identical to the mammalian enzyme, respectively. Very recently (457), a homologous gene was found in the prokaryote *Acinetobacter johnsonii*. The protein was found to have PTPase activity in vitro and to dephosphorylate a novel bacterial PTK that autophosphorylated on tyrosine (457). This suggests that LMPTPs are likely to be involved in the regulation of an ancient and perhaps fundamental cellular function. On the other hand, disruption of the two yeast genes did not cause any observable loss of viability or phenotypic chances (455,456).

Already in 1989, G. Ramponi's group showed that LMPTP readily dephosphorylates PTyr in a protein substrate as well as free PTyr, while not hydrolyzing PThr or PSer (458). LMPTP also dephosphorylates other aromatic phosphates *in vitro* (459), and is not yet entirely clear if LMPTP acts only as a PTPase in intact cells. The amino acid sequence of LMPTP showed that the enzyme contains a minimal PTPase signature sequence, which is the only recognizable homology to other PTPases, and which is found in a unique location in the sequence: in the extreme N-terminus (figure 3). LMPTP is also remarkably small, only 18 kDa, which is much less than the mere PTPase domain of classical PTPases. The crystal structure of LMPTP-A (460) and LMPTP-B(461) reveal that the cysteine residue (C12) of the signature sequence is located in a catalytic pocket much like in other PTPases, while the rest of the enzyme has a unique folding. Cys-12 was already known from biochemical studies to be crucial for catalysis (459,462)The amino acids encoded by exons 3 or 4 (referred to as the 'variable loop') form one side of the catalytic pocket, indicating that the two isoforms are likely to select substrates with different amino-acid residues next to the target PTyr. The two isoforms also differ in catalytic properties and stimulation by nucleotides (462).

The biological function of LMPTP is still unclear. A number of reports by G. Ramponi's group suggest that LMPTP negatively regulates cell growth and transformation by oncogenes (463,464) and counteracts the platelet-derived growth factor (465,466) and insulin (467) receptors by dephosphorylating specific tyrosine residues on these receptors. Also in our hands (454), overexpression of LMPTP-A or -B in NIH3T3 cells causes some reduction in growth factor-induced gene activation. Interestingly, the inactive LMPTP-C isoform had the opposite effect, suggesting that it might compete with endogenous LMPTP in a dominant negative fashion. We have also found that LMPTP-B is phosphorylated on tyrosines 131 and 132 in T cells and that such phosphorylation *in vitro* activates the enzyme (18). In co-transfected COS cells, the T cell Src-family kinase Lck was particularly efficient in phosphorylating LMPTP. A recent paper by Rigacci and co-workers reported that LMPTP-A is tyrosine phosphorylated in v-Src transformed NIH3T3 cells, and that Src was able to phosphorylate LMPTP *in vitro* (19). Interestingly, the C isoform was not phosphorylated by Lck in co-transfected COS cells or even *in vitro*, despite still having the two tyrosines. This indicates that the three-dimensional folding of LMPTP is important for the recognition of Tyr-131 and Tyr-132 by Lck. These two residues are next to the catalytic pocket and it is conceivable that their phosphorylation affects the interaction of LMPTP with substrates. The amino acid residues encoded by exons 3 or 4 form the other rim of the catalytic cleft, and are therefore likely to affect substrate binding.

In conclusion, LMPTP is a small phosphatase with strong preference for PTyr over PSer or PThr, but with somewhat unclear substrate specificity in intact cells. The specificity and activity of the enzyme are regulated by alternative splicing and tyrosine phosphorylation, but its physiological substrates and biological function remain unclear.

5. 2. PRL-1, 2 and 3 - isoprenylated nuclear enzymes

The first gene of this family, PRL-1, was identified as an immediate early gene in proliferating hepatocytes (73), giving the gene its name PRL-1 for phosphatase of regenerating liver-1. More recently, two additional members of the family, termed OV-1 (or PRL-2) and PRL-3 were described (74). PRL-1 and OV-1 were also found in a screen for proteins that are isoprenylated or farnesylated (468). This covalent modification with a hydrophobic group occurs on a C-terminal cysteine residue (468) and confers affinity for cellular membranes in the case of the Ras proteins. The PRL phosphatases, however, are located in the nucleus and their overexpression has a positive effect on cell growth and can induce tumor formation (73,468,469). The substrates and physiological function of these enzymes remain to be discovered.

6. CONCLUDING REMARKS

Our understanding of the role of tyrosine phosphorylation in the regulation of cell proliferation and transmembrane signaling has improved greatly during the past few years. Still, many important questions remain open, particularly with regard to the PTPases that both counteract the PTKs and regulate them. Given the central role of lymphoid cells in host defense, a deeper understanding of these molecular events would greatly aid the design of rational pharmacological approaches to modulate the immune system, augment defense against pathogens and interfere with the growth of lymphoid leukemias, a process that may be associated with aberrant signaling events. The known crystal structure and small

size of many PTPases make them ideal targets for rational drug design. Before these enzymes can become sufficiently attractive as targets for the pharmaceutical industry, however, we must gain considerably more insight into their physiological functions and importance. We also need to clarify their substrate specificity and selectivity, their redundancy and their regulation.

Lymphocytes express many PTPases, only some of which have currently understood functions. These include CD45, SHP1 and HePTP. There is recent evidence (470), however, that T cell membranes contain a PTPase activity that efficiently keeps the TCR signal transduction machinery, including the Src and Syk family PTKs, in a resting phosphorylation state. Inhibition of this activity, which was not attributable to CD45, SHP1 or HePTP, induced the same ordered sequence of phosphorylation events as normally seen after TCR ligation (470). It remains to be seen if this membrane-bound PTPase is identical to one or several PTPases discussed in this review or yet another novel enzyme.

A very exciting new area of investigation is the involvement or loss of PTPases in human malignant diseases. The surface expression of CD45 has long been used as a marker for differentiation of leukemic cells (471,472). There is no evidence, however, that CD45 would be directly associated with the transforming event or progression of leukemias or lymphomas. The first examples of a potential role for a PTPase in neoplasia was the finding that HePTP might be overexpressed in myelodysplasia and deleted in leukemias (211). The recent discovery that both PTEN is deleted or mutated in multiple human cancers, including leukemias, and that and CDC25 is overexpressed in many cancers, add to the notion that PTPases are likely to involved in clinically relevant carcinogenesis. Finally, loss of MKP-1 expression or activity was found to be associated with malignant transformation and clinical progression in a subset of epithelial tumors (473). As overexpression of many PTKs can cause malignant transformation, it is natural to assume that loss of the PTPases that counteract them would also cause neoplasia. Furthermore, genetic damage is perhaps more likely to cause deletion or loss of function rather than overexpression and gain of function. We predict that several PTPase genes will be found in the near future to be altered in human malignancies. This underscores the importance of studying these enzymes and the value of increased understanding of their regulation and substrates for a rational drug development to treat human diseases.

7. ACKNOWLEDGEMENTS

Work reported herein was supported by grants GM48960, AI35603, AI41481, and AI40552 from the National Institutes of Health (T.M.) and fellowships from the Benzon Foundation (J.B) and the Swedish Cancer Foundation (A. G.-W.). This is publication # 266 from the La Jolla Institute for Allergy and Immunology.

8. REFERENCES

1. Cantley, L. C. K. R. Auger, C. Carpenter, B. Duckworth, A. Graziani, R. Kapeller & S. Soltoff: Oncogenes and signal transduction. Cell 64, 281-302 (1991)
2. Hunter, T.: A thousand and one protein kinases. Cell 50, 823-829 (1987)
3. Bishop, M. J.: Molecular themes in oncogenesis. Cell 64, 235-248 (1991)
4. Tonks, N. K. & B. G. Neel: From form to function: Signaling by protein tyrosine phosphatases. Cell 87, 365-368 (1996)
5. Mustelin, T.: Src family tyrosine kinases in leukocytes. R.G. Landes Co. Austin, TX 1-155 (1994)
6. Mustelin, T., K. M. Coggeshall & A. Altman: Rapid activation of the T cell tyrosine protein kinase $pp56^{lck}$ by the CD45 phosphotyrosine phosphatase. Proc Natl Acad Sci USA 86, 6302-6306 (1989)
7. Mustelin, T. & A. Altman: Dephosphorylation and activation of the T cell tyrosine kinase $pp56^{lck}$ by the leukocyte common antigen (CD45). Oncogene 5, 809-813 (1990)
8. Mustelin, T., T. Pessa-Morikawa, M. Autero, M. Gassman, C. G. Gahmberg, L. C. Andersson & P. Burn: Regulation of the $p59^{fyn}$ tyrosine protein kinase by the CD45 phosphotyrosine phosphatase. Eur J Immunol 22, 1173-1178 (1992)
9. Mustelin, T. & P. Burn: Regulation of src family tyrosine kinases in lymphocytes. Trends Biochem Sci18, 215-220 (1993)
10. Burns, C. M., K. Sakaguchi, E. Appella & J. D. Ashwell: CD45 regulation of tyrosine phosphorylation and enzyme activity of src family kinases. J Biol Chem 269, 13594-13600 (1994)
11. Stover, D. R., H. Charbonneau, N. K. Tonks & K. A. Walsh: Protein-tyrosine-phosphatase CD45 is phosphorylated transiently on tyrosine upon activation of Jurkat T cells. Proc Natl Aca. Sci USA 88, 7704-7707 (1994)
12. Autero, M., J. Saharinen, T. Pessa-Morikawa, M. Soula-Rothhut, C. Oetken, M. Gassmann, M. Bergman, K. Alitalo, P. Burn, C. G. Gahmberg & T. Mustelin: Tyrosine phosphorylation of the CD45 phosphotyrosine phosphatase by the $p50^{csk}$ kinase creates a binding site for the $p56^{lck}$ tyrosine kinase and activates the phosphatase. Mol Cell Biol 14, 1308-1321 (1994)
13. Su, J., A. Batzner & J. Sap: Receptor tyrosine phosphatase R-PTP- is tyrosine phosphorylated and associated with the adaptor protein Grb2. J Biol Chem 269, 18731-18734 (1994)
14. Lorenz, U., K. S. Ravichandran, D. Pei, C. T. Walsh, S. J. Burakoff & B. G. Neel: Lck-dependent tyrosyl phosphorylation of the phosphotyrosine phosphatase SH-PTP1 in murine T cells. Mol Cell Biol 14, 1824-1834 (1994)
15. Feng, G.-S., C.-C. Hui & T. Pawson: SH2-containing phosphotyrosine phosphatase as a target of protein-tyrosine kinases. Science 259, 1607-1611 (1993)
16. Vogel, W., R. Lammers, J. Huang & A. Ullrich: Activation of a phosphotyrosine phosphatase by tyrosine phosphorylation. Science 259, 1611-1614 (1993)
17. Tailor, P., T. Jascur, S. Williams, M. von Willebrand, C. Couture & T. Mustelin: Involvement of Src-homology-2-domain-containing protein tyrosine phosphatase 2 in T cell activation. Eur J Biochem 237, 736-742 (1996)
18. Tailor, P., S. Williams, J. Gilman, C. Couture & T. Mustelin: Regulation of the low molecular weight

phosphotyrosine phosphatase (LMPTP) by phosphorylation at tyrosines 131 and 132. J Biol Chem 272, 5371-5376 (1997)

19. Rigacci, S., D. Degl'Innocenti, M. Bucciantini, P. Cirri, A. Berti & G. Ramponi: pp60^{src} phosphorylates and activates low molecular weight phosphotyrosine-protein phosphatase. J Biol Chem 271, 1278-1281 (1996)
20. Swieter, M., E. H. Berenstein, W. D. Swaim & R. P. Siraganian: Aggregation of IgE receptor in rat basophilic leukemia 2H3 cells induces tyrosine phosphorylation of the cytosolic protein-tyrosine phosphatase HePTP. J Biol Chem 270, 21902-21906 (1995)
21. Oetken, C., M. von Willebrand, M. Autero, T. Ruutu, L. C. Andersson & T. Mustelin: Phenylarsine oxide augments tyrosine phosphorylation in hematopoietic cells. Eur J Hematol 49, 208-214 (1992)
22. O'Shea, J. J., D. W. McVivar, T. L. Bailey, C. Burns & M. J. Smyth: Activation of human peripheral blood T lymphocytes by pharmacological induction of protein-tyrosine phosphorylation. Proc Natl Acad Sci USA 89, 10306-10310 (1992)
23. Secrist, J. P., L. A. Burns, L. Karnitz, G. A. Koretzky & R. T. Abraham: Stimulatory effects of the protein tyrosine phosphatase inhibitor, pervanadate, on T-cell activation events. J Biol Chem 268, 5886-5893 (1993)
24. Iivanainen, A. V., C. Lindqvist, T. Mustelin & L. C. Andersson: Phosphotyrosine phosphatases are involved in reversion of T lymphoblastic proliferation. Eur J Immunol 20, 2509-2512 (1990)
25. Hsi, E. D., J. N. Siegel, Y. Minami, E. T. Luong, R. D. Klausner, & L. E. Samelson: T cell activation induces rapid tyrosine phosphorylation of a limited number of cellular substrates. J Biol Chem 264, 10836-10842 (1989)
26. June, C. M., M. C. Fletcher, J. A. Ledbetter & L. E. Samelson: Increases in tyrosine phosphorylation are detected before phospholipase C activation after T cell receptor stimulation. J Immunol 144, 1591-1598 (1990)
27. Garcia-Morales, P., Y. Minami, E. Luong, R. D. Klausner & L. E. Samelson: Tyrosine phosphorylation in T cells is regulated by phosphatase activity: Studies with phenylarsine oxide. Proc Natl Acad Sci USA 87, 9255-9259 (1990)
28. Mustelin, T.: T cell antigen receptor signaling: Three families of tyrosine kinases and a phosphatase. Immunity 1, 351-356 (1994)
29. Zenner, G., J. Zurhausen, P. Burn & T. Mustelin: Towards unravelling the complexity of T cell signal transduction. BioEssays 17, 967-975 (1995)
30. Mustelin, T., K. M. Coggeshall, N. Isakov & A. Altman: Tyrosine phosphorylation is required for T cell antigen receptor-mediated activation of phospholipase C. Science 247, 1584-1587 (1990)
31. June, C. H., M. C. Fletcher, J. A. Ledbetter, G. L. Schieven, J. N. Siegel, A. F. Phillips & L. E. Samelson: Inhibition of tyrosine phosphorylation prevents T-cell receptor-mediated signal transduction. Proc Natl Acad Sci USA 87, 7722-7727 (1990)
32. Cooke, M. P., K. M. Abraham, K. A. Forbush & R. M. Perlmutter: Regulation of T cell receptor signaling by a src family protein-tyrosine kinase (p59^{fyn}). Cell 65, 281-291 (1991)
33. Stein, P. L., H.-M. Lee, S. Rich & P. Soriano: pp59^{fyn} mutant mice display differential signaling in thymocytes and peripheral T cells. Cell 70, 741-750 (1992)
34. Appleby, M. W., J. A. Gross, M. P. Cooke, S. D. Levin, X. Qian & R. M. Perlmutter: Defective T cell receptor signaling in mice lacking the thymic isoform of p59^{fyn}. Cell 70, 751-763 (1992)
35. Rudd, C. E., J. M. Trevillyan, J. D. Dasgupta, L. L. Wong & S. F. Schlossman: The CD4 receptor is complexed in detergent lysates to a protein-tyrosine kinase (pp58) from human T lymphocytes. Proc Natl Acad Sci USA 85, 5190-5194 (1988)
36. Veillette, A., M. A. Bookman, E. M. Horak & J. B. Bolen: T CD4 and CD8 T cell surface antigens are associated with the internal membrane tyrosine-protein kinase p56^{lck}. Cell 55, 301-308 (1988)
37. Abraham, N., M. C. Miceli, J. R. Parnes & A. Veillette: Enhancement of T-cell responsiveness by the lymphocyte-specific tyrosine protein kinase p56^{lck}. Nature 350, 62-66 (1991)
38. Mustelin, T. & A. Altman: Do CD4 and CD8 control T cell activation via a specific tyrosine protein kinase? Immunol Today 10, 189-192 (1989)
39. Straus, D. B. & A. Weiss: Genetic evidence for the involvement of the lck tyrosine kinase in signal transduction through the T cell antigen receptor. Cell 70, 585-593 (1992)
40. Couture, C., G. Baier, A. Altman & T. Mustelin: p56^{lck} -independent activation and tyrosine phosphorylation of p72^{syk} by TCR/CD3 stimulation. Proc Natl Acad Sci USA 91, 5301-5305 (1994)
41. Arpaia, E., M. Shahar, H. Dadi, A. Cohen & C. M. Roifman: Defective T cell receptor signaling and CD8^{+} thymic selection in humans lacking Zap-70 kinase. Cell 76, 947-958 (1994)
42. Oetken, C., C. Couture, M. Bergman, N. Bonnefoy-Bérard, S. Williams, K. Alitalo, P. Burn & T. Mustelin: TCR/CD3-triggering causes activation of the p50^{csk} tyrosine kinase and engagement of its SH2 domain. Oncogene 9, 1625-1631 (1994)
43. Bergman, M., T. Mustelin, C. Oetken, J. Partanen, N. A. Flint, K. E. Amrein, M. Autero, P. Burn & K. Alitalo: The human p50^{csk} tyrosine kinase phosphorylates p56^{lck} at Tyr-505 and down-regulates its catalytic activity. EMBO J 11, 2919-2924 (1992)
44. August, A., S. Gibson, Y. Kawakami, T. Kawakami, G. Mills & B. Dupont: CD28 is associated with and induces the immediate tyrosine phosphorylation and activation of the Tec family kinase ITK/EMT in the human Jurkat leukemic T-cell line. Proc Natl Acad Sci USA 91, 9347-9351 (1994)
45. Liao, X. C. & D. R. Littman: Altered T cell receptor signaling and disrupted T cell development in mice lacking Itk. Immunity 3, 757-769 (1996)
46. Tycko, B., S. D. Smith & J. Sklar: Chromosomal translocations joining LCK and TCRB loci in human T cell leukemia. J Exp Med 174, 867-873 (1991)
47. Wright, D. D., B. M. Sefton & M. P. Kamps: Oncogenic activation of the Lck protein accompanies translocation of the LCK gene in the human HSB2 T-cell leukemia. Mol Cell Biol 14, 2429-2437 (1994)

48. Fargnoli, M. C., R. L. Edelson, C. L. Berger, S. Chimenti, C. Couture, T. Mustelin & R. Halaban: TCR diminished signaling in cutaneous T-cell lymphoma is associated with decreased kinase activities of Syk and membrane-associated Csk. Leukemia 11, 1338-1346 (1997)
49. Weiss, A.: T cell antigen receptor signal transduction: A tale of tails and cytoplasmic protein-tyrosine kinases. Cell 73, 209-212 (1993)
50. Klausner, R. D. & L. E. Samelson T cell antigen receptor activation pathways: The tyrosine kinase connection. Cell 64, 875-878 (1991)
51. Weiss, A. & D. Littman: Signal transduction by lymphocyte antigen receptors. Cell 76, 263-274 (1994)
52. Hunter, T.: Protein-tyrosine phosphatases: The other side of the coin. Cell 58, 1013-1016 (1989)
53. Tonks, N. K. & H. Charbonneau: Protein tyrosine dephosphorylation and signal transduction. Trends Biochem Sci 14, 497-500 (1989)
54. Fischer, E. H., H. Charbonneau & N. K. Tonks: Protein tyrosine phosphatases: A diverse family of intracellular and transmembrane enzymes. Science 253, 401-406 (1991)
55. Charbonneau, H. & N. K. Tonks: 1002 protein phosphatases. Annu Rev Cell Biol 8, 463-493 (1992)
56. Walton, K. M. & J. E. Dixon: Protein tyrosine phosphatases. Annu Rev Biochem 62, 101-120 (1993)
57. Tonks, N. K., C. D. Diltz & E. H. Fischer: Characterization of the major protein-tyrosine-phosphatase of human placenta. J Biol Chem 263, 6731-6740 (1988)
58. Charbonneau, H., N. K. Tonks, S. Kumar, C. D. Diltz, M. Harrylock, D. E. Cool, E. G. Krebs, E. H. Fischer & K. A. Walsh: Human placenta protein-tyrosine-phosphatase: amino acid sequence and relationship to a family of receptor-like proteins. Proc Natl Acad Sci USA 86, 5252-5256 (1989)
59. Guan, K., R. S. Haun, S. J. Watson, R. L. Geahlen & J. E. Dixon: Cloning and expression of a protein-tyrosine-phosphatase. Proc Natl Acad Sci USA 87, 1501-1505 (1990)
60. Tonks, N. K., H. Charbonneau, C. D. Diltz, E. H. Fischer & K. A. Walsh: Demonstration that the leukocyte common antigen CD45 is a protein tyrosine phosphatase. Biochemistry 27, 8695-8701 1988
61. Barford, D., A. J. Flint & N. K. Tonks: Crystal structure of human protein tyrosine phosphatase 1B. Science 263, 1397-1404 (1994)
62. Jia, Z., D. Barford, A. J. Flint & N. K. Tonks: Structural basis for phosphotyrosine peptide recognition by protein tyrosine phosphatase 1B. Science 268, 1754-1758 (1995)
63. Pannifer, A. D., A. J. Flint, N. K. Tonks & D. Barford: Visualization of the cysteinyl-phosphate intermediate of a protein-tyrosine phosphatase by x-ray crystallography. J Biol Chem 273, 10454-10462 (1998)
64. Denu, J. M., J. A. Stuckey, M. A. Saper & J., E. Dixon: Form and function in protein dephosphorylation. Cell 87, 361-364 (1996)
65. Guan, K. L., S. S. Bryoles & J. E. Dixon: A Tyr/Ser protein phosphatase encoded by vaccinia virus. Nature 350, 359-362 (1991)
66. Ishibashi, T., D. P. Bottaro, A. Chan, T. Kiki & S. A. Aaronson: Expression cloning of a human dual-specificity phosphatase. Proc Natl Acad Sci USA 89, 12170-12174 (1992)
67. Ward, Y. & K. Kelly: The MAP kinase phosphatases. Adv Prot Phosphatases 8, 87-97 (1994)
68. Keyse, S. M.: An emerging family of dual specificity MAP kinase phosphatases. Biochem. Biophys. Acta 1265, 152-160 (1995)
69. Keyse, S. M.: Protein phosphatases and the regulation of MAP kinase activity. Semin Cell Dev Biol 9, 143-152 (1998)
70. Hoffmann, I. & E. Karsenti: The role of cdc25 in checkpoints and feedback controls in the eukaryotic cell cycle. J Cell Sci Suppl 18, 75-79 (1994)
71. Hannon, G. J., D. Casso & D. Beach: KAP: A dual specificity phosphatase that interacts with cyclin-dependent kinases. Proc Natl Acad Sci USA 91, 1731-1735, (1994)
72. Wo, Y.-Y. P., A. L. McCormack, J. Shabanowitz, D. F. Hunt, J. P. Davis, G. L. Mitchell & R. L. Van Etten: Sequencing, cloning, and expression of human red cell-type acid phosphatase, a cytoplasmic phosphotyrosyl protein phosphatase. J Biol Chem 267, 10856-10865 (1992)
73. Diamond, R. H., D. E. Cressman, T. M. Laz, C. S. Abrams & R. Taub: PRL-1, a unique nuclear protein tyrosine phosphatase, affects cell growth. Mol Cell Biol 14, 3752-3762 (1994)
74. Zeng, Q., W. Hong, & Y. H. Tan: Mouse PRL-2 and PRL-3, two potentially prenylated protein tyrosine phosphatases homologous to PRL-1. Biochem Biophys Res Comm 244, 421-427 (1998)
75. Li, J., C. Yen, D. Liaw, K. Podsypanina, S. Bose, S. I. Wang, J. Puc, C. Miliaresis, L. Rodgers, R. McCombie, S. H. Bigner, B. C. Giovanella, M. Ittmann, B. Tycko, H. Hibshoosh, M. H. Wigler & R. Parsons: PTEN, a putative protein tyrosine phosphatase gene mutated in human brain, breast, and prostate. Science 275, 1943-1947 (1997)
76. Li, D. M. & H. Sun: TEP1, encoded by a candidate tumor suppressor locus, is a novel protein tyrosine phosphatase regulated by transforming growth factor beta. Cancer Res 57, 2124-2129 (1997)
77. Takagi, T., C. R. Moore, F. Diehn & S. Buratowski: An RNA 5'-triphosphatase related to the protein tyrosine phosphatases. Cell 89, 867-873 (1997)
78. Maehama, T. & J. E. Dixon: The tumor suppressor, PTEN/MMAC1, dephosphorylates the lipid second messenger, phosphatidylionsitol 3,4,5-trisphosphate. J Biol Chem 273, 13375-13378 (1998)
79. Zanke, B., H. Suzuki, K. Kishihara, L. Mizzen, M. Minden, A. Pawson & T. W. Mak: Cloning and expression of an inducible lymphoid-specific, protein tyrosine phosphatase (HePTPase). Eur J Immunol 22, 235-239 (1992)
80. Adachi, M., M. Sekiya, M. Isobe, Y. Kumura, Z. Ogita, Y. Hinoda, K. Imai & A. Yachi: Molecular cloning and chromosomal mapping of a human protein-tyrosine phosphatase LC-PTP. Biochem Biophys Res Commun 186, 1607-1615 (1992)
81. Lombroso, P. J., G. Murdoch & M. Lerner: Molecular characterization of a protein-tyrosine-phosphatase enriched in striatum. Proc Natl Acad Sci USA 88, 7242-7246 (1991)

82. Shiozuka, K., Y. Watanabe, T. Ikeda, S. Hashimoto & H. Kawashima: Cloning and expression of PCPTP1 encoding protein tyrosine phosphatase. Gene 162, 279-284 (1995)
83. Ogata, M., M. Sawada, Y. Fujino & T. Hamaoka: cDNA cloning and characterization of a novel receptor-type protein tyrosine phosphatase expressed predominantly in the brain. J Biol Chem 270, 2337-2343 (1995)
84. Sharma, E. & P. J. Lombroso: A neuronal protein tyrosine phosphatase induced by nerve growth factor. J Biol Chem 270, 49-53 (1995) [erratum in J Biol Chem 270, 23234 (1995)]
85. Ohsugi, M., S. Kuramochi, S. Matsuda & T. Yamamoto: Molecular cloning and characterization of a novel cytoplasmic protein-tyrosine phosphatase that is specifically expressed in spermatocytes. Proc Natl Acad Sci USA 272, 33092-33099 (1997)
86. Cool, D. E., N. K. Tonks, H. Charbonneau, K. A. Walsh, E. H. Fischer & E. G. Krebs: cDNA isolated from a human T-cell library encodes a member of the protein-tyrosine phosphatase family. Proc Natl Acad Sci USA 86, 5257-5261 (1989)
87. Matthews, R. J., D. B. Bowne, E. Flores & M. L. Thomas: Characterization of hematopoietic intracellular protein tyrosine phosphatases: Description of a phosphatase containing an SH2 domain and another enriched in proline-, glutamic acid-, serine-, and threonine-rich sequences. Mol Cell Biol 12, 2396-2405 (1992)
88. Shen, S.-H., L. Bastien, B. I. Posner & P. Chrétien: A protein-tyrosine phosphatase with sequence similarlity to the SH2 domain of the protein-tyrosine kinases. Nature 352, 736-739 (1991)
89. Yi, T., J. L. Cleveland & J. N. Ihle: Protein tyrosine phosphatase containing SH2 domains: Characterization, preferential expression in hematopoietic cells, and localization to human chromosome 12p12-p13. Mol Cell Biol 12, 836-846 (1992)
90. Plutzky, J., B. G. Neel & R. D. Rosenberg: Isolation of a src homology 2-containing tyrosine phosphatase. Proc Natl Acad Sci USA 89, 1123-1127 (1992)
91. Freeman, R. M., J. Plutzky & B. G. Neel: Identification of a human src homology 2-containing protein-tyrosine-phosphatase: A putative homolog of Drosophila corkscrew. Proc Natl Acad Sci USA 89, 11239-11243 (1992)
92. Ahmad, S., D. Banville, Z. Zhao, E. H. Fischer & S.-H. Shen: A widely expressed human protein-tyrosine phosphatase containing src homology 2 domains. Proc Natl Acad Sci USA 90, 2197-2201 (1993)
93. Feng, G.-S., C-C. Hui & T. Pawson: SH2-containing phosphotyrosine phosphatase as a target of protein-tyrosine kinases. Science 259, 1607-1611 (1993)
94. Dechert, U., A. M. Duncan, L. Bastien, C. Duff, M. Adam & F. R. Jirik: Protein-tyrosine phosphatase SH-PTP2 (PTPN11) is localized to 12q24.1-24.3. Hum Genet 96, 609-615 (1995)
95. Takekawa, M., F. Itoh, Y. Hinoda, Y. Arimura, M. Toyota, M. Sekiya, M. Adachi, K. Imai & A. Yachi: Cloning and characterization of a human cDNA encoding a novel putative cytoplasmic protein-tyrosine-phosphatase. Biochem Biophys Res Commun 189, 1223-1230 (1992)
96. Yang, Q., D. Co, J. Sommercorn & N. K. Tonks: Cloning and expression of PTP-PEST. J Biol Chem 268, 6622-6628 (1993)
97. Yi, T., J. L. Cleveland & N. Ihle: Identification of novel protein tyrosine phosphatases of hematopoietic cells by polymerase chain reaction amplification. Blood 78, 2222-2228 (1991)
98. Cheng, J., L. Daimaru, C. Fennie & L. A. Lasky: A novel protein tyrosine phosphatase expressed in $lin^{lo}CD34^{hi}Sca^{hi}$ hematopoietic progenitor cells. Blood 88, 1156-1167 (1996)
99. Huang, K., C. L Sommers, A. Grinberg, C. A. Kozac & P. E. Love: Cloning and characterization of PTP-K1, a novel nonreceptor protein tyrosine phosphatase highly expressed in bone marrow. Oncogene 13, 1567-1573 (1996)
100. Aoki, N., Y. Yamaguchi-Aoki & A. Ullrich: The novel protein-tyrosine phosphatase PTP20 is a positive regulator of PC12 cell neuronal differentiation. J Biol Chem 271, 29422-29426 (1996)
101. Dosil, M., N. Leibman & I. Lemischka: Cloning and characterization of fetal liver phosphatase 1, a nuclear protein tyrosine phosphatase isolated from hematopoietic stem cells. Blood 88, 4510-4525 (1996)
102. Kim, Y. W., H. Wang, I. Sures, R. Lammers, K. J. Martell & A. Ullrich: Characterization of the PEST family protein tyrosine phosphatase BDP1. Oncogene 13, 2275-2279 (1996)
103. Gu, M., I. Warshawsky & P. W. Majerus: Cloning and expression of a cytosolic megakaryocyte protein-tyrosine-phosphatase with sequence homology to retinaldehyde-binding protein and yeast SEC14p. Proc Natl Acad Sci USA 89, 2980-2984 (1992)
104. Yang, Q. & N. K. Tonks: Isolation of a cDNA clone encoding a human protein-tyrosine phosphatase with homology to the cytoskelal-associated proteins band 4.1, ezrin, and talin. Proc Natl Acad Sci USA 88, 5949-5953 (1991)
105. Gu, M., J. D. York, I. Warshawsky & P. W. Majerus: Identification, cloning, and expression of a cytosolic megakaryocyte protein-tyrosine-phophatase with sequence homology to cytoskeletal protein 4.1. Proc Natl Acad Sci USA 88, 5867-5871 (1991)
106. Moller, N. P., R. Lammers, A. Kharitonenkov, I. Sures & A. Ullrich: Src kinase associates with a member of a distinct subfamily of protein-tyrosine phosphatases containing an ezrin-like domain. Proc Natl Acad Sci USA 91, 7477-7481 (1994)
107. L'Abbe, D., D. Banville, Y. Tong, R. Stocco, S. Masson, S. Ma, G. Fantus & S. H. Shen: Identification of a novel protein tyrosine phosphatase with sequence homology to the cytoskeletal proteins of band 4.1 family. FEBS Lett 356 351-356 (1994)
108. Higashitsuji, H., S. Arii, M. Furutani, M. Imamura, Y. Kaneko, J. Takenawa, H. Nakayama & J. Fujita: Enhanced expression of multiple protein tyrosine phosphatases in the regenerating mouse liver: Isolation of PTP-RL10, a novle cytoplasmic type phosphatase with sequence homology to cytoskeletal protein 4.1. Oncogene 10, 407-414 (1995)
109. Vega, Q. C., K. M. Walton & J. E. Dixon: Tyrosine phosphatases and the cytoskeleton. Adv Prot Phos 9, 165-182 (1995)

110. Sato, T., S. Irie, S. Kitada & J. C. Reed: FAP-1: A protein tyrosine phosphatase that associates with Fas. Science 268, 411-415 (1995)
111. Saras, J., L. Claesson-welsh, C. H. Heldin, & L. J. Gonez: Cloning and characterization of PTPL1, a protein tyrosine phosphatase with sinilarities to cytoskeletal-associated proteins. J Biol Chem 269, 24082-24089 (1994)
112. Banville, X., S. Ahmad, R. Stocco & S. H. Shen: A novel protein-tyrosine phosphatase with homology to both the cytoskeletal proteins of the band 4.1 family and junction-associated guanylate kinase. J Biol Chem 269, 22320-22327 (1994)
113. Maekawa, K., N. Imagawa, M. Nagamatsu & S. Harada: Molecular cloning of novel protein-tyrosine phosphatase containing a membrane-binding domain and GLGF repeats. FEBS Lett 337, 200-206 (1994)
114. Sawada, M., M. Ogata, Y. Fujino & T. Hamaoka: cDNA cloning of a novel protein tyrosine phosphatase with homology to cytoskeletal protein 4.1 and its expression in T-lineage cells. Biochem Biophys Res Commu. 203, 479-484 (1994)
115. Smith, A., P. J. Mitchell, J. Shipley, B. A. Gusterson, M. V. Rogers & M. R. Crompton: PEZ: A novel human cDNA encoding protein tyosine phosphatase and ezrin-like domains. Biochem Biophys Res Commun 209, 959-965 (1995)
116. Rohan, P. J., P. Davis, C. A. Moskaluk, M. Kearns, H. Krutzsch, U. Siewbenlist & K. Kelly: PAC-1: A mitogen-induced nuclear protein tyrosine phosphatase. Science 259, 1763-1766 (1993)
117. Keyse, S. M. & E. A. Emslie: Oxidative stress and heat shock induce a human gene encoding a protein tyrosine phosphatase. Nature 359, 644-647 (1992)
118. Sun, H., C. H. Charles, L. F. Lau & N. K. Tonks: MKP-1 (3CH134), an immediate early gene product, is a dual specificity phosphatase that dephosphorylates MAP kinase in vivo. Cell 75, 487-493 (1994)
119. Noguchi, T., R. Metz, L. Chen, M. G. Mattei, D. Carrasco & R. Bravo: Structure, mapping, and expression of erp, a growth factor-inducible gene encoding a nontransmembrane protein tyrosine phosphatase, and effect of ERP on cell growth. Mol Cell Biol 13, 5195-5205 (1993)
120. King, A. G., B. W. Ozanne, C. Smythe & A. Ashworth: Isolation and characterisation of a uniquely regulated threonine, tyrosine phosphatase (TYP 1) which inactivates ERK2 and p54jnk. Oncogene 11, 2553-2563 (1995)
121. Guan, K. L. & E. Butch: Isolation and characterization of a novel dual specific phosphatase, HVH2, which selectively dephosphorylates the mitogen-activated protein kinase. J Biol Chem 270, 7197-7203 (1995)
122. Groom, L. A., A. A. Sneddon, D. R. Alessi, S. Dowd & S. M. Keyse: Differential regulation of the MAP, SAP and RK/p38 kinases by Pyst1, a novel cytosolic dual-specificity phosphatase. EMBO J 15, 3621-3632 (1996)
123. Muda, M., U. Boschert, R. Dickinson, J. C. Martinou, I. Martinou, M. Camps, W. Schlegel & S. Arkinstall: MKP-3, a novel cytosolic protein-tyrosine phosphatase that exemplifies a new class of mitogen-activated protein kinase phosphatase. J Biol Chem 271, 4319-4326 (1996)
124. Muda, M., U. Boschert, A. Smith, B. Antonsson, C. Gillieron, C. Chabert, M. Camps, L. Martinou, A. Ashworth & S. Arkinstall.: Molecular cloning and functional characterization of a novel mitogen-activated protein kinase phosphatase, MKP4. J Biol Chem 272, 5141-5151 (1997)
125. Shin, D. Y., T. Ishibashi, T. S. Choi, E. Chung, I. Y. Chung, S. A. Aaronson & D. P. Bottaro: A novel human ERK phosphatase regulates H-ras and v-raf signal transduction. Oncogene 14, 2633-2639 (1997)
126. Smith, A., C. Price, M. Cullen, M. Muda, A. Kling, B. Ozanne, A. Arkinstall & A. Ashworth: Chromosomal licalization of three human dual specificity phosphatase genes (DUSP4, DUSP6, and DUSP7). Genomics 42, 524-527 (1997)
127. Ishibashi, T., D. P. Bottaro, P. Michieli, C. A. Kelley & S. A. Aaronson: A novel dual specificity phosphatase induced by serum stimulation and heat shock. J Biol Chem 269, 29897-29902 (1994)
128. Martell, K. J., S. Kwak, D. J. Hakes, J. E. Dixon & J. M. Trent: Chromosomal localization of four human VH1-like protein-tyrosine phosphatases. Genomics 22, 462-464 (1994)
129. Muda, M., A. Theodosiou, N. Rodrigues, U. Boschert, M. Camps, C. Gillieron, K. Davies, A. Ashworth & S. Arkinstall: The dual specificity phosphatases M3/6 and MKP-3 are highly selective for inactivation of distinct mitogen-activated protein kinases. J Biol Chem 271, 27205-27208 (1996)
130. Nesbit, M. A,, M. D. Hodges, L. Campbell, T. M. de Meulemeester, M. Alders, N. R. Rodrigues, K. Talbot, A. M. Theodosiou, M. A. Mannens, Y. Nakamura, P. F. Little & K. E. Davies: Genomic organization and chromosomal localixzation of a member of the MAP kinase phosphatase gene family to human chrosmosome 11p15.5 and a pseudogene to 10q11.2. Genomics 42, 284-294 (1997)
131. Couture, C., G. Baier, C. Oetken, S. Williams, D. Telford, A. Marie-Cardine, G. Baier-Bitterlich, S. Fischer, P. Burn, A. Altman & T. Mustelin: Activation of $p56^{lck}$ by $p72^{syk}$ through physical association and N-terminal tyrosine phosphorylation. Mol Cell Biol 14, 5249-5258 (1994)
132. Huyer, G., J. Kelly, J. Moffat, R. Zamboni, Z. Jia, M. J. Gresser & C. Ramachandran: Affinity selection from peptide libraries to determine substrate specificity of protein tyrosine phosphatases. Anal Biochem 258, 19-30 (1998)
133. Zhang, Z.-Y., D. Maclean, D. J. McNamara, T. K. Sawyer & J. E. Dixon: Protein tyrosine phosphatase substrate specificity: Size and phosphotyrosine positioning requirements in peptide substrates. Biochemistry 33, 2285-2290 (1994)
134. Mauro, L. J. & J. E. Dixon: 'Zip codes' direct intracellular protein tyrosine phosphatases to the correct cellular 'address'. Trends Biochem Sci 19, 1151-1155 (1994)
135. Watts, J. D., M. Affolter, D. L. Krebs, R. L. Wange, L. E. Samelson & R. Aebersold: Identification by electrospray ionization mass spectrometry of the sites of tyrosine phosphorylation induced in activated Jurkat T cells on the protein tyrosine kinase ZAP-70. J Biol Chem 269, 29520-29529 (1994)
136. Couture, C., M. Deckert, S. Williams, F. Otero Russo, A. Altman & T. Mustelin: Identification of the site in the Syk protein tyrosine kinase that binds the SH2 domain of Lck. J Biol Chem 271, 24294-24299 (1996)

137. Couture, C., Z. Songyang, T. Jascur, S. Williams, P. Tailor, L. C. Cantley & T. Mustelin: Regulation of the Lck SH2 domain by tyrosine phosphorylation. J Biol Chem 271, 24880-24884 (1996)
138. Wange, R. L., R. Guitian, N. Isakov, J. D. Watts, Aebershold & L. E. Samelson: Activating and inhibitory mutations in adjacent tyrosines in the kinase domain of ZAP-70. J Biol Chem 270, 18730-18733 (1995)
139. Peng, Z. Y. & C. A. Cartwright: Regulation of the Src tyrosine kinase and Syp tyrosine phosphatase by their cellular association. Oncogene 11, 1955-1962 (1995)
140. Oetken, C., M. von Willebrand, A. Marie-Cardine, T. Pessa-Morikawa, A. Ståhls, S. Fischer & T. Mustelin: Induction of hyperphosphorylation and activation of the $p56^{lck}$ protein tyrosine kinase by phenylarsine oxide, a phosphotyrosine phosphatase inhibitor. Mol Immunol 31, 1295-1302 (1994)
141. Ståhls, A., G. Liwszyc, C. Couture, T. Mustelin & L. C. Andersson: Triggering of human natural killer cells through CD16 induces tyrosine phosphorylation of the $p72^{syk}$ kinase. Eur J Immunol 24, 2491-2496 (1994)
142. Mustelin, T., S. Williams, P. Tailor, C. Couture, G. Zenner, P. Burn, J. D. Ashwell & A. Altman: Regulation of the $p70^{zap}$ tyrosine protein kinase by the CD45 phosphotyrosine phosphatase in T cells. Eur J Immunol 25, 942-946 (1995)
143. Park, D. J., H. W. Rho & S. G. Rhee: CD3 stimulation causes phosphorylation of phospholipase C-gamma1 on serine and tyrosine residues in a human T-cell line. Proc Natl Acad Sci USA 88, 5453-5456 (1991)
144. Weiss, A., G. Koretzky, R. C. Schatzman & T. Kadlecek: Functional activation of the T-cell antigen receptor induces tyrosine phosphorylation of phospholipase C-gamma1. Proc Natl Acad Sci USA 88, 5484-5488 (1991)
145. Secrist, J. P., L. Karnitz & R. T. Abraham: T-cell antigen receptor ligation induces tyrosine phosphorylation of phospholipase C-gamma1. J Biol Chem 266, 12135-12139 (1991)
146. Rhee, S. G.: Insositol phospholipid-specific phospholipase C: Interaction of the gamma1 isoform with tyrosine kinase. Trends Biochem Sci 16, 297-301 (1991)
147. Kim, H. K., J. W. Kim, A. Zilberstein, B. Margolis, J. G. Kim, J. Schlessinger & S. G. Rhee: PDGF stimulation of inositol phospholipid hydrolysis requires PLC-gamma1 phosphorylation on tyrosine residues 783 and 1254. Cell 65, 435-441 (1991)
148. Altman, A., K. M. Coggeshall & T. Mustelin: Molecular events mediating T cell activation. Adv Immunol 48, 277-360 (1990)
149. Zhang, W., J. Sloan-Lancaster, J. Kitchen, R. P. Trible & L. E. Samelson: LAT: The ZAP-70 tyrosine kinase substrate that links T cell receptor to cellular activation. Cell 92, 83-92 (1998)
150. Ravichandran, K. S., K. K. Lee, Z. Songyang, L. C. Cantley, P. Burn & S. J. Burakoff: Interaction of Shc with the chain of the T cell receptor upon T cells activation. Science 262, 902-905 (1993)
151. Rozakis-Adcock, M., J. McGlade, G. Mbamalu, G. Pelicci, R. Daly, W. Li, A. Batzer, S. Thomas, J. Brugge, P. G. Pelicci, J. Schlessinger & T. Pawson: Association of the Shc and Grb2/Sem5 SH2-containing proteins is implicated in activation of the Ras pathway by tyrosine kinases. Nature 360, 689-692 (1992)
152. Simon, M. A., G. S. Dodson & G. M. Rubin: An SH3-SH2-SH3 protein is required for $p21^{ras1}$ activation and binds to sevenless and Sos proteins in vitro. Cell 73, 269-277 (1993).
153. Huang, W., A. Alessandrini, C. M. Crews & R. L. Erikson: Raf-1 forms a stable complex with Mek1 and activates Mek1 by serine phosphorylation. Proc Natl Acad Sci USA 90, 10947-10951 (1993)
154. Vojtek, A. B., S. M. Hollenberg & J. A. Cooper: Mammalian Ras interacts directly with the serine/threonine kinase Raf. Cell 74, 205-214 (1993)
155. Zheng, C.-F. & K.-L. Guan: Activation of MEK family kinases requires phosphorylation of two conserved Ser/Thr residues. EMBO J 13, 1123-1131 (1994)
156. Dérijard, B., J. Raingeaud, T. Barrett, I.-H. Wu, J. Han, R. J. Ulevitch & R. J. Davis: Independent human MAP kinase signal transduction pathways defined by MEK and MKK isoforms. Science 267, 682-685 (1995)
157. Nel, A. E., C. Hanekom, A. Rheeder, K. Williams, S. Pollack, R. Katz & G. Landreth: Stimulation of MAP-2 kinase activity in T lymphocytes by anti-CD3 or anti-Ti monoclonal antibody is partially dependent on protein kinase C. J Immunol 144, 2683-2689 (1990)
158. Lange-Carter, C. A., C. M. Pleiman, A. M. Gardner, K. J. Blumer & G. L. Johnson: A divergence in the MAP kinase regulatory network defined by MEK kinase and Raf. Science 260, 315-319 (1993)
159. Thomas, G.: MAP kinase by any other name smells just as sweet. Cell 68, 3-6 (1992)
160. Maller, J.: MAP kinase activation. Curr Biol 1, 334-335 (1991)
161. Alberola-Ila, J., K. A. Forbush, R. Seger, E. G. Krebs & R. M. Perlmutter: Selective requirement for MAP kinase activation in thymocyte differentiation. Nature 373, 620-623 (1995)
162. Egerton, M., D. R. Fitzpatrick, A. D. Catling & A. Kelso: Differential activation of T cell cytokine production by the extracellular signal-regulated kinase (ERK) signaling pathway. Eur J Immunol 26, 2279-2285 (1996)
163. DeSilva, D. R., E. A. Jones, M. F. Favata, B. D. Jaffee, R. L. Magolda, J. M. Trzaskos & P. A. Scerle: Inhibition of mitogen-activated protein kinase kinase blocks T cell proliferation but does not induce or prevent anergy. J Immunol 160, 4175-4181 (1998)
164. Li, W., C. D. Whaley, A. Mondino & D. L. Mueller: Blocked signal transduction to the Erk and Jnk protein kinases in anergic $CD4^+$ T cells. Science 271, 1272-1276 (1996)
165. Margolis, B., P. Hu, S. Katzav, W. Li, J. M. Oliver, A. Ullrich, A. Weiss & J. Schlessinger: Tyrosine phosphorylation of vav proto-oncogene product containing SH2 domain and transcription factor motifs. Nature 356, 71-74 (1992)
166. Tarakhovsky, A., M. Turner, S. Schaal, P. J. Mee, L. P. Duddy, K. Rajewsky & V. L. J. Tybulewicz: Defective antigen receptor-mediated proliferation of B and T cells in the absence of Vav. Nature 374, 467-470 (1995)
167. Zang, R., F. W. Alt, L. Davidson, S. H. Orkin & W. Swat: Defective signalling through the T- and B-cell

antigen receptors in lymphoid cells lacking the vav proto-oncogene. Nature 374, 470-473 (1995)
168. Crespo, P., K. E. Schuebel, A. A. Ostrom, J. S. Gutkind & X. R. Bustelo: Phosphotyrosine-dependent activation of Rac-1 GDP/GTP exchange by the vav proto-oncogene product. Nature 385, 169-172 (1997)
169. Karin, M.: The regulation of AP-1 activity by mitogen-activated protein kinases. J Biol Chem 270, 16483-16486 (1995)
170. Foletta, V. C., D. H. Segal & D. R. Cohen: Transcriptional regulation in the immune system: all roads lead to AP-1. J Leuk Biol 63, 139-152 (1998)
171. Rao, A., C. Luo & P. G. Hogan: Transcription factors of the NFAT family: Regulation and function. Annu Rev Immunol 15, 707-747 (1997)
172. Jain, J., C. Loh & A. Rao: Transcriptional regulation of the Interleukin 2 gene. Curr Opin Immunol 7, 333-342 (1995)
173. Whitehurst, C. E. & T. D. Geppert: Mek1 and the extracellular signal-regulated kinases are required for the stimulation of IL-2 gene transcription in T cells. J Immunol 156, 1020-1029 (1996)
174. Rooney, J. W., Y.-L. Sun, L. H. Glimcher & T. Hoey: Novel NFAT sites that mediate activation of the interleukin -2 promoter in response to T-cell receptor stimulation. Mol Cell Biol 15, 6299-6310 (1995)
175. Han, J., B. Richter, Z. Li, V. Kravchenko & R. J. Ulevitch: Molecular cloning of human p38 kinase. Niochim Biophys Acta 1265, 224-227 (1995)
176. Fukuzawa, T., K. A. Reedquist, T. Trub, S. Soltoff, G. Panchamoorthy, B. Druker, L. C. Cantley, S. E. Shoelson & H. Band: The SH3 domain-binding T cell tyrosyl phosphoprotein p120. J Biol Chem 270, 19141-19150 (1995)
177. Meisner, H., B. R. Conway, D. Hartley & M. P. Czech: Interactions of Cbl with Grb2 and phosphatidylinositol 3'-kinase in activated Jurkat Cells. Mol Cell Biol 15, 3571-3578 (1995)
178. Fournel, M., D. Davidson, R. Weil & A. Veillette: Association of tyrosine protein kinase Zap-70 with the protooncogene product $p120^{c\text{-}cbl}$ in T lymphocytes. J Exp Med 183, 301-306 (1996)
179. Jackman, J. K., D. G. Motto, Q. Sun, M. Tanemoto, C. W. Turck, G. A. Peltz, G. A. Koretzky & P. R. Findell: Molecular cloning of SLP-76, a 76-kDa tyrosine phosphoprotein associated with Grb2 in T cells. J Biol Chem 270, 7029-7032 (1995)
180. Clements, J. L., B. Yang, S. E. Ross-Barta, S. L. Eliason, R. F. Hrstka, R. A. Williamson & G. A. Koretzky: Requirement for the leukocyte-specific adapter protein SLP-76 for normal T cell development. Science 281, 416-419 (1998)
181. Yablonski, D., M. R. Kuhne, T. Kadlecek & A. Weiss: Uncoupling of nonreceptor tyrosine kinase from PLC-gamma1 in an SLP-76-deficient T cell. Science 281, 413-416 (1998)
182. Sieh, M., A. Batzer, J. Schlessinger & A. Weiss: GRB2 and phospholipase C-gamma1 associate with a 36- to 38-kilodalton phosphotyrosine protein after T-cell receptor stimulation. Mol Cell Biol 14, 4435-4442 (1994)
183. Fukuzawa, T., K. A. Reedquist, G. Panchamoorthy, S. Soltoff, T. Trub, B. Druker, L. C. Cantley, S. E. Shoelson & H. Band: T cell activation-dependent association between the p85 subunit of the phosphatidylinositol 3-kinase and Grb2/phospholipase C-gamma1-binding phosphotyrosyl protein pp36/38. J Biol Chem 270, 20177-20182 (1995)
184. von Willebrand, M., S. Williams, P. Tailor & T. Mustelin: Phosphorylation of the Grb2- and phosphatidylinositol 3-kinase p85-binding p36/38 by Syk in Lck-negative T cells. Cell Signal 10, 681-689 (1998)
185. Thomas, M. L.: The leukocyte common antigen family. Annu Rev Immunol 7, 339-369 (1989)
186. Trowbridge, I. S. & M. L. Thomas: CD45: An emerging role as a protein tyrosine phosphatase required for lymphocyte activation and development. Annu Rev Immunol 12, 85-116 (1994)
187. Furukawa, K., Y. Funakoshi, M. Autero, V. Horejsi, A. Kobata & C. G. Gahmberg: Structural study of the O-linked sugar chains of human leukocyte tyrosine phosphatase CD45. Eur J Biochem 251, 288-294 (1998)
188. Baum, L. G., M. Pang, N. L. Perillo, T. Wu, A. Delegeane, C. H. Uittenbogaart, M. Fukuda & J. J. Seilhamer: Human thymic epithelial cells express an endogenous lectin, galectin-1, which binds to core 2 O-glycans on thymocytes and T lymphoblastoid cells. J Exp Med 181, 877-887 (1995)
189. Pingel, J. T. & M. L. Thomas: Evidence that the leukocyte-common antigen is required for antigen-induced T lymphocyte proliferation. Cell 58, 1055-1065 (1989)
190. Koretzky, G. A., M. A. Kohmetscher, T. Kadleck & A. Weiss: Restoration of T Cell receptor-mediated signal transduction by transfection of CD45 cDNA into a CD45-deficient variant of the Jurkat T cell line. J Immunol 149, 1138-1142 (1992)
191. Desai, D. M., J. Sap, J. Schlessinger & A. Weiss: Ligand-mediated negative regulation of a chimeric transmembrane receptor tyrosine phosphatase. Cell 73, 541-554 (1993)
192. Hovis, R. R., J. A. Donovan, M. A. Musci, D. G. Motto, F. D. Goldman, S. E. Ross & G. A. Koretzky: Rescue of signaling by a chimeric protein containing the cytoplasmic domain of CD45. Science 260, 544-546 (1993)
193. Volarevic, S., B. B. Niklinska, C. M. Burns, C. H. June, A. M. Weissman & J. D. Ashwell: Regulation of TCR signaling by CD45 lacking transmembrane and extracellular domains. Science 260, 541-544 (1993)
194. McKenney, D. W., H. Onodera, L. Gorman, T. Mimura & D. M. Rothstein: Distinct isoforms of CD45 protein-tyrosine phosphatase differentially regulate interleukin 2 secretion and activation signal pathways involving Vav in T cells. J Biol. Chem 270, 24949-24954 (1995)
195. Koretzky, G. A., J. Picus, T. Schultz & A. Weiss: Tyrosine phosphatase CD45 is required for T-cell antigen receptor and CD2-mediated activation of a protein tyrosine kinase and interleukin 2 production. Proc Natl Acad Sci USA 88, 2037-2041 (1991)
196. Koretzky, G. A., J. Picus, M. L. Thomas & A. Weiss: Tyrosine phosphatase CD45 is essential for coupling T-cell antigen receptor to the phosphatidyl inositol pathway. Nature 346, 66-68 (1990)
197. Volarevic, S., B. B. Niklinska, C. M. Burns, H. Yamada, C. H. June, F. J. Dumont & J. D. Ashwell: The

CD45 tyrosine phosphatase regulates phosphotyrosine homeostasis and its loss reveals a novel pattern of late T cell receptor-induced Ca^{2+} oscillations. J Exp Med 176, 835-844 (1992)

198. Wallace, V. A., J. M. Penninger, K. Kishiharta, E. Timms, A. Shahinian, H. Pircher, T. M. Kundig, P. S. Ohashi & T. W. Mak: Alterations in the level of CD45 surface expression affect the outcome of thymic selection. J Immunol 158, 3205-3214 (1997)

199. Ostergaard, H. L., D. A. Shackelford, T. R. Hurley, P. Johnson, R. Hyman, B. M. Sefton & I. S. Trowbridge: Expression of CD45 alters phosphorylation of the lck-encoded tyrosine protein kinase in murine lymphoma T-cell lines. Proc Natl Acad Sci USA 86, 8959-8963 (1989)

200. Shiroo, M., L. Goff, M. Biffen, E. Shivnan & D. Alexander: CD45 tyrosine phosphatase-activated p59*fyn* couples the T cell antigen receptor to pathways of diacylglycerol production, protein kinase C activation and calcium influx. EMBO J 11, 4887-4897 (1992)

201. Hurley, T. R., R. Hyman & B. M. Sefton: Differential effects of expression of the CD45 tyrosine protein phosphatase on the tyrosine phosphorylation of the lck, fyn and c-src tyrosine protein kinases. Mol Cell Biol 13, 1651-1656 (1993)

202. Cahir McFarland, E. D., T. R. Hurley, J. T. Pingel, B. M. Sefton, A. Shaw & M. L. Thomas: Correlation between Src family member regulation by the protein-tyrosine-phosphatase CD45 and transmembrane signaling through the T-cell receptor. Proc Natl Acad Sci USA 90, 1402-1406 (1993)

203. Gervais, F. G. & A. Veillette: The unique amino-terminal domain of p56lck regulates interactions with tyrosine protein phosphatases in T lymphocytes. Mol Cell Biol 15, 2393-2401 (1995).

204. Furukawa, T., M. Itoh, N. X. Krueger, M. Streuli & H. Saito: Specific interaction of the CD45 protein-tyrosine phosphatase with tyrosine-phosphorylated CD3 zeta chain. Proc Natl Acad Sci USA 91, 10928-10932 (1994)

205. Monks, C. R. F., B. A. Freiberg, H. Kupfer, N. Sciaky & A. Kupfer: Three-dimensional segregation of supramolecular activation clusters in T cells. Nature 395, 82-86 (1997)

206. Shaw, A. S. & M. L. Dustin: Making the T cell receptor go the distance: A topological view of T cell activation. Immunity 6, 361-369 (1997)

207. Adachi, M., T. Miyachi, M. Sekiya, Y. Hinoda, A. Yachi & K. Imai: Structure of the human LC-PTP (HePTP) gene: similarity in genomic organization within protein-tyrosine phosphatase genes. Oncogene 9, 3031-3035 (1994)

208. Sharma, E., F. Zhao, A. Bult & P. J. Lombroso: Identification of two alternatively spliced transcripts of STEP: a subfamily of brain-enriched protein tyrosine phosphatases. Brain Res Mol Brain Res 32, 87-93 (1995)

209. Bult, A., F. Zhao, R. Dirkx Jr, A. Raghunathan, M. Solimena & P. J. Lombroso: STEP: a family of brain-enriched PTPs. Alternative splicing produces transmembrane, cytosolic and truncated isoforms. Eur J Cell Biol 72, 337-344 (1997)

210. Boulanger, L. M., P. J. Lombroso, A. Raghunathan, M. J. During, P. Wahle & J. R. Naegele: Cellular and molecular characterization of a brain-enriched protein tyrosine phosphatase. J Neurosci 15, 1532-1544 (1995)

211. Zanke, B., J. Squire, H. Griesser, M. Henry, H. Suzuki, B. Patterson, M. Minden & T. W. Mak: A hematopoietic protein tyrosine phosphatase (HePTP) gene that is amplified and overexpressed in myeloid malignancies maps to chromosome 1q32.1. Leukemia 8, 236-244 (1994)

212. Hall, L. R., M. Streuli, S. F. Schlossman & H. Saito: Complete exon-intron organization of the human leukocyte common antigen (CD45) gene. J Immunol 141, 2781-2787 (1988)

213. Sweiter, M., E. H. Berenstein, W. D. Swaim & R. P. Siraganian: Aggregation of IgE receptors in rat basophilic leukemia 2H3 cells induces tyrosine phosphorylation of the cytosolic protein-tyrosine phosphatase HePTP. J Biol Chem 270, 21902-21906 (1995)

214. Fonatsch, C., D. Haase, M. Freund, H. Bartels & H. Tesch: Partial trisomy 1q. A nonrandom primary chromosomal abnormality in myelodysplastic syndromes? Cancer Genet Cytogenet 56, 243-253 (1991)

215. Mamaev, N., S. E. Mamaeva, V. Pavlova & D. Patterson: Combined trisomy 1q and monosomy 17p due to translocation t(1;17) in a patient with myelodysplastic syndrome. Cancer Genet Cytogenet 35, 21-25 (1988)

216. Mitelman, F., Y. Kaneko & J. M. Trent: Report of the committee on chromosome changes in neoplasia. Cytogenet Cell Genet 55, 358-86 (1990)

217. Saxena, M., S. Williams, J. Gilman & T. Mustelin: Negative regulation of T cell antigen receptor signaling by hematopoietic tyrosine phosphatase (HePTP). J Biol Chem 273, 15340-15344 (1998)

218. Saxena, M., S. Williams, J. Brockdorff, J. Gilman & T. Mustelin: Inhibition of T cell signaling by MAP kinase-targeted hematopoietic tyrosine phosphatase (HePTP). Submitted (1998)

219. Arab, S., H. Suzuki, B. Iafrate, V. Ha, S. Berger & B. Zanke: Hematopoietic protein tyrosine phosphatase (HePTP) inhibits cytokine signaling and MAPK activation. Submitted (1998)

220. Cool, D. E., N. K. Tonks, H. Charbonneau, E. D. Fischer & E. G. Krebs: Expression of a human T-cell protein tyrosine phosphatase in baby hamster kidney cells. Proc Natl Acad Sci USA 87, 7280-7284 (1990)

221. Mosinger, B., U. Tillmann, H. Westphal & M. L. Tremblay: Cloning and characterization of a mouse cDNA encoding a cytoplasmic protein-tyrosine phosphatase. Proc Natl Acad Sci USA 89, 499-503 (1992)

222. Champion-Arnaud, P., M.-C. Gesnel, N. Foulkes, C. Ronsin, P. Sassone-Corsi & R. Breathnach: Activation of transcription via AP-1 or CREB regulatory sites is blocked by protein tyrosine phosphatases. Oncogene 6, 1203-1209 (1991)

223. Lorenzen, J. A., C. Y. Dadabay & E. H. Fischer: COOH-terminal sequence motifs target the T cell protein tyrosine phosphatase to the ER and nucleus. J Cell Biol 131, 631-643 (1995)

224. Swarup, G., S. Kamatkar, V. Radha & V. Rema: Molecular cloning and expression of a protein-tyrosine phosphatase showing homology with transcription factors Fos and Jun. FEBS Lett 280, 65-69 (1991)

225. Reddy, R. S. & G. Swarup: Alternative splicing generates four different forms of a non-transmembrane

protein tyrosine phosphatase mRNA. DNA and Cell Biol 14, 1007-1015 (1995)
226. Johnson, C. V., D. E. Cool, M. B. Glaccum, N. Green, E. H. Fischer, A. Bruskin, D. E. Hill & J. B. Lawrence: Isolation and mapping of human T-cell protein tyrosine phosphatase sequences: localization of genes and pseudogenes discriminated using fluorescence hybridization with genomic versus cDNA probes. Genomics 16, 619-629 (1993)
227. You-Ten, K. E., E. S. Muise, A. Itie, E. Michaliszyn, J. Wagner, S. Jothy, W. S. Lapp & M. L. Tremblay: Impaired bone marrow microenvironment and immune function in T cell protein tyrosine phosphatase-deficient mice. J Exp Med 186, 683-693 (1997)
228. Zander, N. F., J. A. Lorenzen, D. E. Cool, N. K. Tonks, G. Daum, E. G. Krebs & E. H. Fischer: Purification and characterization of a human recombinant T-cell protein-tyrosine-phosphatase from a baculovirus expression system. Biochemistry 30, 6964-6970 (1991)
229. Brown-Shimer, S., K. A. Johnson, J. B. Lawrence, C. Johnson, A. Bruskin, N. R. Green & D. E. Hill: Molecular cloning and chromosome mapping of the human gene encoding protein phosphotyrosyl phosphatase 1B. Proc Natl Acad Sci USA 87, 5148-5152 (1990)
230. Chernoff, J., A. R. Schievella, D. A. Jost, R. L. Erikson & B. G. Neel: Cloning of a cDNA for a major human protein-tyrosine-phosphatase. Proc Natl Acad Sci USA 87, 2735-2739 (1990)
231. Guan, K., R. S. Haun, S. J. Watson, R. L. Geahlen & J. E. Dixon: Cloning and expression of a protein-tyrosine-phosphatase. Proc Natl Acad Sci USA 87, 1501-1505 (1990)
232. Frangioni, J. V., P. H. Beahm, V. Shifrin, C. A. Jost & B. G. Neel: The nontransmembrane tyrosine phosphatase PTP-1B localizes to the endoplasmic reticulum via its 35 amino acid C-terminal sequence. Cell 68, 545-560 (1992)
233. Cool, D. E., P. R. Andreassen, N. K. Tonks, E. G. Krebs, E. H. Fischer & R. L. Morgolis: Cytokinetic failure and asynchronous nuclear division in BHK cells overexpressing a truncated protein-tyrosine-phosphatase. Proc Natl Acad Sci USA 89, 5422-5426 (1992)
234. Zander, N. F., D. E. Cool, C. D. Diltz, L. R. Rohrschneider, E. G. Krebs & E. H. Fischer: Suppression of v-fms-induced transformation by overexpression of a truncated T cell-protein tyrosine phosphatase. Oncogene 8, 1175-1182 (1993)
236. Lammers, R., B. Bossenmaier, D. E. Cool, N. K. Tonks, J. Schlessinger, E. H. Fischer & A. Ullrich: Differential activities of protein tyrosine phosphatases in intact cells. J Biol Chem 268, 22456-22462 (1993)
235. Tiganis, T., A. J. Flint, S. A. Adam & N. K. Tonks: Association of the T-cell protein tyrosine phosphatase with nuclear import factor p97. J Biol Chem 272, 21548-21557 (1997)
237. Tiganis, T., A. M. Bennett, K. S. Ravichandran & N. K. Tonks: Epidermal growth factor receptor and the adaptor protein p52 Shc are specific substrates of T-cell protein tyrosine phosphatase. Mol Cell Biol 18, 1622-1634 (1998)
238. Tsui, H. W., K. A. Siminovitch, L. de Souza & F. W. L. Tsui: Motheaten and viable motheaten mice have mutations in the haematopoietic cell phosphatase gene. Nature Genetics 4, 124-129 (1993)
239. Kozlowski, M., I. Mlinaric-Rascan, G-S. Feng, R. Shen, T. Pawson & K. A. Siminovitch: Expression and catalytic activity of the tyrosine phosphatase PTP1C is severely impaired in motheaten and viable motheaten mice. J Exp Med 178, 2157-2163 (1993)
240. Uchida, T., T. Matozaki, K. Matsuda, T. Suzuki, S Matozaki, O. Nakano, K. Wada, Y. Konda, C. Sakamoto & M. Kasuga: Phorbol ester stimulates the activity of a protein tyrosine phosphatase containing SH2 domains (PTP1C) in HL-60 leukemia cells by increasing gene expression. J Biol Chem 268, 11845-11850 (1993)
241. Shultz, L. D. & M. C. Green: Motheaten, an immunodeficient mutant of the mouse. J Immunol 116, 936-943 (1976)
242. Pei, D., J. Wang & C. T. Walsh: Differential functions of the two Src homology 2 domains in protein tyrosine phosphatase SH-PTP1. Proc Natl Acad Sci USA 93, 1141-1145 (1996)
243. Hof, P., S. Pluskey, S. Dhe-Paganon, M. J. Eck & S. E. Shoelson: Crystal structure of the tyrosine phosphatase SHP-2. Cell 92, 441-450 (1998)
244. Pei, D., U. Lorenz, U. Klingmüller, B. G. Neel & C. T. Walsh: Intramolecular regulation of protein tyrosine phosphatase SH-PTP1: A new function for Src homology 2 domains. Biochemistry 33, 15483-15493 (1994)
245. Townley, R., S-H. Shen, D. Banville & C. Ramachandran: Inhibition of the activity of protein tyrosine phosphatase 1C by its SH2 domains. Biochemistry 32, 13414-13418 (1993)
246. Zhao, Z., R. Larocque, W-T. Ho, E. H. Fischer & S-H. Shen: Purification and characterization of PTP2C, a widely distributed protein tyrosine phosphatase containing two SH2 domains. J Biol Chem 269, 8780-8785 (1994)
247. Dechert, U., M. Adam, K. W. Harder, I. Clark-Lewis & F. Jirik: Characterization of protein tyrosine phosphatase SH-PTP2. J Biol Chem 269, 5602-5611 (1994)
248. Pluskey, S., T. J. Wandless, C. T. Walsh & S. E. Shoelson: Potent stimulation of SH-PTP2 phosphatase activity by simultaneous occupancy of both SH2 domains. J Biol Chem 270, 2897-2900 (1995)
249. Ottinger, E. A., M. C. Botfield & S. E. Shoelson: Tandem SH2 domains confer high specificity in tyrosine kinase signaling. J Biol Chem 273, 729-735 (1998)
250. O'Reilly, A. M. & B. G. Neel: Structural determinants of SHP-2 function and specificity in Xenopus mesoderm induction. Mol Cell Biol 18, 161-177 (1998)
251. Tenev, T., H. Keilhack, S. Tomic, B. Stoyanov, M. Stein-Gerlach, R. Lammers, A. V. Krivtsov, A. Ullrich & F-D. Böhmer: Both SH2 domains are involved in interaction of SHP-1 with the epidermal growth factor receptor but cannot confer receptor-directed activity to SHP-1/SHP-2 chimera. J Biol Chem 272, 5966-5973 (1997)
252. D'Ambrosio, D., K. L. Hippen, S. A. Minskoff, I. Mellman, G. Pani, K. A. Siminovitch & J. C. Cambier: Recruitment and activation of PTP1C in negative regulation of antigen receptor signaling by FcgammaRIIB1. Science 268, 293-297 (1995)
253. Unkeless, J. C. & J. Jin: Inhibitory receptors, ITIM sequences and phosphatases. Curr. Opin. Immunol. 9, 338-343 (1997)

254. Vivier, E. & M. Daëron: Immunoreceptor tyrosine-based inhibition motifs. Immunol. Today 18, 286-291 (1997)
255. Muta, T., T. Kurosaki, Z. Misulovin, M. Sanchez, M. C. Nussenzweig & J. V. Ravetch: A 13-amino-acid motif in the cytoplasmic domain of FcgammaRIIB modulates B-cell receptor signalling. Nature 368, 70-73 (1994)
256. Torres, R. M., C-L. Law, L. Santos-Argumedo, P. A. Kirkham, K. Grabstein, R. M. E. Parkhouse & E. A. Clark: Identification and characterization of the murine homologue of CD22, a B lymphocyte-restricted adhesion molecule. J Immunol 149, 2641-2649 (1992)
257. Wilson, G. L., C. H. Fox, A. S. Fauci & J. H. Kehrl: cDNA cloning of the B cell membrane protein CD22: A mediator of B-B cell interactions. J Exp Med 173, 137-146 (1991)
258. Wagtmann, N., R. Biassoni, C. Cantoni, S. Verdiani, M. S. Malnati, M. Vitale, C. Bottino, L. Moretta, A. Moretta & E. O. Long: Molecular clones of the p58 NK cell receptor reveal immunoglobulin-related molecules with diversity in both the extra- and intracellular domains. Immunity 2, 439-449 (1995)
259. Colonna, M. & J. Samaridis: Cloning of immunoglobulin-superfamily members associated with HLA-C and HLA-B recognition by human natural killer cells. Science 268, 405-408 (1995)
260. Phillips, J. H., J. E. Gumperz, P. Parham & L. L. Lanier: Superantigen-dependent, cell-mediated cytotoxicity inhibited by MHC class I receptors on T lymphocytes. Science 268, 403-405 (1995)
261. D'Andrea, A., C. Chang, K. Franz-Bacon, T. McClanahan, J. H. Phillips & L. L. Lanier: Molecular cloning of NKB1. A natural killer cell receptor for HLA-B allotypes. J Immunol 155, 2306-2310 (1995)
262. Meyaard, L., G. J. Adema, C. Chang, E. Woollatt, G. R. Sutherland, L. L. Lanier & J. H. Phillips: LAIR-1, a novel inhibitory receptor expressed on human mononuclear leukocytes. Immunity 7, 283-290 (1997)
263. Cosman, D., N. Fanger, L. Borges, M. Kubin, W. Chin, L. Peterson & M-L. Hsu: A novel immunoglobulin superfamily receptor for cellular and viral MHC class I molecules. Immunity 7, 273-282 (1997)
264. Samaridis, J. & M. Colonna: Cloning of novel immunoglobulin superfamily receptors expressed on human myeloid and lymhoid cells: structural evidence for new stimulatory and inhibitory pathways. Eur J Immunol 27, 660-665 (1997)
265. Colonna, M., F. Navarro, T. Bellón, M. Llano, P. García, J. Samaridis, L. Angman, M. Cella & M. López-Botet: A common inhibitory receptor for major histocompatibility complex class I molecules on human lymphoid and myelomonocytic cells. J Exp Med 186, 1809-1818 (1997)
266. Cella, M., C. Döhring, J. Samaridis, M. Dessing, M. Brockhaus, A. Lanzavecchia & M. Colonna: A novel inhibitory receptor (ILT3) expressed on monocytes, macrophages, and dendritic cells involved in antigen processing. J Exp Med 185, 1743-1751 (1997)
267. Kuroiwa, A., Y. Yamashita, M. Inui, T. Yuasa, M. Ono, A. Nagabukuro, Y. Matsuda & T. Takai: Association of tyrosine phosphatases SHP-1 and SHP-2, inositol 5-phosphatase SHIP with gp49B1, and chromosomal assignment of the gene. J Biol Chem 273, 1070-1074 (1998)
268. Castells, M. C., X. Wu, J. P. Arm, K. F. Austen & H. R. Katz: Cloning of the gp49B gene of the immunoglobulin superfamily and demonstration that one of its two products is an early-expressed mast cell surface protein originally described as gp49. J Biol Chem 269, 8393-8401 (1994)
269. Hayami, K., D. Fukuta, Y. Nishikawa, Y. Yamashita, M. Inui, Y Ohyama, M. Hikida, H. Ohmori & T. Takai: Molecular cloning of a novel murine cell-surface glycoprotein homologous to killer cell inhibitory receptors. J Biol Chem 272, 7320-7327 (1997)
270. Guthmann, M. D., M. Tal & I. Pecht: A secretion inhibitory signal transduction molecule on mast cells is another C-type lectin. Proc Natl Acad Sci USA 92, 9397-9401 (1995)
271. Hoegen, I. V., E. Nakayama & J. R. Parnes: Identification of a human protein homologous to the mouse Lyb-2 B cell differentiation antigen and sequence of the corresponding cDNA. J Immunol 144, 4870-4877 (1990)
272. Lazetic, S., C. Chang, J. P. Houchins, L. L. Lanier & J. H. Phillips: Human natural killer cell receptors involved in MHC class I recognition are disulfide-linked heterodimers of CD94 and NKG2 subunits. J Immunol 157, 4741-4745 (1996)
273. Houchins, J. P., T. Yabe, C. McSherry & F. H. Bach: DNA sequence analysis of NKG2, a family of related cDNA clones encoding type II integral membrane proteins on human natural killer cells. J Exp Med 173, 1017-1020 (1991)
274. Yokoyama, W. M., L. B. Jacobs, O. Kanagawa, E. M. Shevach & D. I. Cohen: A murine T lymphocyte antigen belongs to a supergene family of type II integral membrane proteins. J Immunol 143, 1379-1386 (1989)
275. Nagasawa, R., J. Gross, O. Kanagawa, K. Townsend, L. L. Lanier, J. Chiller & J. P. Allison: Identification of a novel T cell surface disulfide-bonded dimer distinct from the / antigen receptor. J Immunol 138, 815-824 (1987)
276. Uchida, T., T. Matozaki, T. Noguchi, T. Yamao, K. Horita, T. Suzuki, Y. Fujioka, C. Sakamoto & M. Kasuga: Insulin stimulates the phosphorylation of Tyr^{538} and the catalytic activity of PTP1C, a protein tyrosine phosphatase with Src homology-2 domains. J Biol Chem 269, 12220-12228 (1994)
277. Bouchard, P., Z. Zhao, D. Banville, F. Dumas, E. H. Fischer & S-H. Shen: Phosphorylation and identification of a major tyrosine phosphorylation site in protein tyrosine phosphatase 1C. J Biol Chem 269, 19585-19589 (1994)
278. Lorenz, U., K. S. Ravichandran, D. Pei, C. T. Walsh, S. J. Burakoff & B. G. Neel: Lck-dependent tyrosyl phosphorylation of the phosphotyrosine phosphatase SH-PTP1 in murine T cells. Mol Cell Biol 14, 1824-1834 (1994)
279. Songyang, Z., S. E. Shoelson, M. Chaudhuri, G. Gish, T. Pawson, W. G. Haser, F. King, T. Roberts, S. Ratnofsky, R. J. Lechleider, B. G. Neel, R. B. Birge, J. E. Fajardo, M. M. Chou, H. Hanafusa, B. Schaffhausen & L. C. Cantley: SH2 domains recognize specific phosphopeptide sequences. Cell 72, 767-778 (1993)
280. Kon-Kozlowski, M., G. Pani, T. Pawson & K. A. Siminovitch: The tyrosine phosphatase PTP1C associates

with Vav, Grb2, and mSos1 in hematopoietic cells. J Biol Chem 271, 3856-3862 (1996)
281. Chen, H. E., S. Chang, T. Trub & B. G. Neel: Regulation of colony-stimulating factor 1 receptor signaling by the SH2 domain-containing tyrosine phosphatase SHPTP1. Mol Cell Biol 16, 3685-3697 (1996)
282. Baixeras, E., G. Kroemer, E. Cuende, C. Márquez, L. Boscá, J. E. A. Alés-Martínez & C. Martínez: Signal transduction pathways involved in B-cell induction. Immunol Rev 132, 5-47 (1993)
283. Clark, E. A. & P. J. L. Lane: Regulation of human B-cell activation and adhesion. Annu Rev Immunol 9, 97-127 (1991)
284. Hombach, J., T. Tsubata, L. Leclercq, H. Stappert & M. Reth: Molecular components of the B-cell antigen receptor complex. Nature 343, 760-762 (1990)
285. Hippen, K. L., A. M. Buhl, D. D'Ambrosio, K. Nakamura, C. Persin & J. C. Cambier: Fc-gammaRIIB1 inhibition of BCR-mediated phosphoinositide hydrolysis and Ca^{2+} mobilization is integrated by CD19 dephosphorylation. Immunity 7, 49-58 (1997)
286. Cyster, J. G. & C. C. Goodnow: Protein tyrosine phosphatase 1C negatively regulates antigen receptor signaling in B lymphocytes and determines thresholds for negative selection. Immunity 2, 13-24 (1995)
287. Ono, M., H. Okada, S. Bolland, S. Yanagi, T. Kurosaki & J. V. Ravetch: Deletion of SHIP or SHP-1 reveals two distinct pathways for inhibitory signaling. Cell 90, 293-301 (1997)
288. Gupta, N., A. M. Scharenberg, D. N. Burshtyn, N. Wagtmann, M. N. Lioubin, L. R. Rohrschneider, J-P. Kinet & E. O. Long: Negative signaling pathways of the killer cell inhibitory receptor and Fc-gammaRIIbeta1 require distinct phosphatases. J Exp Med 186, 473-478 (1997)
289. Doody, G. M., L. B. Justement, C. C. Delibrias, R. J. Matthews, J. Lin, M. L. Thomas & D. T. Fearon: A role in B cell activation for CD22 and the protein tyrosine phosphatase SHP. Science 269, 242-244 (1995)
290. Smith, K. G. C., D. M. Tarlinton, G. M. Doody, M. L. Hibbs & D. T. Fearon: Inhibition of the B cell by CD22: A requirement for Lyn. J Exp Med 187, 807-811 (1998)
291. Bléry, M., H. Kubagawa, C-C. Chen, F. Vély, M. D. Cooper & E. Vivier: The paired Ig-like receptor PIR-B is an inhibitory receptor that recruits the protein-tyrosine phosphatase SHP-1. Proc Natl Acad Sci USA 95, 2446-2451 (1998)
292. Maeda, A., M. Kurosaki, M. Ono, T. Takai & T. Kurosaki: Requirement of SH2-containing protein tyrosine phosphatases SHP-1 and SHP-2 for paired immunoglobulin-like receptor B (PIR-B)-mediated inhibitory signal. J Exp Med 187, 1355-1360 (1998)
293. Janeway, C. A.: A primitive immune system. Nature 341, 108 (1989)
294. Raulet, D. H. & W. Held: Natural killer cell receptors: The offs and ons of NK cell recognition. Cell 82, 697-700 (1995)
295. Lanier, L. L., J. J. Ruitenberg & J. H. Phillips: Functional and biochemical analysis of CD16 antigen on natural killer cells and granulocytes. J Immunol 141, 3478-3485 (1998)
296. Ravetch, J. V. & B. Perussia: Alternative membrane forms of Fc-gammaRIII (CD16) on human NK cells and neutrophils: cell-type specific expression of two genes which differ in single nucleotide substitutions. J Exp Med 170, 481-497 (1989)
297. Lanier, L. L., S. Cwirla, G. Yu, R. Testi & J. H. Phillips: Membrane anchoring of a human IgG Fc receptor (CD16) determined by a single amino acid. Science 246, 1611-1613 (1989)
298. Anderson, P., M. Caliguri, J. Ritz & S. F. Schlossman: CD3-negative natural killer cells express zeta TCR as a part of a novel molecular complex. Nature 341, 159-162 (1989)
299. Lanier, L.L., G. Yu, J. H. Phillips: Co-association of CD3zeta with a receptor (CD16) for IgG Fc on human natural killer cells. Nature 342, 803-805 (1989)
300. Vivier, E., P. Morin, C. O'Brien, B. Druker, S. F. Schlossman & P. Anderson: Tyrosine phosphorylation of the Fc-gammaRIII(CD16): complex in human natural killer cells. J Immunol 146, 206-210 (1991)
301. Bonnerot, C., S. Amigorena, D. Choquet, R. Pavlovich, V. Choukroun & W. H. Fridman: Role of associated gamma-chain in tyrosine kinase activation via murine Fc-gammaRIII. EMBO J 11, 2747-2757 (1992)
302. Burshtyn, D. N., A. M. Scharenberg, N. Wagtmann, S. Rajagopalan, K. Berrada, T. Yi, J-P. Kinet & E. O. Long: Recruitment of tyrosine phosphatase HCP by the killer cell inhibitory receptor. Immunity 4, 77-85 (1996)
303. Dréan, E. L., F. Vély, L. Olcese, A. Cambiaggi, S. Guia, G. Krystal, N. Gervois, A. Moretta, F. Jotereau & E. Vivier: Inhibition of antigen-induced T cell response and antibody-induced NK cell cytotoxicity by NKG2A: Association of NKG2A with SHP-1 and SHP-2 protein-tyrosine phosphatases. Eur J Immunol 28, 264-276 (1998)
304. Pani, G., K.-D. Fischer, I. Mlinaric-Rascan & K. A. Siminovitch: Signaling capacity of the T cell antigen receptor is negatively regulated by the PTP1C tyrosine phosphatase. J Exp Med 184, 839-852 (1996)
305. Lorenz, U., K. S. Ravichandran, S. J. Burakoff & B. G. Neel: Lack of SHPTP1 results in src-family kinase hyperactivation and thymocyte hyperresponsiveness. Proc Natl Acad Sci USA 93, 9624-9629 (1996)
306. Somani, A.-K., J. S. Bignon, G. B. Mills, K. A. Siminovitch & D. R. Branch: Src kinase activity is regulated by the SHP-1 protein-tyrosine phosphatase. J Biol Chem 272, 21113-21119 (1997)
307. Musci, M. A., S. L. Beaves, S. E. Ross, T. Yi & G. A. Koretzky: Surface expression of hemopoietic cell phosphatase fails to complement CD45 deficiency and inhibits TCR-mediated signal transduction in a Jurkat T cell clone. J Immunol 158, 1565-1571 (1997)
308. Plas, D. R., R. Johnson, J. T. Pingel, R. J. Matthews, M. Dalton, G. Roy, A. C. Chan & M. L. Thomas: Direct regulation of ZAP-70 by SHP-1 in T cell antigen receptor signaling. Science 272, 1173-1176 (1996)
309. Raab, M. & C. E. Rudd: Hematopoietic cell phosphatase (HCP) regulates $p56^{LCK}$ phosphorylation and ZAP-70 binding to T cell receptor chain. Biochem Biophys Res Commun 222, 50-57 (1996)
310. Migone, T.-S., N. A. Cacalano, N. Taylor, T. Yi, T. A. Waldmann & J. A. Johnston: Recruitment of SH2-containing protein tyrosine phosphatase SHP-1 to the

interleukin 2 receptor; loss of SHP-1 expression in humanT-lymphotropic virus type I-transformed T cells. Proc Natl Acad Sci USA 95, 3845-3850 (1998)
311. Yi, T., J. Zhang, O. Miura & J. N. Ihle: Hematopoietic cell Phosphatase associates with erythropoietin (Epo) receptor after Epo-induced receptor tyrosine phosphorylation: Identification of potential binding sites. Blood 85, 87-95 (1995)
312. Klingmüller, U., U. Lorenz, L. C. Cantley, B. G. Neel & H. F. Lodish: Specific recruitment of SH-PTP1 to the erythropoietin receptor causes inactivation of JAK2 and termination of proliferative signals. Cell 80, 729-738 (1995)
313. Hackett, R. H., Y-D. Wang, S. Sweitzer, G. Feldman, W. I. Wood & A. C. Larner: Mapping of a cytoplasmic domain of the human growth hormone receptor that regulates rates of inactiation of Jak2 and Stat proteins. J Biol Chem 272, 11128-11132 (1997)
314. Ram, P. A. & D. J. Waxman: Interaction of growth hormone-activated STATs with SH2-containing phosphotyrosine phosphatase SHP-1 and nuclear JAK2 tyrosine kinase. J Biol Chem 272, 17694-17702 (1997)
315. Lorenz, U., A. D. Bergemann, H. N. Steinberg, J. G. Flanagan, X. Li, S. J. Galli & B. G. Neel: Genetic analysis reveals cell type-specific regulation of receptor tyrosine kinase c-Kit by the protein tyrosine phosphatase SHP1. J Exp Med 184, 1111-1126 (1996)
316. Kozlowski, M., L. Larose, F. Lee, D. M. Le, R. Rottapel & K. A. Siminovitch: SHP-1 binds and negatively modulates the c-Kit receptor by interaction with tyrosine 569 in the c-Kit juxtamembrane domain. Mol Cell Biol 18, 2089-2099 (1998)
317. Yi, T., J. N. Ihle: Association of hematopoietic cell phosphatase with c-Kit after stimulation with c-Kit ligand. Mol Cell Biol 13, 3350-3358 (1993)
318. Yeung, Y.-G., K. L. Berg, F. J. Pixley, R. H. Angeletti & E. R. Stanley: Protein tyrosine phosphatase-1C is rapidly phosphorylated in tyrosine in macrophages in response to colony stimulating factor-1. J Biol Chem 267, 23447-23450 (1992)
319. Bone, H., U. Dechert, F. Jirik, J. W. Schrader & M. J. Welham: SHP1 and SHP2 protein-tyrosine phosphatases associate with c after interleukin-3-induced receptor tyrosine phosphorylation. J Biol Chem 272, 14470-14476 (1997)
320. Yi, T., A. L. - F. Mui, G. Krystal & J. N. Ihle: Hematopoietic cell phosphatase associates with the interleukin-3 (IL-3) receptor chain and down-regulates IL-3-induced tyrosine phosphorylation and mitogenesis. Mol Cell Biol 13, 7577-7586 (1993)
321. David, M., H. E. Chen, S. Goelz, A. C. Larner & B. G. Neel: Differential regulation of the alpha/beta interferon-stimulated Jak/Stat pathway by the SH2 domain-containing tyrosine phosphatase SHPTP1. Mol Cell Biol 15, 7050-7058 (1995)
322. Yetter, A., S. Uddin, J. J. Krolewski, H. Jiao, T. Yi & L. C. Platanias: Association of the interferon-dependent tyrosine kinase Tyk-2 with the hematopoietic cell phosphatase. J Biol Chem 270, 18179-18182 (1995)
323. You, M. & Z. Zhao: Positive Effects of SH2 Domain-containing tyrosine phosphatase SHP-1 on epidermal growth factor- and interferon- -stimulated activation of STAT transcription factors in HeLa cells. J Biol Chem 272, 23376-23381 (1997)
324. Su, L., Z. Zhao, P. Bouchard, D. Banville, E. H. Fischer, E. G. Krebs & S-H. Shen: Positive Effect of Overexpressed Protein-tyrosine phosphatase PTP1C on mitogen-activated signaling in 293 cells. J Biol Chem 271, 10385-10390 (1996)
325. Tomic, S., U. Greiser, R. Lammers, A. Kharitonenkov, E. Imyanitov, A. Ullrich & F-D. Böhmer: Association of SH2 domain protein tyrosine phosphatases with the epidermal growth factor receptor in human tumor cells. J Biol Chem 270, 21277-21284 (1995)
326. Yu, Z., L. Su, O. Hoglinger, M. L. Jaramillo, D. Banville & S-H. Shen: SHP-1 Associates with both platelet-derived growth factor receptor and the p85 subunit of phosphatidylinositol 3-kinase. J Biol Chem 273, 3687-3694 (1998)
327. Bennett, A. M., T. L. Tang, S. Sugimoto, C. T. Walsh & B. G. Neel: Protein-tyrosine-phosphatase SHPTP2 couples platelet-derived growth factor receptor to Ras. Proc Natl Acad Sci USA 91, 7335-7339 (1994)
328. Li, W., R. Nishimura, A. Kashishian, A. G. Batzer, W. J. H. Kim, J. A. Cooper & J. Schlessinger: A new function for a phosphotyrosine phosphatase: Linking GRB2-Sos to a receptor tyrosine kinase. Mol Cell Biol 14, 509-517 (1994)
329. Frearson, J. A., T. Yi & D. R. Alexander: A tyrosine-phosphorylated 110-120-kDa protein associates with the C-terminal SH2 domain of phosphotyrosine phosphatase-1D in T cell receptor-stimulated T cells. Eur J Immunol 26, 1539-1543 (1996)
330. Adachi, M., M. Ishino, T. Torigoe, Y. Minami, T. Matozaki, T. Miyazaki, T. Taniguchi, Y. Hinoda & K. Imai: Interleukin-2 induces tyrosine phosphorylation of SHP-2 through IL-2 receptor chain. Oncogene 14, 1629-1633 (1997)
331. Frearson, J. A. & D. R. Alexander: The phosphotyrosine phosphatase SHP-2 participates in a multimeric signaling complex and regulates T cell receptor (TCR) coupling to the Ras/mitogen-activated protein kinase (MAPK) pathway in Jurkat T cells. J Exp Med 187, 1417-1426 (1998)
332. Marengère, L. E. M., P. Waterhouse, G. S. Duncan, H-W. Mittrücker, G-S. Feng & T. W. Mak: Regulation of T cell receptor signaling by tyrosine phosphatase SYP association with CTLA-4. Science 272, 1170-1173 (1996)
333. Sagawa, K., T. Kimura, M. Swieter & R. P. Siraganian: The protein-tyrosine phosphatase SHP-2 associates with tyrosine-phosphorylated adhesion molecule PECAM-1 (CD31). J Biol Chem 272, 31086-31091 (1997)
334. Manié, S. N., A. Astier, N. Haghayeghi, T. Canty, B. J. Druker, H. Hirai & A. S. Freedman: Regulation of integrin-mediated $p130^{Cas}$ tyrosine phosphorylation in human B cells. J Biol Chem 272, 15636-15641 (1997)
335. Olcese, L., P. Lang, F. Vély, A. Cambiaggi, D. Marguet, M. Bléry, K. L. Hippen, R. Biassoni, A. Moretta, L. Moretta, J. C. Cambier & E. Vivier: Human and mouse killer-cell inhibitory receptors recruit PTP1C and PTP1D protein tyrosine phosphatases. J Immunol 156, 4531-4534 (1996)
336. Kuroiwa, A., Y. Yamashita, M. Inui, T. Yuasa, M. Ono, A. Nagabukuro, Y. Matsuda & T. Takai: Association of tyrosine phosphatases SHP-1 and SHP-2, inositol 5-phosphatase SHIP with gp49B1, and chromosomal assignment of the gene. J Biol Chem 273, 1070-1074 (1998)

337. Tauchi, T., G.-S. Feng, M. S. Marshall, R. Shen, C. Mantel, T. Pawson & H. E. Broxmeyer: The ubiquitously expressed Syp phosphatase interacts with c-kit and Grb2 in hematopoietic cells. J Biol Chem 269, 25206-25211 (1994)
338. Tauchi, T., G-S. Feng, R. Shen, M. Hoatlin, G. C. Bagby Jr., D. Kabat, L. Lu & H. E. Broxmeyer: Involvement of SH2-containing phosphotyrosine phosphatase Syp in erythropoietin receptor signal transduction pathways. J Biol Chem 270, 5631-5635 (1995)
339. Tauchi, T., J. E. Damen, K. Toyama, G.-S. Feng, H. E. Broxmeyer & G. Krystal: Tyrosine 425 within the activated erythropoietin receptor binds Syp, reduces the erythropoietin required for Syp tyrosine phosphorylation, and promotes mitogenesis. Blood 87, 4495-4501 (1996)
340. Barber, D. L., C. N. Corless, K. Xia, T. M. Roberts & A. D. D'Andrea: Erythropoietin activates Raf1 by an Shc-independent pathway in CTLL-EPO-R cells. Blood 89, 55-64 (1997)
341. Itoh, T., A. Muto, S. Watanabe, A. Miyajima, T. Yokota & K-I. Arai: Granulocyte-macrophage colony-stimulating factor provokes RAS activation and transcription of c-fos through different modes of signaling. J Biol Chem 271, 7587-7592 (1996)
342. Okuda, K., L. Smith, J. D. Griffin & R. Foster: Signaling functions of the tyrosine residues in the c chain of the granulocyte-macrophage colony-stimulating factor receptor. Blood 90, 4759-4766 (1997)
343. Itoh, T., R. Liu, T. Yokota, K-I. Arai & S. Watanabe: Definition of the role of tyrosine residues of the common subunit regulating multiple signaling pathways of granulocyte-macrophage colony-stimulating factor receptor. Mol Cell Biol 18, 742-752 (1998)
344. Carlberg, K. & L. R. Rohrschneider: Characterization of a novel tyrosine phosphorylated 100-kDa protein that binds to SHP-2 and phosphatidylinositol 3'-kinase in myeloid cells. J Biol Chem 272, 15943-15950 (1997)
345. Welham, M. J., U. Dechert, K. B. Leslie, F. Jirik & J. W. Schrader: Interleukin (IL)-3 and granulocyte/macrophage colony-stimulating Factor, but not IL-4, induce tyrosine phosphorylation, activation, and association of SHPTP2 with Grb2 and phosphatidylinositol 3'-kinase. J Biol Chem 269, 23764-23768 (1994)
346. Liu, L., J. E. Damen, M. D. Ware & G. Krystal: Interleukin-3 induces the association of the inositol 5-phosphatase SHIP with SHP2. J Biol Chem 272, 10998-11001 (1997)
347. Bone, H., U. Dechert, F. Jirik, J. W. Schrader & M. J. Welham: SHP1 and SHP2 protein-tyrosine phosphatases associate with c after interleukin-3-induced receptor tyrosine phosphorylation. J Biol Chem 272, 14470-14476 (1997)
348. Craddock, B. L. & M. J. Welham: Interleukin-3 induces association of the protein-tyrosine phosphatase SHP2 and phosphatidylinositol 3-kinase with a 100-kDa tyrosine-phosphorylated protein in hemopoietic cells. J Biol Chem 272 (46), 29281-29289 (1997)
349. Sattler, M., R. Salgia, G. Shrikhande, S. Verma, J-L. Choi, L. R. Rohrschneider & J. D. Griffin: The phosphatidylinositol polyphosphate 5-phosphatase SHIP and the protein tyrosine phosphatase SHP-2 form a complex in hematopoietic cells which can be regulated by BCR/ABL and growth factors. Oncogene 15, 2379-2384 (1997)
350. Gu, H., J. D. Griffin & B. G. Neel: Characterization of two SHP-2-associated binding proteins and potential substrates in hematopoietic cells. J Biol Chem 272, 16421-16430 (1997)
351. Welham, M. J., H. Bone, M. Levings, L. Learmonth, L-M. Wang, K. B. Leslie, J. H. Pierce & J. W. Schrader: Insulin receptor substrate-2 is the major 170-kDa protein phosphorylated on tyrosine in response to cytokines in murine lymphohemopoietic cells. J Biol Chem 272, 1377-1381 (1997)
352. Pazdrak, K., T. Adachi & R. Alam: Src homology 2 protein tyrosine phosphatase (SHPTP2)/Src homology 2 phosphatase 2 (SHP2) tyrosine phosphatase is a positive regulator of the interleukin 5 receptor signal transduction pathways leading to the prolongation of eosinophil survival. J Exp Med 186, 561-568 (1997)
353. Boulton, T. G., N. Stahl & G. D. Yancopoulos: Ciliary neurotrophic factor/leukemia inhibitory factor/interleukin 6/oncostatin M family of cytokines induces tyrosine phosphorylation of a common set of proteins overlapping those induced by other cytokines and growth factors. J Biol Chem 269, 11648-11655 (1994)
354. Stahl, N., T. J. Farruggella, T. G. Boulton, Z. Zhong, J. E. Darnell Jr. & G. D. Yancopoulos: Choice of STATs and other substrates specified by modular tyrosine-based motifs in cytokine receptors. Science 267, 1349-1353 (1995)
355. Sengupta, T. K., E. M. Schmitt & L. B. Ivashkiv: Inhibition of cytokines and JAK-STAT activation by distinct signaling pathways. Proc Natl Acad Sci USA 93, 9499-9504 (1996)
356. Fukada, T., M. Hibi, Y. Yamanaka, M. Takahashi-Tezuka, Y. Fujitani, T. Yamaguchi, K. Nakajima & T. Hirano: Two signals are necessary for cell proliferation induced by a cytokine receptor gp130: Involvement of STAT3 in anti-apoptosis. Immunity 5, 449-460 (1996)
357. Sawada, T., K. L. Milarski & A. R. Saltiel: Expression of a catalytically inert Syp blocks activation of MAP kinase pathway downstream of $p21^{rras}$. Biochem Biophys Res Commun 214, 737-743 (1995)
358. Takada, T., T. Matozaki, H. Takeda, K. Fukunaga, T. Noguchi, Y. Fujioka, I. Okazaki, M. Tsuda, T. Yamao, F. Ochi & M. Kasuga: Roles of the complex formation of SHPS-1 with SHP-2 in insulin-stimulated mitogen-activated protein kinase activation. J Biol Chem 273, 9234-9242 (1998)
359. Seely, B. L., D. R. Reichart, P. A. Staubs, B. H. Jhun, D. Hsu, H. Maegawa, K. L. Milarski, A. R. Saltiel & J. M. Olefsky: Localization of the insulin-like growth factor I receptor binding sites for the SH2 domain proteins p85, Syp, and GTPase activating protein. J Biol Chem 270, 19151-19157 (1995)
360. Kazlauskas, A., G.-S. Feng, T. Pawson & M. Valius: The 64-kDa protein that associates with the platelet-derived growth factor receptor beta subunit via Tyr-1009 is the SH2-containing phosphotyrosine phosphatase Syp. Proc Natl Acad Sci USA 90, 6939-6942 (1993)
361. Lechleider, R. L., S. Sugimoto, A. M. Bennett, A. S. Kashishian, J. A. Cooper, S. E. Shoelson, C. T. Walsh & B. G. Neel: Activation of the SH2-containing phosphotyrosine phosphatase SH-PTP2 by its binding site, phosphotyrosine 1009, on the human platelet-derived growth factor receptor beta. J Biol Chem 268, 21478-21481 (1993)

362. Wong, L. & G. R. Johnson: Epidermal growth factor induces coupling of protein-tyrosine phosphatase 1D to GRB2 via the COOH-terminal SH3 domain of GRB2. J Biol Chem 271, 20981-20984 (1996)
363. Kharitonenkov, A., J. Schnekenburger, Z. Chen, P. Knyazev, S. Ali, E. Zwick, M. White & A. Ullrich: Adapter function of protein-tyrosine phosphatase 1D in insulin receptor/insulin receptor substrate-1 interaction. J Biol Chem 270, 29189-29193 (1995)
364. Rocchi, S., S. Tartare-Deckert, D. Sawka-Verhelle, A. Gamha & E. V. Obberghen: Interaction of SH2-containing protein tyrosine phosphatase 2 with the insulin receptor and the insulin-like growth factor-I receptor: Studies of the domains involved using the yeast two-hybrid system. Endocrinology 137, 4944-4952 (1996)
365. Noguchi, T., T. Matozaki, K. Horita, Y. Fujioka & M. Kasuga: Role of SH-PTP2, a protein-tyrosine phosphatase with Src homology 2 domains, in insulin-stimulated Ras activation. Mol Cell Biol 14, 6674-6682 (1994)
366. Tang, T. L., R. M. Freeman Jr., A. M. O'Reilly, B. G. Neel & S. Y. Sokol: The SH2-containing protein-tyrosine phosphatase SH-PTP2 is required upstream of MAP kinase for early Xenopus Development. Cell 80, 473-483 (1995)
367. Wright, J. H., P. Drueckes, J. Bartoe, Z. Zhao, S-H. Shen & E. G. Krebs: A role for the SHP-2 tyrosine phosphatase in nerve growth factor-induced PC12 cell differentiation. Mol. Biol. Cell. 8, 1575-1585 (1997)
368. Tauchi, T., G.-S. Feng, R. Shen, H. Y. Song, D. Donner, T. Pawson & H.E. Broxmeyer: SH2-containing phosphotyrosine phosphatase Syp is a target of p210bcr-abl tyrosine kinase. J Biol Chem 269, 15381-15387 (1994)
369. Okuda, K., T. R. Golub, D. G. Gilliland & J. D. Griffin: $p210^{BCR/ABL}$, $p190^{BCR/ABL}$, and TEL/ABL activate similar signal transduction pathways in hematopoietic cell lines. Oncogene 13, 1147-1152 (1996)
370. Tauchi, T., K. Miyazawa, G.-S. Feng, H. E. Broxmeyer & K. Toyama: A coiled-coil tetramerization domain of BCR-ABL is essential for the interactions of SH2-containing signal transduction molecules. J Biol Chem 272, 1389-1394 (1997)
371. Fujioka, Y., T. Matozaki, T. Noguchi, A. Iwamatsu, T. Yamao, N. Takahashi, M. Tsuda, T. Takada & M. Kasuga: A Novel Membrane glycoprotein, SHPS-1, that binds the SH2-domain-containing protein tyrosine phosphatase SHP-2 in response to mitogens and cell adhesion. Mol Cell Biol 16, 6887-6899 (1996)
372. Kharitonenkov, A., Z. Chen, I. Sures, H. Wang, J. Schilling & A. Ullrich: A family of proteins that inhibit signalling through tyrosine kinase receptors. Nature 386, 181-186 (1997)
373. Brooke, G. P., K. R. Parsons & C. J. Howard: Cloning of two members of the SIRPalpha family of protein tyrosine phosphatase binding proteins in cattle that are expressed on monocytes and a subpopulation of dendritic cells and which mediate binding to CD4 T cells. Eur J Immunol 28, 1-11 (1998)
374 Ochi, F., T. Matozaki, T. Noguchi, Y. Fujioka, T. Yamao, T. Takada, M. Tsuda, H. Takeda, K. Fukunaga, Y. Okabayashi & M. Kasuga: Epidermal growth factor stimulates the tyrosine phosphorylation of SHPS-1 and association of SHPS-1 with SHP-2, a SH2 domain-containing protein tyrosine phosphatase. Biochem Biophys Res Commun 239, 483-487 (1997)
375 Ye, Z. S. & D. Baltimore: Binding of Vav to Grb2 through dimerization of Src homology 3 domains. Proc Natl Acad Sci USA 91, 12629-12633 (1994)
376 Rogers, S., R. Wells & M. Rechsteiner: Amino acid sequences common to rapidly degraded proteins: the PEST hypothesis. Science 234, 364-368 (1986)
377 Flores, E., G. Roy, D. Patel, A. Shaw & M.L. Thomas: Nuclear localization of the PEP protein tyrosine phosphatase. Mol Cell Biol 14, 4938-4946 (1994)
378 Charest, A., J. Wagner, S. H. Shen, & M. L. Tremblay: Murine protein tyrosine phosphatase-PEST, a stable cytosolic protein tyrosine phosphatase. Biochem J 308, 425-432 (1995)
379 Cloutier, J. F. & A. Veillette: Association of inhibitory tyrosine protein kinase $p50^{csk}$ with protein tyrosine phosphatase PEP in T cells and other hemopoietic cells. EMBO J 15, 4909-4918 (1996)
380 Garton, A. & N. K. Tonks: PTP-PEST: a protein tyrosine phosphatase regulated by serine phosphorylation. EMBO J 13, 3763-3771 (1994)
381 Habib, T., R. Herrera & S. J. Decker: Activators of protein kinase C stimulate association of Shc and the PEST tyrosine phosphatase. J Biol Chem 269, 25243-25246 (1994)
382 Charest, A., J. Wagner, S. Jacob, C. J. McGlade & M. L. Tremblay: Phosphotyrosine-independent binding of SHC to the NPLH sequence of murine protein-tyrosine phosphatase-PEST. J Biol Chem 271, 8424-8429 (1996)
383 Charest, A., J. Wagner, M. Kwan & M. L. Tremblay: Coupling of the murine protein tyrosine phosphatase PEST to the epidermal growth factor (EGF) receptor through a Src homology (SH3) domain-mediated association with Grb2. Oncogene 14, 1643-1651 (1997)
384 Garton, A. J., M. R. Burnham, A. H. Bouton & N. K. Tonks: Association of PTP-PEST with the SH3 domain of $p130^{cas}$; a novel mechanism of protein phosphatase substrate recognition. Oncogene 15, 877 -885 (1997)
385 Davidson, D., J. F. Cloutier, A. Gregorieff & A. Veillette: Inhibitory tyrosine protein kinase $p50^{csk}$ is associated with protein-tyrosine phosphatase PTP-PEST in hemopoietic and non-hemopoietic cells. J Biol Chem 272, 23455-23462 (1997)
386 Shen, Y., G. Schneider, J. F. Cloutier, A. Veillette & M. D. Schaller: Direct association of protein-tyrosine phosphatase PTP-PEST with paxillin. J Biol Chem 273, 6474-6481 (1998)
387 Spencer, S., D. Dowbenko, J. Cheng, W. Li, J. Brush, S. Utzig, V. Simanis & L. A. Lasky: PSTPIP: A tyrosine phosphorylated cleavage furrow-associated protein that is a substrate for a PEST tyrosine phosphatase. J Cell Biol 138, 845-860 (1997)
388. Fankhauser, C., A. Raymond, L. Cerutti, S. Utzig, K. Hofmann & V. Simanis: The S. pombe cdc15 gene is a key element in the reorganization of F-actin at mitosis. Cell 82, 435-444 (1995)
389. Thomas, S., P. Soriano & A. Imamoto: Specific and redunant roles of Src and Fyn in organizing the cytoskeleton. Nature 376, 267-271 (1995)
390. Nada, S., M. Okada, A. MacAuley, J. A. Cooper & H. Nakagawa: Cloning of a complementary DNA for protein-tyrosine kinase that specifically phosphorylates a

negative regulatory site of $p60^{c\text{-}src}$. Nature 351, 69-72 (1991)

391. Bergman, M., V. Joukov, I. Virtanen & K. Alitalo: Overexpressed Csk tyrosine kinase is localized in focal adhesions, causes reorganization of $alpha_v beta_5$ integrin, and interferes with HeLa cell spreading. Mol Cell Biol 15, 711-722 (1995)

392. Sabe, H., A. Hata, M. Okada, H. Nakagawa & H. Hanafusa: Analysis of the binding of the Src homolgy 2 domain of Csk to tyrosine-phosphorylated proteins in the suppression and mitotic activation of c-Src. Proc Natl Acad Sci USA 91, 3984-3988 (1994)

393. Chow, L. M. L., M. Fournel, D. Davidson & A. Veillette: Negative regulation of T-cell receptor signalling by tyrosine protein kinase $p50^{csk}$. Nature 365, 156-160 (1993)

394. Bougeret, C., T. Delaunay, F. Romero, P. Jullien, H. Sabe, H. Hanafusa, R. Benarous & S. Fischer: Detection of a physical and functional interaction between Csk and Lck which involves the SH2 domain of Csk and is mediated by autophosphorylation of Lck on tyrosine 394. J Biol Chem 271, 7465-7472 (1996)

395. Oberdick, J., F. Levinthal & C. Levinthal: A purkinje cell differentiation marker shows a partial DNA sequence homology to the cellular sis/PDGF2 gene. Neuron 1, 367-376 (1998)

396. Arpin, M., E. Friederich, M. Algrain, F. Vernel & D. Lauvard: Functional differences between L- and T-plastin isoforms. J Cell Biol 127, 1995-2008 (1994)

397. Mafatia, S. M., R. A. Lue, D. Branton, & A. H. Chishti: Identification of the protein 4.1 binding interface on glycophorin C and p55, a homologue of the Drosphila discs-large tumor suppressor protein. J Biol Chem 270, 715-719 (1995)

398. Tsukita, S., K. Oishi, N. Sato, J. Sagara, A. Kawayi & S. Tsukita: ERM Family member as molecular linkers between the cell surface glycoprotein CD44 and actin-based cytoskeletons. J Cell Biol 126, 391-401 (1994)

399. Zhang, S. H., W. R. Eckberg, Q. Yang, A. A. Samatar & N. K. Tonks: Biochemical characterization of a human band 4.1 related protein-tyrosine phosphatase, PTPH1. J Biol Chem 270, 20067-20072 (1995)

400. Zhang, S. H. S., R. Kobayashi, P. R.Graves, H. Piwnica-Worms & N. K. Tonks: Serine phosphorylation-dependent association of the band 4.1-related protein-tyrosine phosphatase PTPH1 with 14-3-3 protein. J Biol Chem 272, 27281-27287 (1997)

401. Cho, K. O., C. A. Hunt & M. B. Kennedy: The rat brain postsynaptic density fraction contains a homolog of the Drosophila discs-large tumor suppressor protein. Neuron 9, 929-942 (1992)

402. Woods, D. F. & P. J. Bryant: ZO-1, DlgA and PSD-95/SAP90: Homologous proteins in tight, septate and synaptic cell junctions. Mech Dev 44, 85-89 (1993)

403. Doyle, D. A., A. Lee, J. Lewis, E. Kim & R. McKinnon: Crystal structures of a complexed and peptide-free membrane protein-binding domains: Molecular basis of peptide recognition by PDZ. Cell 85, 1067-1076 (1996).

404. Songyang, Z., A. S. Fanning, C. Fu, J. Xu, S. M. Mafatia, A. H. Chishti, A. Crompton, A. C. Chan, J. M. Anderson & L. C. Cantley: Recognition of unique carboxyl-terminal motifs by distinct PDZ domains. Science 275, 73-77 (1997)

405. Kim, E., T. A.Day, J. L. Bennett & R. A. Pax: Cloning and functional expression of a Shaker-related voltage-gated potassium channel gene from Schistosoma mansoni (Trematoda: Digenea). Parasitology 110, 171-180 (1995)

406. Niethammer, M., E. Kim, & M. Sheng: Interaction between the C terminus of NMDA receptor subunits and multiple members of the PSD-95 family of membrane-associated guanylate kinases. J Neurosci 16, 2157-2163 (1996)

407. Cuppen, E., H. Gertis, B. Peppers, B. Wieringa & W. Handriks: PDZ motif in PTP-BL and RIL bind to internal protein segments in the LIM domain protein RIL. Mol Biol Cell 9, 61-683 (1998)

408. Suda, T., T. Takahashi and S. Nagata: Molecular cloning and expression of the Fas ligand, a novel member of the tumor necrosis factor family. Cell 17, 1169-1178 (1993)

409. Cheng, J., T. Zhou, C. Liu, J. P. Shapiro, J. M. Brauer, M. C. Kiefer J. P. Barr & J. D. Mountz: Protection from Fas-mediated apoptosis by a soluble form of the Fas molecule. Science 263, 1759-1762 (1994)

410. Yanagisawa, J., M. Takahashi, H. Kanki, H. Yano-Yanagisawa, T. Tazunoki, E. Sawa, T. Nishitoba, M. Kamishohara, E. Kobayashi, S Kataoka and T. Sato: The molecular interaction of Fas and FAP-1. A tripeptide blocker of human Fas interaction with FAP-1 promotes Fas-induced apoptosis. J Biol Chem 272, 8539-8545 (1997)

411. Yuvaniyama, J., J. M. Denu, J. E. Dixon & M. A. Saper: Crystal structure of the dual specificity protein phosphatase VHR. Science 272, 1328-1331 (1996)

412. Zhou, G., J. M. Denu, L. Wu & J. E. Dixon: The catalytic role of Cys124 in the dual specificity phosphatase VHR. J Biol Chem 269, 28084-28090 (1994)

413. Denu, J. M. & J. E. Dixon: A catalytic mechanism for the dual-specific phosphatases. Proc Natl Acad Sci USA 92, 5910-5914 (1995)

414. Denu, J. M., G. Zhou, Y. Guo & J. E. Dixon: The catalytic role of aspartic acid-92 in a human dual-specific protein-tyrosine-phosphatase. Biochemistry 34, 3396-3403 (1995)

415. Denu, J. M., D. L. Lohse, J. Vijayalakshmi, M. A. Saper & J. E. Dixon: Visualization of intermediate and transition-state structures in protein-tyrosine phosphatase catalysis. Proc Acad Natl Sci USA 93, 2493-2498 (1996)

416. Hengge, A. C., J. M. Denu & J. E. Dixon: Transition-state structures for the native dual-specific phosphatase VHR and D92N and S131A mutants. contributions to the driving force for catalysis. Biochemistry 35, 7084-7092 (1996)

417. Kamb, A., A. Futeral, J. Rosenthal, C. Cochran, K. D. Harshman, Q. Liu, R. S. Phelps, S. V. Tavtigian, T. Tran, C. Hussey, R. Bell, Y. Miki, J. Swenson, M. R. Hobbs, J. Marks, M. Bennett, J. C. Barrett, R. W. Wiseman & D. Shattuck-Eidens: Localization of the VHR phosphatase gene and its analysis as a candidate for BRCA1. Genomics 23, 163-167 (1994)

418. Denu, J. M., G. Zhou, L. Wu, R. Zhao, J. Yuvaniyama, M. A. Saper & J. E. Dixon: The purification and characterization of a human dual-specific protein tyrosine phosphatase. J Biol Chem 270, 3796-3803 (1995)

419. Chen, L., J. Montaserat, D. S. Lawrence & Z.-Y. Zhang: VHR and PTP1 protein phosphatases exhibit remarkably different active site specificity toward low

molecular weight nonpeptidic substrates. Biochemistry 35, 9349-9354 (1996)
420. Dorfman, K., D. Carrasco, M. Gruda, C. Ryan, S. A. Lira & R. Bravo: Disruption of the erp/mkp-1 gene does not affect mouse development: normal MAP kinase activity in ERP/MKP-1-deficient fibroblasts. Oncogene 13, 925-931 (1996)
421. Charles, C. H., H. Sun, L. F. Lau & N. K. Tonks: The growth factor-inducible immediate-early gene 3CH134 encodes a protein-tyrosine-phosphatase. Proc Natl Acad Sci USA 90, 5292-6 (1993)
422. Sun, H., N. K. Tonks & D. Bar-Sagi: Inhibition of Ras-induced DNA synthesis by expression of the phosphatase MKP-1. Science 266, 285-288 (1994)
423. Steck, P. A., M. A. Pershouse, S. A. Jasser, W. K. A. Yung, H. Lin, A. H. Ligon, L. A. Langford, M. L. Baumgard, T. Hattier, T. Davis, C. Frye, R. Hu, B. Swedlund, D. H. F. Teng & S. V. Tavitigian: Identification of a candidate tumor suppressor gene, MMAC1, at chromosome 10q23.3 that is mutated in multiple advanced cancers. Nature Genet 15, 356-362 (1997)
424. Speaks, S. L., W. G. Sanger, A. S. Masih, D. S. Harrington, M. Hess & J. O. Armitage: Recurrent abnormalities of chromosome bands 10q23-25 in non-Hodgkin's lymphoma. Genes Chromosomes Cancer 5, 239 (1992)
425. Takeuchi, S., C. R. Bartram, M. Wada, A. Reiter, Y. Hatta, T. Seriu, E. Lee, C. W. Miller, I. Miyoshi & H. P. Koeffler: Allelotype analysis of childhood acute lymphoblastic leukemia. Cancer Res 55, 5377-5382 (1995)
426. Teng, D. H., R. Hu, H. Lin, T. Davis, D. Iliev, C. Frye, B. Swewdlund, K. L. Hansen, V. L. Vinson, K. L. Gumpper, L. Ellis, A. EI-Naggar, M. Frazier, S. Jasser, L. A. Langford, J. Lee, G. B. Mills, M. A. Pershouse, R. E. Pollack, C. Tornos, P. Troncoso, W. K. A. Yung, G. Fujii, A. Berson, R. Bookstein & J. B. Bolen: MMAC1/PTEN mutations in primary tumor specimens and tumor cell lines. Cancer Res 57, 5221-5225 (1997)
427. Gronbaek, K., J. Zeuthen, P. Guldberg, E. Ralfkiaer, K. Hou-Jensen: Alterations of the MMAC1/PTEN gene in lymphoid malignancies. Blood 91, 4388-4390 (1998)
428. Eng, C., V. Murday, S. Seal, S. Mohammed, S. V. Hodgson, M. A. Chaudary, I. S. Fentiman, B. A. J. Ponder & R. A. Eeles: Cowden syndrome and Lhermitte-Duclos disease in a family: a single genetic syndrome with pleiotropy? J Med Genet 31, 458-461 (1994)
429. Marsh, D. J., P. L. M. Dahia, Z. Zheng, D. Liaw, R. Parsons, R. J. Gorlin & Eng C: Germline mutations in PTEN are present in Bannayan-Zonana syndrome. Nature Genet 16, 333-334 (1997)
430. Myers, M. P., J. Stolarov, C. Eng, J. Li, S. I. Wang, M. H. Wigler, R. Parsons & N. K. Tonks: P-TEN, the tumor suppressor from human chromosome 10q23, is a dual-specificity phosphatase. Proc Natl Acad Sci USA 94, 9052-9057 (1997)
431. Auger, K. R. & L. C. Cantley: Novel polyphosphoinositides in cell growth and activation. Cancer Cells 3, 263-275 (1991)
432. He, H., T. Watanabe, X. Zhan, C. Huang, E. Schuuring, K. Fukami, T. Takenawa, C. C. Kumar, R. J. Simpson, H. Maruta: Role of phosphatidylinositol 4,5-bisphosphate in Ras/Rac-induced disruption of the cortactin-actomyosin II complex and malignant transformation. Mol Cell Biol 18, 3829-3837 (1998)
433. Liaw, D., D. J. Marsh, J. Li, P. L. M. Dahia, S. I. Wang, Z. Zheng, S. Bose, K. M. Call, H.C. Tsou, M. Peacocket, C. Eng & R. Paesons: Germline mutations of the PTEN gene in Cowden disease, an inherited breast and thyroid cancer syndrome. Nature Genet 16, 64-67 (1997)
434. Rhei, E., L. Kang, F. Bogomolniy, M. G. Federici, P. I. Borgen & J. Boyd: Mutation analysis of the putative tumor suppressor gene PTEN/MMAC1 in primary breast carcinomas. Cancer Res 57, 3657-3659 (1997)
435. Tashiro, H., M. S. Blazes, R. Wu, K. R. Cho, S. Bose, S. I. Wang, J. Li, R. Parsons & H. Ellenson: Mutations in PTEN are frequent in endometrial carcinoma but rare in other common gynecological malignancies. Cancer Res 57, 3935-3940 (1997)
436. Nelen, M. R., W. C. G. Staveren, E. A. J. Peeters, M. B. Hassel, R.J. Gorlin, H. Hamm, C. F. Lindboe, J. P. Fryns, R. H. Sijmons, S. D. Geoffrey Woods, E. C. M. Mariman, G. W. Padberg & H. Kremer: Germline mutation in the PTEN/MMAC1 gene in patients with Cowden disease. Hum Mol Genet 6, 1383-1387 (1997)
437. Myers, M. P. & N. K. Tonks: PTEN: Sometimes taking it off can be better than leaving it on. Am J Hum Genet 61, 1234-1238 (1997)
438. Barford, D., Z. Jia & N. K. Tonk: Protein tyrosine phosphatases take off. Nature Struct Biol 2, 1043-1053 (1995)
439. Furnari, F. B., H. Lin, H. S. Huang & W. K. Cavenee: Growth suppression of glioma cells by PTEN requires a functional phosphatase catalytic domain. Proc Natl Acad Sci USA 94, 12479-12484 (1997)
440. Smith, A. & A. Ashworth: Cancer predisposition: Where's the phosphate? Curr Biol 8, R241-243 (1998)
441. Tamura, M., J. Gu, K. Matsumoto, S. Aota, R. Parsons & K. M. Yamada: Inhibition of cell migration, spreading, and focal adhesions by tumor suppressor PTEN. Science 280, 1614-1617 (1998)
442. Jinno, S., K. Suto, A. Nagata, M. Igarash, Y. Kanaoka, H. Nojima & H. Okayama: Cdc25A is a novel phosphatase functioning early in the cell cycle. EMBO J 13, 1549-1556 (1994)
443. Sebastian, B., A. Kakizuka & T. Hunter: Cdc25M2 activation of cyclin-dependent kinases by dephosphorylation of threonine-14 and tyrosine-15.Proc Natl Acad Sci USA 90, 3521-3524 (1993)
444. Lammer, C., S. Wagerer, R. Saffrich, D. Mertens, W. Ansorge & I. Hoffmann: The cdc25B phosphatase is essential for the G2/M phase transition in human cells.J Cell Sci 111, 2445-2453 (1998)
445. Baldin, V., A. Cans, G. Superti-Furga & B. Ducommun: Alternative splicing of the human CDC25B tyrosine phosphatase. Possible implications for growth control? Oncogene 14, 2485-2495 (1997)
446. Galaktionov, K., A. K. Lee, J. Eckstein, G. Draetta, J. Meckler, M. Loda & D. Beach: CDC25 phosphatases as potential human oncogenes. Science 269, 1575-1577 (1995)
447. Jackman, M. R. & J. N. Pines: Cyclins and the G2/M transition. Cancer Surv 29, 47-73 (1997)
448. Doree, M. & S. Galas: The cyclin-dependent protein kinases and the control of cell division. FASEB J 8, 1114-1121 (1994)
449. Heinrikson, R. L.: Purification and characterization of a low molecular weight acid phosphatase from bovine liver. J Biol Chem 244, 299-307 (1969)

450. Dissing, J., A. H. Johnsen & G. F. Sensabaugh: Human red cell acid phosphatase (ACP1). The amino acid sequence of the two isozymes Bf and Bs encoded by the ACP1*B allele. J Biol Chem 266, 20619-20625 (1991)
451. Dissing, J. & A. H. Johnsen: Human red cell acid phosphatase (ACP1): The primary structure of the two pairs of isozymes encoded by the ACP1*A and ACP1*C alleles. Biochim Biophys Acta 1121, 261-268 (1992)
452. Zhang, M., C. V. Stauffacher & R. L. Van Etten: The three dimensional structure, chemical mechanism and function of the low molecular weight protein tyrosine phosphatases. Adv Prot Phosphatases 9, 1-23 (1995)
453. Mitchell Bryson, G. L., H. Massa, B. J. Trask & R. L. Van Etten: Gene structure, sequence, and chromosomal localization of the human red cell-type low-molecular-weight acid phosphotyrosyl protein phosphatase gene, ACP1. Genomics 30, 133-140 (1995)
454. Tailor, P., J. Gilman, S. Williams & T. Mustelin: A novel isoform of the low molecular weight protein tyrosine phosphatase, LMPTP-C, arising from alternative mRNA splicing. Submitted (1998)
455. Ostanin, K., C. Pokalsky, S. Wang & R. L. Van Etten: Cloning and characterization of a *Saccharomyces cerevisiae* gene encoding the low molecular weight protein-tyrosine phosphatase. J Biol Chem 270, 18491-18499 (1995)
456. Mondesert, O., S. Moreno & P. Russell: Low molecular weight protein-tyrosine phosphatases are highly conserved between fission yeast and man. J Biol Chem 269, 27996-27999 (1994)
457. Grangeasse, C., P. Doublet, C. Vincent, E. Vaganay, M. Riberty, B. Duclos & A. J. Cozzone: Functional characterization of the low-molecular-mass phosphotyrosine-protein phosphatase of *Acinetobacter johnsonii*. J Mol Biol 278, 339-347 (1998)
458. Ramponi, G., G. Manao, G. Camici, G. Cappugi, M. Ruggiero & D. P. Bottaro: The 18 kDa cytosolic acid phosphatase from bovine liver has phosphotyrosine phosphatase activity on the autophosphorylated epidermal growth factor receptor. FEBS Lett 250, 469-473 (1989)
459. Cirri, P., P. Chiarugi, G. Camici, G. Manao, G. Raugie, G. Cappugi & G. Ramponi: The role of Cys12, Cys17 and Arg18 in the catalytic mechanism of low-Mr cytosolic phosphotyrosine protein phosphatase. Eur J Biochem 214, 647-657 (1993)
460. Zhang, M., C. V. Stauffacher, D. Lin & R. L. Van Etten: Crystal structure of a human low molecular weight phosphotyrosyl phosphatase. J Biol Chem 273, 21714-21720 (1998)
461. Su, X.-D., N. Taddei, S. Massimo, G. Ramponi & P. Nordlund: The crystal structure of a low-molecular-weight phosphotyrosine protein phosphatase. Nature 370, 575-578 (1994)
462. Ramponi, G.: The low Mr cytosolic phosphotyrosine protein phosphatase. Adv. Prot. Phosphatases 8, 1-25 (1994).
463. Ramponi, G., M. Ruggiero, G. Raugei, A. Berti, A. Modesti, D. Degl'Innocenti, L. Magnelli, C. Pazzagli, V. P. Chiarugi & G. Camici: Overexpression of a synthetic phosphotyrosine protein phosphatase gene inhibits normal and transformed cell growth. Int J Cancer 51, 652-656 (1992)
464. Ruggiero, M., C. Pazzagli, S, Rigacci, L. Magnelli, G. Raugie, A. Berti, V. P. Chiarugi, J. H. Pierce, G. Camici & G. Ramponi: Negative growth control by a novel low Mr phosphotyrosine protein phosphatase in normal and transformed cells. FEBS Lett 326, 294-298 (1993)
465. Berti, A., S. Rigacci, G. Raugei, D. Degl'Innocenti & G. Ramponi: Inhibition of cellular response to platelet-derived growth factor by low Mr phosphotyrosine protein phosphatase overexpression. FEBS Lett 349, 7-12 (1994)
466. Chiarugi, P., P. Cirri, F. Marra, G. Raugei,T. Fiasci, G. Camici, G. Manao, R. G. Romanelli & G. Ramponi: The Src and signal transducers and activators of transcription pathways as specific targets for low molecular weight phosphotyrosine-protein phosphatase in platelet-derived growth factor signaling. J Biol Chem 273, 6776-6785 (1998)
467. Chiarugi, P., P. Cirri, F. Marra, G. Raugie, G. Camici, G. Manao & G. Ramponi: LMW-PTP is a negative regulator of insulin-mediated mitotic and metabolic signaling. Biochem Biophys Res Commun 238, 676-682 (1997)
468. Cates, C. A., R. L. Michael, K. R. Stayrook, K. A. Harvey, Y. D. Burke, S. K. Randall, P. L. Crowell & D. N. Crowell: Prenylation of oncogenic human PTP(CAAX) protein tyrosine phosphatases. Cancer Lett 110, 49-55 (1996**)**
469. Diamond, R. H., C. Peters, S. P. Jung, L. E. Greenbaum, B. A. Haber, D. G. Silberg, P. G. Traber & R. Taub: Expression of PRL-1 nuclear PTPase is associated with proliferation in liver but with differentiation in intestine. Am J Physiol 271, 121-129 (1996)
470. Jin, Y.-J., J. Friedman & S. J. Burakoff: Regulation of tyrosine phosphorylation in isolated T cell membrane by inhibition of protein tyrosine phosphatases. J Immunol 161, 1743-1750
471. Taetle, R., H. Ostergaard, M. Smedsrud & I. Trowbridge: Regulation of CD45 expression in human leukemia cells. Leukemia 5, 309-314 (1991)
472. Kawano, S., E. Tatsumi, N.Yoneda, A. Tani & F. Nakamura: Expression pattern of CD45 RA/RO isoformic antigens in T-lineage neoplasms. Am J Hematol 49, 6-14 (1995)
473. Loda, M., P. Capodieci, R. Mishra, H. Yao, C. Coless, W. Grigioni, Y. Wang, C. Magi-Galluzzi & P. J. Stork: Expression of mitogen-activated protein kinase phosphatase-1 in the early phases of human epithelial carcinogenesis. Am J Pathol 149, 1553-1564 (1996)

Key words: Review, Phosphatases, PTPases, PTKs, Lck, Fyn, Syk, Zap-70, T cell activation, HePTP, STEP, PCPTP, PTP1B, TCPTP, SHP1, SHP2, PEP, PTP-PEST, PTP-HSCF, PTP-MEG2, PTPH1, PTP-MEG1, FAP-1, PTP-BAS, PTP36, VHR, Pac-1, MKP-1, MKP-2, MKP-3, MKP-4, MKP-X, B23, hVH4, M3/6, PTEN, LMPTP, PRL-1, OV-1, PRL-2, PRL-3

Send correspondence to: Tomas Mustelin, M.D., Ph.D., Division of Cell Biology, La Jolla Institute for Allergy and Immunology, 10355 Science Center Drive, San Diego, CA 92121, USA. E-mail: tomas_mustelin@liai.org