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Protein Tyrosine Phosphatases in the Human Genome

Review

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Tyrosine phosphorylation is catalyzed by protein tyrosine kinases, which are represented by 90 genes in the human genome. Here, we present the set of 107 genes in the human genome that encode members of the four protein tyrosine phosphatase (PTP) families. The four families of PTPases, their substrates, structure, function, regulation, and the role of these enzymes in human disease will be discussed.

Introduction

Tyrosine phosphorylation is a fundamental mechanism for numerous important aspects of eukaryote physiology, as well as human health and disease (Hunter, 1987; Mustelin et al., 2002a, 2002b). Compared to protein phosphorylation in general, phosphorylation on tyrosine is extensively utilized only in multicellular eukaryotes. Tyrosine phosphorylation is used for communication between and within cells, the shape and motility of cells, decisions to proliferate versus differentiate, cellular processes like regulation of gene transcription, mRNA processing, and transport of molecules in or out of cells. Tyrosine phosphorylation also plays an important role in the coordination of these processes among neighboring cells in embryogenesis, organ development, tissue homeostasis, and the immune system. Abnormalities in tyrosine phosphorylation play a role in the pathogenesis of numerous inherited or acquired human diseases from cancer to immune deficiencies.

Although it is generally agreed that tyrosine phosphorylation is regulated by the equal and balanced action of protein tyrosine kinases (PTKs) and protein tyrosine phosphatases (PTPs), proportionately much more research has focused on PTKs. This is partly for historical reasons: the first PTP was purified (Charbonneau et al., 1989) and cloned (Guan et al., 1990) ten years after the first PTK (Czernilofsky et al., 1980). Recent findings have now led to the emerging recognition that PTPs play specific and active, even dominant, roles in setting the levels of tyrosine phosphorylation in cells and in the regulation of many physiological processes (Fischer et al., 1991; Walton and Dixon, 1993; Tonks and Neel, 1996; Mustelin et al., 2002a, 2002b; Mustelin and Taskén, 2003).

An important step toward a better appreciation of the PTPs is the clarification of the set of genes in the human genome that encode PTPs. This knowledge will allow for a more global approach to key questions in the PTP field and the regulation of tyrosine phosphorylation-dependent cellular processes in health and disease.

The 107 Human PTP Genes

Starting with the amino acid sequence of all published PTPs, we used conserved catalytic motifs and whole PTP domains to search the publicly available databases, as well as the SEED database, for genes encoding PTPs or PTP-like genes. Two of our novel PTPs were also found in the Celera and Incyte databases. The genomic locus, exon-intron structure, expression data, and mouse orthologs were clarified for each PTP. Previously unpublished PTPs were subjected to a more thorough investigation to verify that they represented bona fide expressed genes with orthologs in the mouse and other organisms. Many of these genes have also recently been experimentally verified in our laboratories. The results of this work are a list (Table 1) of all genes in the human genome that encode PTP family members, here defined as all known protein tyrosine phosphatases plus all proteins that contain a domain homologous to the catalytic domain of these known PTPs. The list contains 107 genes, 105 of which have a mouse ortholog (one of the missing genes has a rat ortholog). In addition, we estimate that there are at least as many PTP pseudogenes and there are a few bona fide genes (e.g., paladin, KIAA1274) that encode proteins that contain incomplete or distant PTP-like domains. Of the 107 human genes, 106 are covered by expressed sequence tags (ESTs). The only gene lacking EST coverage is *DUSP27* (*DUPD1*), which earlier was predicted to encode a phosphatase with an N-terminal cyclophilin-like domain. We have been able to amplify a partial cDNA of this gene from testis and muscle mRNA, demonstrating that this gene, too, is expressed. *DUSP27* has four exons and is located at 10q22.3 adjacent to *DUSP13* at 10q22.2, which in fact consists of two phosphatase genes, which we designate as *DUSP13A* and *DUSP13B* (encoding BEDP and TMDP, respectively), which are similar to the catalytic domain of *DUSP27*. In the mouse genome, the corresponding location on chromosome 14 also contains three PTP genes in tandem, although the sequence of *DUSP27* is incomplete. In the chimpanzee genome, there is also a *DUSP27* gene, which is 99% identical to the human within the four exons, but differs in the length of some introns. Thus, it appears that an ancestral gene was triplicated (or duplicated twice) before mice and primates diverged during the Cretaceous, 144–165 million years ago.

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Table 1. The Set of PTP Genes in the Human Genome

Gene	Protein, Synonyms	Chr. Loc.	ESTs	Mouse
A. Class I Cys-Gased PTPs (99 Genes)				
A. 1. Classical PTPs (38 Genes)				
A. 1. 1. Transmembrane Classical PTPs (21 Genes)				
1. *PTPRA*	RPTPα	20p13	YES	YES
2. *PTPRB*	RPTPβ	12q15-q21	YES	YES
3. *PTPRC*	CD45, LCA	1q31-q32	YES	YES
4. *PTPRD*	RPTPδ	9p23-p24.3	YES	YES
5. *PTPRE*	RPTPε	10q26	YES	YES
6. *PTPRF*	LAR	1p34	YES	YES
7. *PTPRG*	RPTPγ	3p21-p14	YES	YES
8. *PTPRH*	SAP1	19q13.4	YES	YES
9. *PTPRJ*	DEP1, CD148, RPTPη	11p11.2	YES	YES
10. *PTPRK*	RPTPκ	6q22.2-23.1	YES	YES
11. *PTPRM*	RPTPμ	18p11.2	YES	YES
12. *PTPRN*	IA-2, Islet cell antigen 512	2q35-q36.1	YES	YES
13. *PTPRN2*	PTPRP, RPTPπ, IA-2β, phogrin,	7q36	YES	YES
14. *PTPRO*	GLEPP1/PTP-U2/PTPROτ isoforms A/B/C	12p13.3-p13.2	YES	YES
15. *PTPRQ*	PTPS31	12q21.31	YES	YES
16. *PTPRR*	PTP-SL, PCPTP,PTPBR7, PC12-PTP1	12q15	YES	YES
17. *PTPRS*	RPTPσ	19p13.3	YES	YES
18. *PTPRT*	RPTPρ	20q12-q13	YES	YES
19. *PTPRU*	PTPJ/PTP-U1/PTPRomicron isoforms 1/2/3	1p35.3-p35.1	YES	YES
20. *PTPRV*	OST-PTP	1q32.1	YES	YES
21. *PTPRZ*	RPTPζ	7q31.3	YES	YES
A. 1.2. NRPTPs (17 Genes)				
22. *PTPN1*	PTP1B	20q13.1-13.2	YES	YES
23. *PTPN2*	TCPTP, MPTP, PTP-S	18p11.3-11.2	YES	YES
24. *PTPN3*	PTPH1	9q31	YES	YES
25. *PTPN4*	PTP-MEG1, TEP	2q14.2	YES	YES
26. *PTPN5*	STEP	11p15.1	YES	YES
27. *PTPN6*	SHP1, PTP1C, SH-PTP1, HCP	12p12-13	YES	YES
28. *PTPN7*	HePTP, LCPTP	1q32.1	YES	YES
29. *PTPN9*	PTP-MEG2	15q23	YES	YES
30. *PTPN11*	SHP2, SH-PTP2, Syp, PTP1D, PTP2C, SH-PTP3	12q24.1	YES	YES
31. *PTPN12*	PTP-PEST, PTP-P19, PTPG1)	7q11.23	YES	YES
32. *PTPN13*	PTP-BAS, FAP-1, PTP1E, RIP, PTPL1, PTP-BL	4q21.3	YES	YES
33. *PTPN14*	PTP36, PEZ, PTPD2	1q32.2	YES	YES
34. *PTPN18*	PTP-HSCF, PTP20, BDP	2q21.2	YES	YES
35. *PTPN20*	TypPTP	10q11.22	YES	YES
36. *PTPN21*	PTPD1, PTP2E, PTP-RL10	14q31.3	YES	YES
37. *PTPN22*	LYP, PEP	1p13.3-p13.1	YES	YES
38. *PTPN23*	HD-PTP, HDPTP, PTP-TD14, KIAA1471, DKFZP564F0923	3p21.3	YES	YES
A. 2. DSPs or VH1-like (61 Genes)				
A. 2. 1. MKPs (11 Genes)				
39. *DUSP1*	MKP-1, 3CH134, PTPN10, erp, CL100/ HVH1	5q34	YES	YES
40. *DUSP2*	PAC-1	2q11	YES	YES
41. *DUSP4*	MKP-2, hVH2/TYP1	8p12-p11	YES	YES
42. *DUSP5*	hVH3/B23	10q25	YES	YES
43. *DUSP6*	PYST1, MKP-3/rVH6	12q22-q23	YES	YES
44. *DUSP7*	PYST2, B59, MKP-X	3p21	YES	YES
45. *DUSP8*	hVH5, M3/6, HB5	11p15.5	YES	YES
46. *DUSP9*	MKP-4, Pyst3	Xq28	YES	YES
47. *DUSP10*	MKP-5	1q41	YES	YES
48. *DUSP16*	MKP-7, MKP-M	12p13	YES	YES
49. *MK-STYX*	MK-STYX	7q11.23	YES	YES

(*continued*)

Table 1. Continued

Gene	Protein, Synonyms	Chr. Loc.	ESTs	Mouse
A. 2. 2. Atypical DSPs (19 Genes)				
50. *DUSP3*	VHR, T-DSP11	17q21	YES	YES
51. *DUSP11*	PIR1	2p13.1	YES	YES
52. *DUSP12*	HYVH1, GKAP, LMW-DSP4	1q21-q22	YES	YES
53. *DUSP13A*[a]	BEDP	10q22.2	YES	YES
54. *DUSP13B*[a]	TMDP, TS-DSP6	10q22.2	YES	YES
55. *DUSP14*	MKP6, MKP-L	17q12	YES	YES
56. *DUSP15*	VHY, Q9H1R2	20q11.21	YES	YES
57. *DUSP18*	*DUSP20*, LMW-DSP20	22q12.2	YES	YES
58. *DUSP19*	*DUSP17*, SKRP1, LDP-2, TS-DSP1	2q32.1	YES	YES
59. *DUSP21*	LMW-DSP21, BJ-HCC-26 tumor antigen	Xp11.4-p11.23	YES	YES
60. *DUSP22*	VHX, MKPX, JSP1, LMW-DSP2, TS-DSP2, JKAP	6p25.3	YES	YES
61. *DUSP23*	MOSP, similar to RIKEN cDNA 2810004N20	11p11.2	YES	YES
62. *DUSP24*	MGC1136	8p12	YES	YES
63. *DUSP25*	VHZ, FLJ20442, LMW-DSP3	1q23.1	YES	YES
64. *DUSP26*	VHP, "similar to RIKEN cDNA 0710001B24"	2q37.3	YES	YES
65. *DUSP27*[b]	*DUPD1*, FMDSP, "similar to cyclophilin"	10q22.3	NO[c]	YES
66. *EPM2A*	Laforin	6q24	YES	YES
67. *RNGTT*	mRNA capping enzyme	6q16	YES	YES
68. *STYX*	STYX	14	YES	YES
A. 2. 3. Slingshots (3 Genes)				
69. *SSH1*	SSH1, slingshot 1	12q24.12	YES	YES
70. *SSH2*	SSH2, slingshot 2	17q11.2	YES	YES
71. *SSH3*	SSH3, slingshot 3	11q13.1	YES	YES
A. 2. 4. PRLs (3 Genes)				
72. *PTP4A1*	PRL-1	6q12	YES	YES
73. *PTP4A2*	PRL-2, OV-1	1p35	YES	YES
74. *PTP4A3*	PRL-3	8q24.3	YES	YES
A. 2. 5. CDC14s (4 Genes)				
75. *CDC14A*	CDC14A	1p21	YES	YES
76. *CDC14B*	CDC14B	9q22.33	YES	YES
77. *CDKN3*	KAP	14q22	YES	YES
78. *PTP9Q22*	PTP9Q22	9q22.32	YES	YES
A. 2. 6. PTENs (5 Genes)				
79. *PTEN*	PTEN, MMAC1, TEP1	10q23.3	YES	YES
80. *TPIP*	TPIPα, TPTE and PTEN homologous	13q12.11	YES	YES
81. *TPTE*	PTEN-like, PTEN2	21p11	YES	YES
82. *TNS*	Tensin	2q35-q36	YES	YES
83. *TENC1*	C1-TEN, TENC1, KIAA1075	12q13.13	YES	YES
A. 2. 7. Myotubularins (16 Genes)				
84. *MTM1*	myotubularin	Xq28	YES	YES
85. *MTMR1*	MTMR1	Xq28	YES	YES
86. *MTMR2*	MTMR2	11q22	YES	YES
87. *MTMR3*	MTMR3, FYVE-DSP1	22q12.2	YES	YES
88. *MTMR4*	MTMR4, FYVE-DSP2	17q22-q23	YES	YES
89. *MTMR5*	MTMR1, SBF1	22q13.33	YES	YES
90. *MTMR6*	MTMR6	13q12	YES	YES
91. *MTMR7*	MTMR7	8p22	YES	YES
92. *MTMR8*	MTMR8	Xq11.2	YES	NO
93. *MTMR9*	MTMR9, LIP-STYX	8p23-p22	YES	YES
94. *MTMR10*	MTMR10	15q13.1	YES	NO[d]
95. *MTMR11*	MTMR11CRA α/β	1q12.3	YES	YES
96. *MTMR12*	MTMR12, 3-PAP	5p13.3	YES	YES
97. *MTMR13*	MTMR13, SBF2, CMT4B2	11p15.3	YES	YES
98. *MTMR14*	FLJ22075, hJumpy, hEDTP	3p26	YES	YES
99. *MTMR15*	KIAA1018	15q13.1	YES	YES

(*continued*)

Table 1. Continued

Gene	Protein, Synonyms	Chr. Loc.	ESTs	Mouse
B. Class II Cys-Based PTPs (1 Gene)				
100. *ACP1*	LMPTP, low Mr PTP, LMWPTP, BHPTP	2p25	YES	YES
C. Class III Cys-Based PTPs (3 Genes)				
101. *CDC25A*	CDC25A	3p21	YES	YES
102. *CDC25B*	CDC25B	20p13	YES	YES
103. *CDC25C*	CDC25C	5q31	YES	YES
D. Asp-Based PTPs (4 Genes)				
104. *EYA1*	Eya1	8q13.3	YES	YES
105. *EYA1*	Eya2	20q13.1	YES	YES
106. *EYA1*	Eya3	1p36	YES	YES
107. *EYA1*	Eya4	6q23	YES	YES
107. Total				

Includes all known PTPs in the published literature, verified PTPs or dual-specificity phosphatases in public data bases, and ORFs found by iterative BLAST searches with all the other sequences to find related genes and to assign alternatively spliced forms to the correct genes. To exclude synonyms, splice variants, and incorrectly assembled sequences, a data base with the amino sequences was created. To exclude pseudogenes, EST and other expression data bases were consulted, and the exon-intron structures and chromosomal locations of every gene were determined.

[a] the human *DUSP13* gene contains two DSP genes: *DUSP13A* (BEDP; 3 exons), two noncoding exons, followed by *DUSP13B* (TMDP; three exons). In the mouse, the two genes are designated as separate genes.

[b] formerly *DUPD1,* but does not contain an N-terminal cyclophilin domain, as originally annotated. The mouse ortholog also lacks cyclophilin domain. Thus, the name *DUPD1* is a misnomer.

[c] we have verified its expression by PCR amplification of a partial cDNA.

[d] there is a rat homolog, suggesting that a mouse homolog probably does exist.

While the 38 classical PTPs have all been published (reviewed in Andersen et al. [2004]), as many as nine of the 107 human PTP genes have not been previously reported (Supplemental Table S1 at http://www.cell.com/cgi/content/full/117/6/699/DC1), although their genomic loci, exon/intron structure, and, in most cases, their homology to PTPs were recognized in databases. These genes include six small phosphatases, *DUSP15*, *DUSP27* (*DUPD1*), and four genes for which we propose the genomic designations *DUSP23*, *DUSP24*, *DUSP25*, and *DUSP26*. The protein encoded by *DUSP15* is a catalytically active PTP we term VHY (VH1-related member Y; Alonso et al., 2004), closely related to VHX encoded by *DUSP22*. The 150 amino acid residue VHZ (VH1-related member Z) encoded by *DUSP25* is the smallest of all catalytically active PTPs (Alonso et al., 2004) and is remarkably well conserved through evolution and even has a 147 amino acid homolog in *Thermococcus kodakaraensis*, which is 30.3% identical and 49.7% similar over 145 residues. We have verified the existence of a 16 kDa VHZ protein in human cells by immunoblotting. The novel PTPs also include two myotubularin-related proteins, for which we propose the genomic designation *MTMR14* and *MTMR15*. The former is the human ortholog of the *Sarcophaga peregrina* egg-derived tyrosine phosphatase (Yamaguchi et al., 1999) and the *Drosophila melanogaster* gene *jumpy* (Seroude et al., 2002), the mutation of which causes a muscle defect characterized by excessive vibrations of the flight muscles (J.D. and M.J. Wishart, unpublished observation). *MTMR15* encodes a catalytically inactive member of the myotubularin group.

Why So Many PTPs?

The number of genes in the human genome that encode members of the PTP families is higher than anticipated and exceeds the number of genes encoding PTKs (Manning et al., 2002). However, a direct comparison of the two numbers, 107 and 90, respectively, is not completely fair: of the 107 PTP genes, 11 are catalytically inactive, 2 dephosphorylate mRNA, and 13 dephosphorylate inositol phospholipids. Thus, 81 PTPs are active protein phosphatases with the ability to dephosphorylate phosphotyrosine. Of the 90 PTKs, 85 are through to be catalytically active. Thus, the numbers of active PTPs and PTKs are very similar and one can therefore assume that they have comparable substrate specificities. Both types of enzymes also display comparable tissue distribution patterns, from ubiquitous to cell type restricted, so that individual cells express 30%–60% of the entire complement of PTPs and PTKs. Neuronal and hematopoietic cells may express even higher portions of all PTPs. That individual PTPs have nonredundant functions is also well illustrated by the unique phenotypes of many of the reported gene deletions in mice. For example, deletion of *PTPN22* (*PTPN8* in the mouse) causes excessive expansion of memory T lymphocytes, prolonged secondary immune responses, and autoimmunity (Hasegawa et al., 2004). A polymorphism in the human *PTPN22* gene also correlates with autoimmune diabetes in humans (Bottini et al., 2004). Other human diseases caused by mutations in PTP genes (see discussion below) also support the notion that individual PTPs have unique and important functions.

Classification of the 107 PTPs into Four Families

Based on the amino acid sequences of their catalytic domains, the PTPs can be grouped into four separate families, each with a range of substrate specificities (Figure 1). Class I cysteine-based PTPs constitute by far the largest family and contain the 38 well-known "classical" PTPs (Andersen et al., 2004), which are strictly tyrosine specific and all have mouse orthologs, and the 61 VH1-like, "dual-specific" protein phospha-

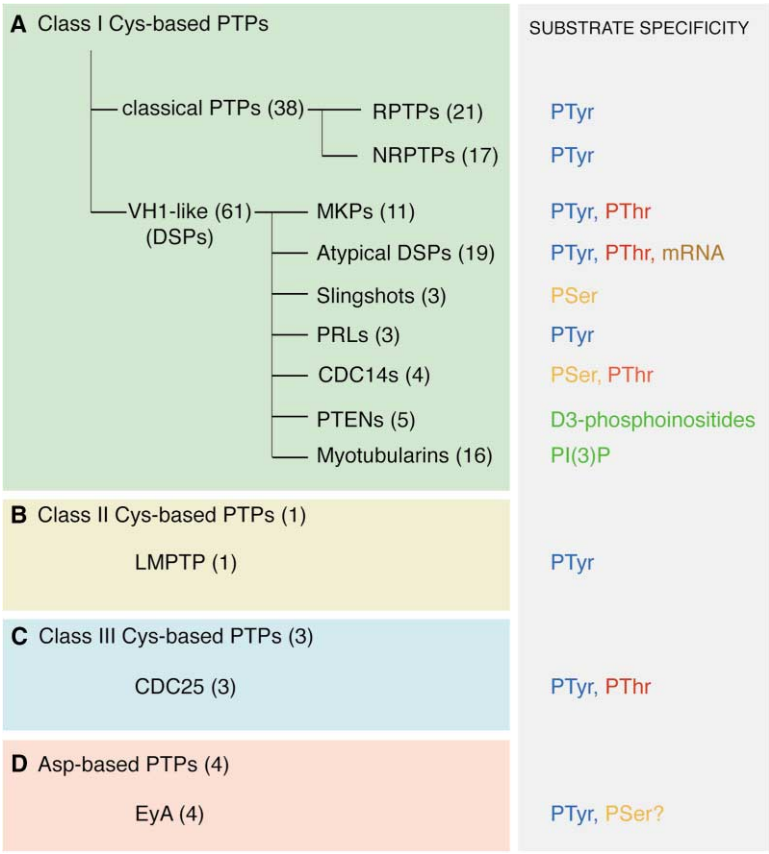

Figure 1. Classification and Substrate Specificity of PTPs

The PTP families are color coded: class I Cys-based PTPs (green), class II Cys-based PTPs (pale yellow), class III Cys-based PTPs (pale blue), and Asp-based PTPs (pink). The substrate specificity of each group or class of PTPs is listed.

tases (DSPs), which is the most diverse group in terms of substrate specificity (Figure 1). All Class I enzymes have evolved from a common ancestor, based upon their similar structural folds for classical PTPs, DSPs, and other VH1-like enzymes. The single class II cysteine-based PTP in humans is a tyrosine-specific low Mr enzyme, the origin of which appears to be more ancient than class I PTPs: representatives of this family are found in a all major phyla, including plants, numerous prokaryotes, and archea. Class II PTPs are structurally related to bacterial arsenate reductases. Class III cysteine-based PTPs are tyrosine/threonine-specific phosphatases that most likely evolved from a bacterial rhodanese-like enzyme. They are only represented by the three $p80^{Cdc25}$ cell cycle regulators. Interestingly, a group of class I PTPs contain a catalytically inactive rhodanese-like domain, referred to as the CDC25 homology (CH2) domain. Despite similarities in catalytic mechanism (Guan and Dixon, 1991) and active site structure (Barford et al., 1994; Yuvaniyama et al., 1996; Su et al., 1994; Fauman et al., 1998), class I, II, and III cysteine-based PTPs evolved independently. Nevertheless, a structural comparison indicates that they may have originated from an ancestral fold by rearrangment of elements. In contrast, the fourth family of PTPs use a different catalytic mechanism with a key aspartic acid and dependence on a cation. This family contains the Eya proteins, which were recently discovered to be tyrosine-, or dual serine- and tyrosine-specific protein phosphatases (Tootle et al., 2003; Rayapureddi et al., 2003; Li et al., 2003). Determination of the substrate specificities of the large family of hydrolases to which the Eya PTPs belong will require extensive analysis. Here, only the four Eya proteins are included because they were shown experimentally to be PTPs.

Class I Cysteine-Based PTPs

The 99 class I cysteine-based family of PTPs can be further classified into several subfamilies based on domain architecture and the degree of homology between catalytic domains. The 38 strictly tyrosine-specific "classical PTPs" can be divided into transmembrane, receptor-like enzymes (RPTPs), and the intracellular, nonreceptor PTPs (NRPTPs). They are represented in the human genome by 21 and 17 genes, respectively (Andersen et al., 2004). As is the case for the protein kinases, the number of PTP catalytic domains encoded by the genome is greater than the number of PTP genes because many of the RPTPs have tandem catalytic domains. The 61 VH1-like enzymes are much more diverse and can be divided into several subgroups, which share much less sequence identity with each other than the RPTPs do with the NRPTPs. Eleven of the 61 VH1-like PTPs encoded by the human genome are specific for the mitogen-activated protein (MAP) kinases Erk, Jnk, and p38 (Alonso et al., 2003a; Keyse, 1998; Saxena and Mustelin, 2000). These MAP kinase phosphatases (MKPs) are characterized by dual phosphothreonine and phosphotyrosine specificity and the presence of a CH2 region and other MAP kinase targeting motifs (Alonso et al., 2003b; Bordo and Bork, 2002). Another subgroup of DSPs, which we have referred to as the "atypical"

DSPs (Alonso et al., 2003b), includes a number of poorly characterized enzymes that lack specific MAP kinase targeting motifs and tend to be much smaller enzymes, less than 250 amino acid residues. The first DSP to be cloned, the VH1 protein from *Vaccinia* virus (Guan et al., 1991), is related to this group, as are the human VHR (Ishibashi et al., 1992) and a number of genes given the genomic designations *DUSP11*, *DUS13*, *DUSP14*, *DUSP15*, *DUSP18*, *DUSP19*, *DUSP21*, *DUSP22*, and others. While VH1 has been reported to dephosphorylate both MAP kinases and Stat1 (Najarro et al., 2001), and VHR can dephosphorylate Erk and Jnk in 293T cells (Todd et al., 1999) and T cells (Alonso et al., 2001, 2003b), it appears that many of these small atypical DSP have functions unrelated to MAP kinases. A true outlier is PIR (*DUSP11*), which dephosphorylates mRNA (Deshpande et al., 1999).

The three slingshots (SSH1, SSH2, and SSH3) and the three PRLs (PRL-1, PRL-2, and PRL-3) are very poorly understood, while the CDC14 group, which includes KAP, is involved in dephosphorylation of the Cdk activation loop phospho-Thr and inactivation of cyclin-dependent kinases and in exit from mitosis (Visintin et al., 1998). Finally, the two last subgroups of DSPs, the PTENs (5 genes) and myotubularins (16 genes), have evolved to specifically dephosphorylate the D3-phosphate of inositol phospholipids (Wishart and Dixon, 2002). Enzymes with this specificity are present also in yeast. While PTEN dephosphorylates phosphatidylinositol-3,4,5-trisphosphate at the plasma membrane, the myotubularins primarily dephosphorylate phosphatidylinositol-3-phosphate on internal cell membranes (Wishart and Dixon, 2002). Both groups also contain catalytically inactive members.

The Class II Cysteine-Based PTPs

This family is represented in the human genome by a single gene, referred to as *ACP1*, which encodes the 18 kDa low Mr phosphatase (LMPTP). Related class II enzymes are widely distributed in living organisms with most bacterial genomes encoding at least one member of this family, which are remarkably well conserved through evolution. For example, the human LMPTP is 31% identical to the corresponding protein in *Saccharomyces cerevisiae* and 39% identical to the YfkJ protein in *Bacillus subtilis*. Despite the paucity of tyrosine phosphorylation in prokaryotes, the bacterial class II PTPs are bona fide tyrosine-specific phosphatases and in many cases dephosphorylate tyrosine "autokinases" involved in regulation of capsule polysaccharide synthesis. This may represent the ancestral form of tyrosine phosphorylation as a mechanism by which cells sense their extracellular environment, from which receptor PTKs and the counterbalancing PTPs may have evolved. Although the human LMPTP can dephosphorylate a number of tyrosine kinases and their substrates, its physiological function is still unclear. The preservation of a class II PTP through evolution to humans and the correlation of allelic variants of LMPTP with many common human diseases (Bottini et al., 2002), such as rheumatoid arthritis, asthma, diabetes, cardiomyopathy, and Alzheimer's disease, indicate that LMPTP likely is involved in the regulation of one or several fundamental processes in cell physiology.

The Class III Cysteine-Based PTPs

These rhodanese-derived PTPs comprise three cell cycle regulators, CDC25A, CDC25B, and CDC25C, in humans. Their function is to dephosphorylate Cdks at their inhibitory dually phosphorylated N-terminal Thr-Tyr motifs, a reaction that is required for activation of these kinases to drive progression of cells through the cell cycle (Honda et al., 1993). CDC25s are themselves regulated by phosphorylation. It is curious that a unique type of PTP evolved to serve regulation of the cell cycle, instead of class I or class II enzymes, which presumably already existed at the time. Interestingly, the budding yeast cell cycle can function in the absence of Cdc28 Tyr-15 phosphorylation, and so this layer of regulation may have been a later addition. In other words, CDC25 appears to have entered cell cycle regulation hand in hand with tyrosine phosphorylation of the Cdks. Alternatively, it is possible that an ancestral CDC25 already acted as a rhodanese-type enzyme on Cdks and was transformed into a phosphatase when Cdk tyrosine/threonine phosphorylation evolved. This possibility would better explain why CDC25, rather than an existing PTP, was utilized.

Asp-Based PTPs

We have listed only the four Eya genes as members of the Asp-based PTPs because they have recently been shown to have Tyr/Ser phosphatase activity (Tootle et al., 2003; Rayapureddi et al., 2003; Li et al., 2003). It is clear that this is a much larger family of enzymes, which play important roles in development (Tootle et al., 2003; Rayapureddi et al., 2003; Li et al., 2003, Satow et al., 2002), sodium stress in yeast (Siniossoglou et al., 2000), and nuclear morphology (Siniossoglou et al., 1998). RNA polymerase II C-terminal domain phosphatase is also a member of this family. However, a clear and structurally based definition of this family of enzymes will be needed before the human gene complement of Asp-based phosphatases can be more accurately determined.

Modular Structure of PTPs

One of the most striking features of the PTP families (Figure 2) is that most enzymes consist of combinations of modular domains. At least 79 of the 107 PTPs contain at least one additional motif or domain (Table 2) outside of their catalytic PTP domain. Many of the domains are protein-protein interaction or phospholipid binding modules. In this respect, PTPs resemble the PTKs (Manning et al., 2002), but they differ markedly from the serine/threonine-specific protein phosphatases. In PTKs, protein-protein interaction domains serve two distinct purposes: regulation and targeting to substrates and/or subcellular compartments. This appears to be the case also for PTPs, although many of the domains in PTPs are still poorly understood. The set of domains found in PTPs are listed in Table 2 and they include domains that bind specific domains or motifs in other proteins (unphosphorylated or phosphorylated), cellular membranes, the cytoskeleton, or specific phospholipids.

It is interesting to note that the set of protein domains found in PTPs is only partly overlapping with those found in PTKs (Manning et al., 2002). While many PTKs have SH3 and SH2 domains, often in combinations, such as

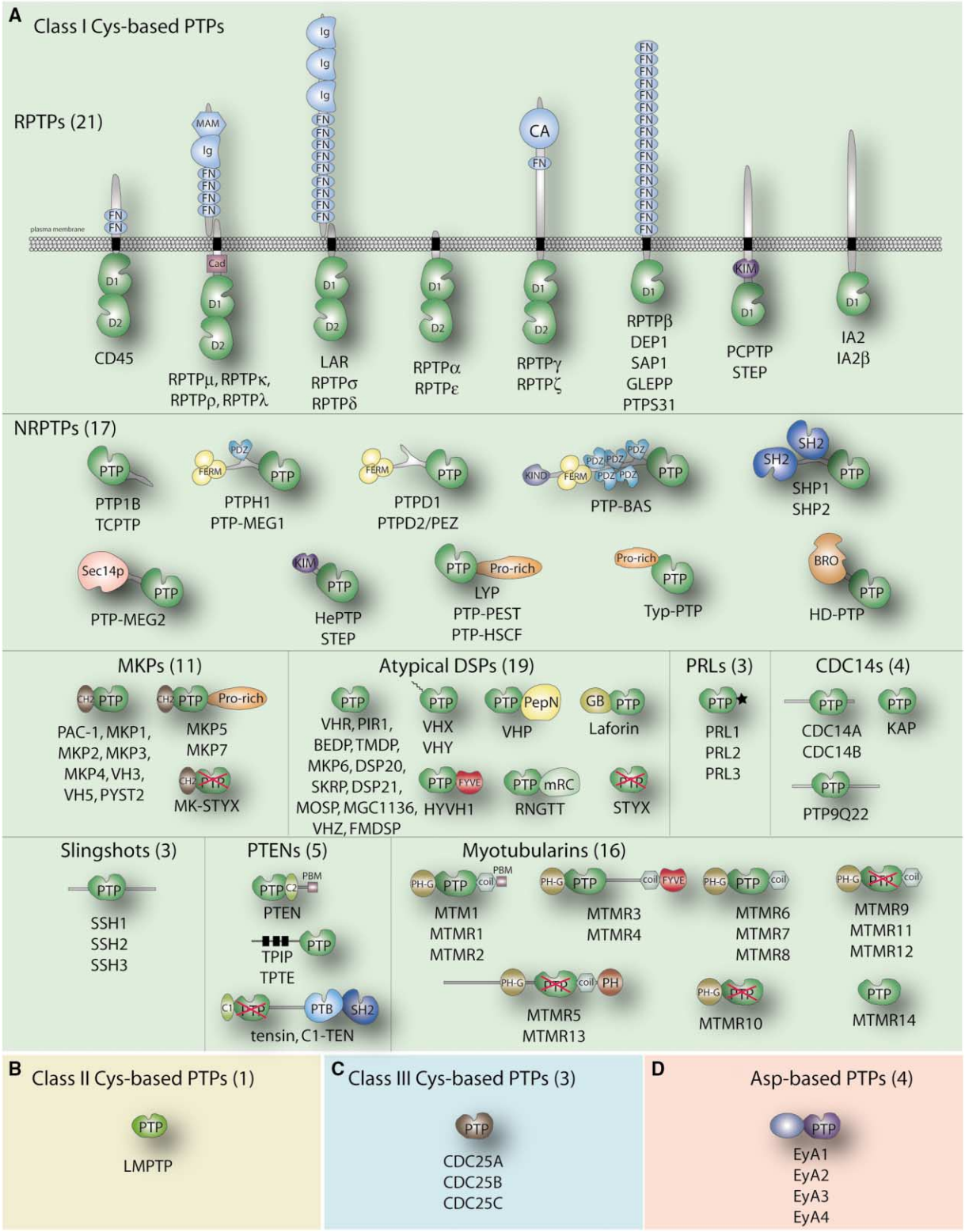

Figure 2. Domain Structure of All PTPs

Schematic view of the domain composition of all members of the four PTP families, which are in color coded areas as in Figure 1. Abbreviations as in Table 2, and: coil, coiled-coil domain; GB, glycogen binding; mRC, mRNA capping; PBM, PDZ binding motif; pepN, N-terminal peptidase-like; PH-G, pleckstrin homology-"GRAM" domain; Pro-rich, proline-rich; Sec14, Sec14p homology (or CRAL/TRIO). In addition, a small black box signifies transmembrane stretch and a red cross over a PTP domain signifies catalytically inactive domain.

Table 2. Other Domains in PTPs

Domain, Motif[a]	PTP
BRO	HD-PTP
C1	C1-ten
C2	PTEN
CA	RPTPγ, RPTPζ
CAAX box	PRL-1, PRL-2, PRL-3
CH2	MKP-1 (*DUSP1*), PAC-1 (*DUSP2*), MKP-2 (*DUSP4*), hVH3/B23 (*DUSP5*), MKP-3 (*DUSP6*), MKP-X (*DUSP7*), hVH5, (*DUSP8*), MKP-4 (*DUSP9*), MKP-5 (*DUSP10*), MKP-7 (*DUSP16*)
CRAL/TRIO	PTP-MEG2
DNA binding	Eya1-4
FERM	PTPH1, PTP-MEG1, PTPD1, PEZ, PTP-BAS
FN	CD45, LAR, RPTPμ, RPTPκ, RPTPρ, RPTPλ, RPTPσ, RPTPδ, RPTPβ, DEP1, SAP1, GLEPP1
FYVE	HYVH1 (*DUSP12*), MTMR3, MTMR4
Ig	LAR, RPTPμ, RPTPκ, RPTPρ, RPTPλ, RPTPσ, RPTPδ
KIM	HePTP, STEP, PTP-SL
KIND	PTP-BAS
MAM	RPTPμ, RPTPκ, RPTPρ, RPTPλ,
mRNA capping	mRNA capping enzyme
PBM	PTEN, MTM1, MTMR1, MTMR2
PDZ	PTPH1, PTP-MEG1, PTP-BAS
peptidase-like	VHP
PH	MTM1, MTMR1-13
PTB	tensin, C1-ten
SH2	SHP1, SHP2, tensin, C1-ten
SH3B	PTP-PEST, LYP, PEZ, DH-PTP
SH4	VHY (*DUSP15*), VHX (*DUSP22*)

[a] Abbreviations: BRO, baculovirus BRO homology; C1, protein kinase C conserved region 1; C2, protein kinase C conserved region 2; CA, carbonic anhydrase-like; CAAX box, farnesylation signal; CH2, cdc25 homology region 2; CRAL/TRIO, cellular retinaldehyde binding protein/trio homology (Sec14p homology); FERM, band 4.1/ezrin/radixin/moesin homology; FN, fibronectin-like; FYVE, Fab1/Yotb/Vac1p/early endosomal antigen-1 homology; Ig, immunoglobulin-like; KIM, kinase interaction motif; KIND, kinase N lobe-like domain; MAM, meprin, A2, RPTPμ homology; PBM, PDZ binding motif; PDZ, postsynaptic density-95/discs large/ZO1 homology; PH, pleckstrin homology (including GRAM domains); PTB, phosphotyrosine-binding domain; SH2, src homology 2; SH3B, src homology 3 domain binding motif; SH4, src homology 4 (myristylation signal).

SH3-SH2 or SH2-SH2, only two human PTPs (SHP1 and SHP2) have SH2 domains organized in a tandem fashion like in the Syk family PTKs. Also, the catalytically inactive PTEN-related tensin and C1-TEN have an SH2 domain adjacent to a PTB domain. In contrast, there are no PTPs with SH3 domains. Conversely, there are no known kinases with CRAL/TRIO (Sec14p homology), rhodanese, FYVE, or mRNA capping domains. Nevertheless, it is interesting to note that different domains may serve similar functions in PTPs compared to PTKs. For example, while PTKs mostly use PH domains to interact with phosphoinositides, PTPs use CRAL/TRIO (Huynh et al., 2003) and FYVE domains for the same purpose. Only the myotubularins have PH domains, but it is unclear if they function to interact selectively with phospholipid since myotubularins mostly do not localize to the plasma membrane. In fact, the PH domain of myotubularins was referred to as a GRAM domain until the crystal structure of MTMR2 (Begley et al., 2003) showed that this region folds as a PH domain.

PTPs also use FERM domains to direct them to the cytoskeleton/plasma membrane interface in a phosphoinositide-dependent manner, analogous to the use of SH3, PH, and C2 domains by kinases. FERM domains may also be able to bind phosphotyrosine, and PTPs may use catalytically inactive PTP ("STYX") domains in a SH2-like manner to interact with tyrosine phosphorylated proteins (Wishart and Dixon, 1998). Together, these differences in domain structure between PTPs and PTKs may reflect the need to regulate these two classes of enzymes in temporally and spatially distinct and often reciprocal manners.

Hints of Function from the Multidomain Architecture

In many PTPs, the nature of their extracatalytic domains gives some indications as to subcellular location or function. For example, all transmembrane classical PTPs have a membrane-spanning α helix (by definition) and are located in cellular membranes, mostly the plasma membrane, where they interact with the extracellular milieu in a receptor-like fashion. All but RPTPα and RPTPε have extended extracellular portions with immunoglobulin, fibronectin, MAM, and carbonic anhydrase domains. Another example is laforin, a PTP that is mutated in an inherited form of progressive myoclonus epilepsy (Lafora's disease; Minassian et al., 1998), characterized histologically by accumulation of glycogen-containing granules in the cytoplasm of cells. Recently, laforin was shown to contain a glycogen binding domain, implying a direct role for laforin in glycogen metabolism (Wang et al., 2002). The 17 nonreceptor classical PTPs are particularly rich in protein-protein interaction domains and many of them have several such domains. Within this group, SHP1 and SHP2 provide a good example of how protein-protein interaction domains can cooperate with a PTP domain to achieve both intramolecular regulation and targeting to substrates. In the absence of ligands for the tandem SH2 domain of these PTPs, the more N-terminal SH2 domain folds onto the catalytic

Table 3. PTPs in Human Diseases Other than Cancer

PTPRC (CD45)	SCID (Kung et al., 2000; Tchilian et al., 2001), multiple sclerosis (Jacobsen et al., 2000)
PTPRN (IA-2)	Antigen for autoimmune diabetes (Solimena et al., 1996)
PTPRN2 (phogrin)	Antigen for autoimmune diabetes (Kawasaki et al., 1996)
PTPN1 (PTP1B)	Insulin resistance, obesity (Andersen et al., 2004)
PTPN6 (SHP1)	Sezary syndrome (Andersen et al., 2004)
PTPN9 (PTP-MEG2)	Autism (Smith et al., 2000)
PTPN11 (SHP2)	Noonan syndrome (Tartaglia et al., 2001)
PTPN22 (LYP)	SNP polymorphism in type I diabetes (Bottini et al., 2004)
PTEN (PTEN)	Bannayan-Zonana (Marsh et al., 1997), Cowden syndrome and Lhermitte-Duclos disease (Liaw et al., 1997)
MTM1 (myotubularin)	X-linked myotubular myopathy (Laporte et al., 1996)
MTMR2 (MTMR2)	Charcot-Marie-Tooth syndrome type 4B (Bolino et al., 2000)
MTMR13 (MTMR13)	Charcot-Marie-Tooth syndrome type 4B (Azzedine et al., 2003)
EPM2A (laforin)	Progressive myoclonus epilepsy (Lafora's disease) (Minassian et al., 1998)
ACP1 (LMPTP)	Polymorphism correlates with many common diseases (Bottini et al., 2002)

domain to block substrate access by the insertion of a loop on the backside of the SH2 domain into the catalytic pocket of the PTP (Hof et al., 1998). When the SH2 domains of this inhibited form of SHP1 or SHP2 encounter a tyrosine phosphorylated ligand, the closed conformation opens and the enzyme is activated some 100-fold (Pei et al., 1994; Pluskey et al., 1995). Under physiological conditions, SH2 domain ligand binding also juxtaposes the PTP domain to its substrates, which contain, or associate with, the phosphorylated SH2 domain ligand.

The DSP subfamily contains 11 members with a CH2 domain, a region derived from the bacterial rhodanese enzyme and adapted to a MAP kinase docking motif (Alonso et al., 2003b; Bordo and Bork, 2002). In CDC25, on the other hand, the rhodanese has evolved into a catalytic PTP domain (Bordo and Bork, 2002). Other noncatalytic domains and motifs found in DSPs include FYVE, glycogen binding, mRNA capping (guanyl methyltransferase), and consensus recognition motifs for N-terminal myristylation or C-terminal prenylation. PTEN contains a C2 domain tightly packed against the PTP domain, while members of the myotubularin family contain PH, FYVE, coiled-coil, and PDZ binding motifs (Wishart and Dixon, 2002). A number of additional protein-protein interaction domains are found in PTPs in other organisms, for example a WW domain in a *C. elegans* PTP (Sudol, 1996), but are not present in the human PTPs either because they have been lost or because they evolved in a separate lineage.

Large Multidomain PTPs versus Multisubunit Ser/Thr Phosphatases

The multidomain structure of most PTPs is in sharp contrast to the serine/threonine protein phosphatases, which generally consist of small catalytic subunits that bind regulatory or targeting subunits encoded by separate genes to form a large number of distinct holoenzymes with different biological functions. This dichotomy may explain the differences in gene numbers: 107 PTPs to counteract 90 PTKs versus many fewer catalytic Ser/Thr phosphatase subunits to counter 428 protein kinases and the extensive phosphorylation of more than a third of all cellular proteins. Presumably, the combinatorial subunit principle of serine/threonine protein phosphatases can generate much more diversity and flexibility, but may lack some of the strict specificity and tight regulation possible with single-chain multidomain PTPs. In this context, it may also be significant that the atypical DSP subgroup of PTPs contains many small enzymes devoid of other domains or motifs. It is possible that these enzymes participate in multisubunit complexes where other subunits provide regulation and substrate targeting. However, no examples of this have yet been found.

Catalytically Inactive PTP Domains

Among the class I cysteine-based PTPs, there are at least 14 catalytically inactive PTP domains, in which critical catalytic residues have been altered. These are the second (D2) domains of CD45, RPTPγ, and RPTPζ, and the only PTP domains of the secretory vesicle-located receptor-like PTP IA-2 (Solimena et al., 1996), a VHR-like protein termed STYX (Wishart et al., 1995), the MKP-like MK-STYX (Wishart and Dixon, 1998), the PTEN-related tensin and C1-ten, and the myotubularin-related proteins MTMR5, MTMR9, MTMR11, MTMR12, MTMR13 (Wishart and Dixon, 2002), and MTMR15. Despite lack of catalytic activity, many of these proteins still play important roles in cells, in many cases by partnering with active PTPs. For example, CD45 needs its inactive D2 domain for dephosphorylation by D1 of its physiological substrates (Kashio et al., 1998). Similarly, the inactive MTMRs seem to act as important regulatory subunits for active members of the group, as shown by the human disease Charcot-Marie-Tooth type 4B, which is caused by mutation of the catalytically active MTMR2 (Bolino et al., 2000) or the catalytically inactive MTMR13 (Azzedine et al., 2003), in both cases with identical pathology and symptoms. It turns out that these two proteins form a heterodimer, in which the activity of MTMR2 depends on MTMR13. There are similar examples where an inactive kinase domain is needed to activate a catalytically competent kinase domain; e.g., LKB1 is activated by STRAD (Baas et al., 2003). In addition to these inherently inactive PTP domains, alternative splicing of PTP transcripts (which occurs in at least half of all PTPs) can create isoforms that have catalytically inactive PTP domains (Tailor et al., 1999), or lack them altogether (Bult et al., 1997). Physiologically important alternative splicing within the catalytic domains is known to create two isoforms of the class II enzyme LMPTP with different

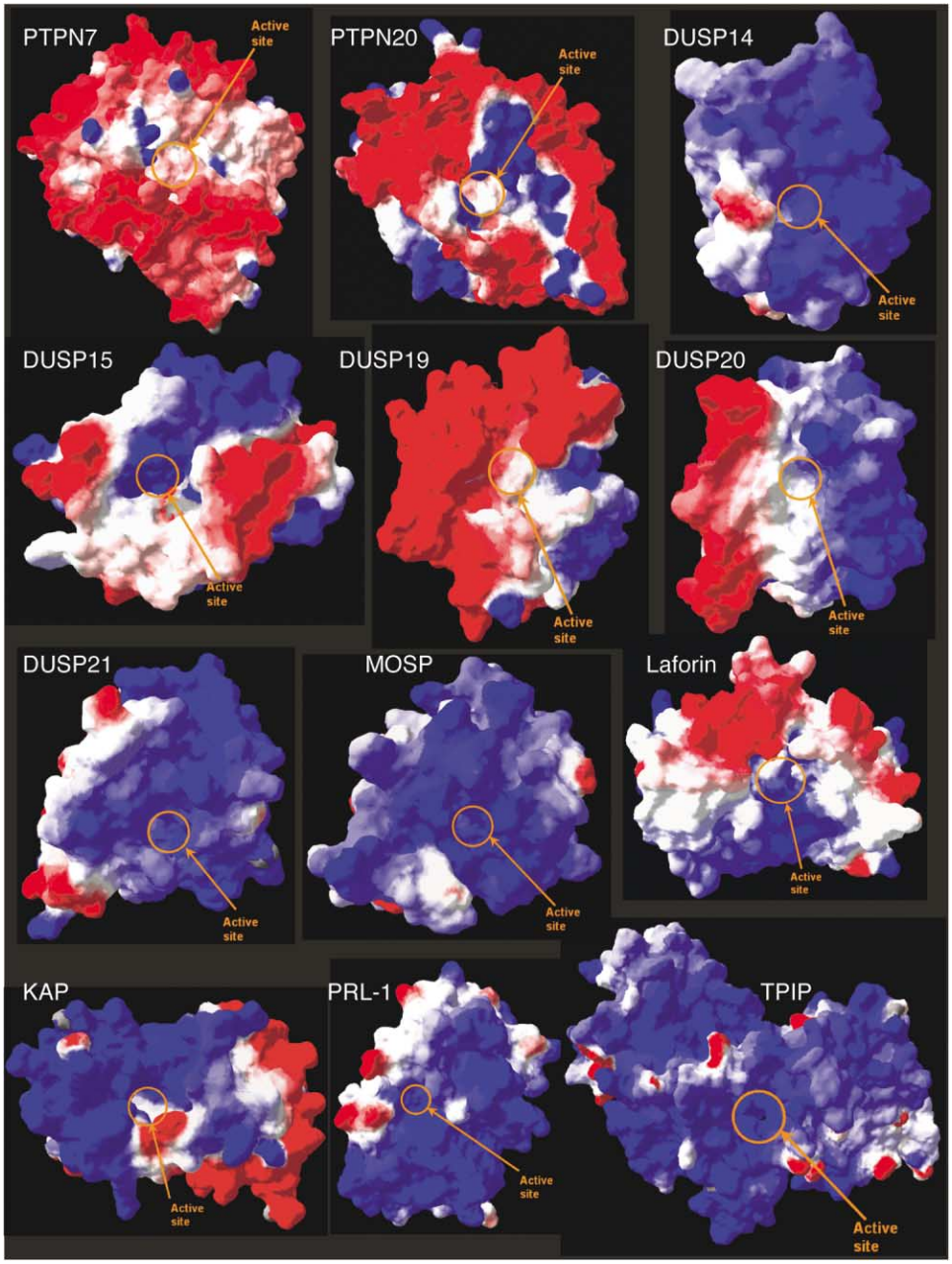

Figure 3. Surface Charge and Topology of a Set of Class I Twelve PTP Domains

These structures were modeled using the crystal structures of PTPs, and the models are colored according to charge of surface-exposed amino acid residues.

specific activity, substrate specificity, and regulation (Mitchell Bryson et al., 1995). In this enzyme, the ratio of the two isoforms is genetically determined and subject to allelic variation, which correlates with the predisposition to several common human diseases (Bottini et al., 2002).

Posttranslational Modifications and Reversible Oxidation of PTPs

The majority of PTPs are posttranslationally modified. Glycosylation appears to be restricted to the transmembrane PTPs, which contain abundant N- and O-linked carbohydrates in their extracellular portions. Two groups of DSPs are modified by fatty acids: VHY (*DUSP15*) and VHX (*DUSP22*) are N-terminally myristylated in a manner reminiscent of Src family PTKs (Alonso et al., 2004), while the PRLs are C-terminally farnesylated similar to Ras GTPases. By far the most common modification is the phosphorylation of PTPs on serine, threonine, and tyrosine. There are many examples where Ser/Thr phosphorylation has been shown to regulate activity. The phosphorylation of PTPs on tyrosine is particularly intriguing as it implies a physical, if not functional, interaction with PTKs (Mustelin and Hunter, 2002). At least 15

PTPs have been reported to be tyrosine phosphorylated, but the physiological significance remains unclear in most cases. Tyrosine phosphorylation also introduces the possibility of autodephosphorylation. In fact, many PTPs become noticeably more phosphorylated on tyrosine when expressed as catalytically inactive mutants. In most cases, however, the phosphorylation sites are clearly inaccessible for intramolecular dephosphorylation, suggesting that dephosphorylation must occur in *trans*. Thus, regulatory networks of PTPs and other protein phosphatases, perhaps in the form of "phosphatase cascades," may exist in cells.

It has been known for many years that the catalytic cysteine of class I and II PTPs is highly susceptible to oxidation in vitro, and it has been speculated that this could play a role in intact cells exposed to oxidizing agents. An exciting new development was the discovery that oxidation of PTP1B does not result in a stable sulfenic acid derivative of the catalytic site cysteine, but rapidly transforms into a sulfenyl amide ring involving the adjacent serine residue (Salmeen et al., 2003; van Montfort et al., 2003). This form is resistant to further oxidation, which would be irreversible, and is readily reduced back to the free cysteinyl, catalytically active form. Together with recent insights into the production of reactive oxygen species and nitrogen oxides in cells during growth factor stimulation in cancer, inflammation, and neurodegenerative diseases, it now seems likely that reversible redox regulation of PTPs occurs in intact cells. Since PTPs often play dominant roles in setting the levels of tyrosine phosphorylation in cells, this regulation may be physiologically very important.

PTPs as Drug Targets

Compared to the PTKs, many inhibitors of which already are in clinical trials, the PTPs are newcomers in the field of drug development. The effect of disruption of the *PTP1B* gene in mice, which indicated that this PTP acts as a negative regulator of insulin signaling (Elchebly et al., 1999), ignited the interest of the pharmaceutical industry. Recent discoveries that many other PTPs also play critical roles in a variety of human disease (Table 3) have sparked a growing interest in PTPs as drug targets. In addition to metabolic, neurological, muscle, and autoimmune diseases, at least 30 PTPs have been implicated in cancer (listed in Andersen et al. [2004]). We expect that with improved understanding of the molecular mechanisms by which PTPs affect the pathophysiology of these diseases, combined with the dominant role that PTPs often play in the regulation of tyrosine phosphorylation-dependent processes, PTP inhibitors will become clinically relevant therapeutics in the future. A rational design of small-molecule inhibitors against PTPs using in silico docking, NMR-based methods, high-throughput crystallization, and specific chemistry will most likely be involved. Following initial concerns about specificity and problems associated with the hydrophilicity of phosphomimetics, promising successes have been achieved by structure-based drug design, particularly those that utilize unique features of the surface topology surrounding the catalytic pocket of each PTP. Figure 3 shows the surface topology and charge distribution of a representative set of catalytic PTP domains to illustrate the striking diversity within the class I PTPs. For example, for PTP1B it was found that a unique second PTyr binding site (Puius et al., 1997; Salmeen et al., 2000) could be used to develop highly specific bidentate inhibitors that bind both sites (Zhang, 2002). This general approach can be used to design highly specific and effective inhibitors.

Concluding Remarks

The main challenge now facing the PTP field in the postgenomic era is to elucidate the physiological role of each individual gene product. This task is multiplied by the capacity of many PTP genes to generate alternatively spliced products, the existence of single-nucleotide polymorphisms that alter function, and the regulatory influences of many posttranslational modifications and protein-protein interactions. The rate of progress is likely to be accelerated by many emerging new technologies. The identification of the physiological substrates for all PTPs is an important task likely to be aided by the development of mass spectrometry technologies to study the entire phosphoproteome of cells in a comprehensive, detailed, and quantitative manner. Genetic approaches and RNA interference will likely promote discovery of physiological functions and will help to address important questions of redundancy. All these issues are important for the full utilization of PTP as drug targets and the treatment of many human diseases in which PTPs play regulatory or even causative roles.

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