

Contents

Preface — V

About the author — IX

1 Tyrosine phosphorylation in cell signaling: Discovery and beyond — 1

- 1.1 Protein phosphorylation — 1
- 1.2 Origins and early work — 4
- 1.3 Tyrosine phosphorylation: Discovery and beginnings — 5
- 1.4 Tyrosine phosphorylation: Current significance — 8
- 1.5 The protein tyrosine kinases — 9
 - 1.5.1 The protein tyrosine kinase catalytic domain — 12
 - 1.5.2 Protein tyrosine kinases: Src as a model — 15
 - 1.5.3 Regulation of Src tyrosine kinase — 16
- 1.6 Phosphotyrosine recognition domains — 18
 - 1.6.1 SH2 domains: Discovery and selectivity — 19
 - 1.6.2 SH2 domains: Structure and function — 20
 - 1.6.3 PTB domains: Discovery and selectivity — 22
 - 1.6.4 PTB domains: Structure and function — 23
 - 1.6.5 SH2 domains versus PTB domains — 25
 - 1.6.6 Atypical phosphotyrosine recognition domains: HYB domain — 26
 - 1.6.7 Atypical phosphotyrosine recognition domains: PKC δ and PKC θ C2 domains — 26
- References — 26

2 Protein phosphatases: Classification and domain architecture — 35

- 2.1 The protein phosphatases — 35
- 2.2 The phosphoprotein phosphatases — 36
 - 2.2.1 Protein phosphatase 1 — 37
 - 2.2.2 Protein phosphatase 2A — 40
 - 2.2.3 Protein phosphatase 2B — 44
 - 2.2.4 Protein phosphatase 5 — 45
 - 2.2.5 Natural toxins as inhibitors of PPP catalytic subunits — 47
- 2.3 The metal-dependent protein phosphatases — 48
- 2.4 FCP/SCP phosphatases — 51
- 2.5 Protein tyrosine phosphatases — 54
 - 2.5.1 The dual-specificity phosphatases — 55
 - 2.5.2 The class II protein tyrosine phosphatases — 65
 - 2.5.3 The class III protein tyrosine phosphatases — 67
 - 2.5.4 The class IV protein tyrosine phosphatases — 68
- References — 70

3	Protein tyrosine phosphatases: Molecular structure and mechanism — 89
3.1	The protein tyrosine phosphatases — 89
3.2	The PTP catalytic domain — 92
3.2.1	The P-loop — 96
3.2.2	The WPD-loop — 97
3.2.3	The Q-loop — 99
3.2.4	The pY-recognition loop — 99
3.2.5	The E-loop — 100
3.3	Catalytic domains of different PTP classes — 101
3.4	The catalytic mechanism — 103
3.5	Differences in the mechanics of class I, II and III PTPs — 105
3.6	Crystallographic strategies to study PTP structure — 105
3.7	Active site determinants — 106
3.8	Accessory substrate binding determinants — 107
3.9	The unique class IV PTPs — 110
3.10	An alternate mechanism for the Class IV PTPs — 112
	References — 113
4	The receptor protein tyrosine phosphatases: Structure and function — 119
4.1	Classification of protein tyrosine phosphatases — 119
4.2	The R1/R6 subtype — 119
4.3	The R2A subtype — 126
4.4	The R2B subtype — 130
4.5	The R3 subtype — 133
4.6	The R4 subtype — 134
4.7	The R5 subtype — 136
4.8	The R7 subtype — 139
4.9	The R8 subtype — 141
	References — 142
5	The double-domain receptor protein tyrosine phosphatases — 155
5.1	Tandem PTP domains in receptor PTPs — 155
5.2	Interdomain interactions holding the tandem PTP domains — 157
5.3	Linker connecting the two domains — 158
5.4	Evolution of the D2 domain — 158
5.4.1	The D2A subclass of D2 domains — 160
5.4.2	The D2B subclass of D2 domains — 161
5.5	D2 domains affect substrate selection of the cognate D1 domains — 162

5.6	D2 modulates the activity of its cognate D1 domain —	162
5.7	Role of inter- and intradomain amino acid networks —	166
5.8	Role of D2 domain as a redox protector —	167
5.9	Dimerization in double-domain receptor PTPs —	172
5.10	Role of D2 domain in receptor cross talk —	174
	References —	175
6	The non-receptor protein tyrosine phosphatases: Part I —	179
6.1	Classification of non-receptor protein tyrosine phosphatases —	179
6.2	The NT1 subclass —	179
6.3	PTP1B: Structure and catalytic function —	181
6.3.1	PTP1B: Substrate identification —	184
6.3.2	PTP1B: Regulation of function —	186
6.3.3	PTP1B: Role in disease —	187
6.3.4	PTP1B: Role in cancer —	189
6.3.5	PTP1B as a therapeutic target —	190
6.4	T-Cell protein tyrosine phosphatase —	192
6.4.1	Biological role of TCPTP —	193
6.5	TCPTP and PTP1B —	194
	References —	195
7	The non-receptor protein tyrosine phosphatases: Part II —	203
7.1	The NT2 subtype of non-receptor PTPs —	203
7.1.1	Structure and regulation of SHPs —	203
7.1.2	Physiological role of SHP1 —	207
7.1.3	SHP2 signaling and function —	208
7.2	The NT3 subtype of non-receptor PTPs —	210
7.3	The NT4 subtype of non-receptor PTPs —	212
7.3.1	The PTP-PEST —	213
7.3.2	Structural architecture of PTP-PEST —	213
7.3.3	PTP-PEST: Mode of physiological function —	215
7.3.4	The PTP-PEP/Lyp tyrosine phosphatase —	215
7.3.5	Role of the tyrosine phosphatase domain of Lyp —	216
7.3.6	Mode of action of Lyp —	217
7.3.7	PTP HSCF/BDP1 —	218
7.4	The NT5 subtype of non-receptor PTPs —	218
7.5	The NT6 subtype of non-receptor PTPs —	220
7.5.1	PTPD1 non-receptor PTP —	220
7.5.2	PTPD2 non-receptor PTP —	222
7.6	The NT7 subtype of non-receptor PTPs —	223
7.7	The NT8 subtype of non-receptor PTPs —	225

7.8	The NT9 subtype of non-receptor PTPs —	226
7.9	The PTPN5 RR subfamily of PTPs —	228
	References —	229
8	Protein tyrosine phosphatases: strategies for drug development —	243
8.1	Natural Products as protein tyrosine phosphatase inhibitors —	244
8.2	Natural Product analogues as protein tyrosine phosphatase inhibitors —	259
8.3	Reversible orthosteric inhibitors of protein tyrosine phosphatases —	261
8.4	Irreversible inhibitors of protein tyrosine phosphatases —	263
8.5	Bidentate inhibitors of protein tyrosine phosphatases —	264
8.6	Allosteric inhibitors of protein tyrosine phosphatases —	266
8.7	Biologics-based therapeutic intervention of protein tyrosine phosphatases —	268
8.8	Concluding remarks —	270
	References —	270
	Index —	279