

Phosphoprotein Phosphatases (Serine/Threonine)

Key References

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Overview

Phosphoprotein phosphatases, which hydrolyze the phosphoester bonds of phosphoserines, phosphothreonines or phosphotyrosines, play an essential role in signal transduction and actively contribute to the regulation of protein phosphorylation. On the basis of their substrate specificity, they are usually divided into phosphoserine and phosphothreonine phosphatases on the one hand, and phosphotyrosine and dual-specificity phosphatases, on the other hand. This division corresponds also to different families of enzymes with different catalytic mechanisms. Genes coding for phosphoserine/threonine phosphatases are less numerous in vertebrate genomes than those for serine/threonine kinases, and the complexity of phosphatases function arises in part from the interactions of catalytic subunits with other proteins.

Prior to the knowledge of their sequence phosphoserine/threonine phosphatases were classified on the basis of their substrate preference and inhibitor sensitivity. Type 1 protein phosphatases (PP1) dephosphorylate the β -subunit of phosphorylase kinase, and are inhibited by phospho-inhibitor-1 and inhibitor-2, whereas type 2 protein phosphatases (PP2) dephosphorylate the α -subunit of phosphorylase kinase, and are resistant to the aforementioned inhibitors. Type 2 phosphatases were further divided depending on their divalent cation requirements for full activity: phosphatase 2A (PP2A) does not require such cations, whereas phosphatase 2B (PP2B also known as calcineurin) and phosphatase 2C (PP2C) are respectively activated by Ca^{2+} and Mg^{2+} .

Molecular cloning revealed that serine/threonine phosphatases belong to two different families each comprising about a dozen genes in mammals: the phosphoprotein

phosphatase P (PPP) family includes PP1, PP2A, PP2B, and a few related enzymes, PP4, PP5, PP6 and PP7, while the phosphoprotein phosphatase M family (PPM) includes PP2C and related enzymes. Sequences of the catalytic domains of PPP family phosphatases are highly related to one another. They have been highly conserved during evolution and are homologous in general aspects of their catalytic mechanism to enzymes found in prokaryotes (e.g. phage λ phosphatase). PPM phosphatases are found in prokaryotes and eukaryotes, and are numerous in plants. Although PPP and PPM families share no sequence homology, they are both metallo-enzymes and their 3-D structures display some general similarities.

The serine/threonine phosphatases of the PPP family are mostly regulated by protein-protein interactions. Both PP1c and PP2Ac are catalytic subunits that interact with a large number of targeting and regulatory subunits. PP1 is targeted to glycogen particles, myofibrils or dendritic spines by specific subunits and regulated by small proteins controlled by phosphorylation. For example, in basal ganglia neurons, PP1c is inhibited by the phosphorylated form of DARPP-32 (32 kDa dopamine and cAMP-regulated protein) that is regulated by dopamine and several other neurotransmitters. The PP2A catalytic subunit forms heterotrimers with two other subunits and interacts with several inhibitory proteins. In contrast, PP2B (calcineurin) is comprised of an A subunit including the catalytic domain and a B subunit structurally related to calmodulin. Calcineurin is activated by direct Ca^{2+} binding to calcineurin B and binding of the Ca^{2+} -calmodulin complex to calcineurin A. PP7 is also activated by Ca^{2+} .

A number of natural toxins produced by a variety of microorganisms are powerful

inhibitors of PP1, PP2A, and PP4-6, with only relatively small differences in affinities. This, combined with the high molar concentrations of these phosphatases found in some cells, makes it sometimes difficult to identify their relative contribution to the dephosphorylation of specific substrates in intact cells through the use of these inhibitors. Calcineurin is the specific target of two immunosuppressant drugs, cyclosporin A and FK506, complexed with their intracellular receptors (immunophilins), cyclophilin and FK506-binding protein (FKBP), respectively.

PPM family members are monomeric enzymes for which regulatory mechanisms or targeting by protein-protein interactions are as yet poorly characterized. It includes the classic PP2C phosphatases, a number of enzymes recently discovered and pyruvate dehydrogenase phosphatases. There are as yet no specific inhibitor of PPM phosphatases.

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GENE FAMILY	PPP	PPP	PPP	PPP	PPP	PPP	PPP	PPM
TYPE	PP1 (P7937)	PP2A (P1868, P1618)	PP2B (C1907)	PP4	PP5	PP6	PP7	PP2C
ALTERNATE NAMES	PPP1	PPP2	PPP3, calcineurin	PPP4, PPX	PPP5	PPP6	PPP7, rdgC	PPM1A,B
MOL MASS CATAL. SUBUNIT (kDA)	~37	~36	~60	~35	~60	35	75	40-60
QUARTEINARY STRUCTURE	Associated with targeting subunits	Heterotrimer: 1 catalytic sub. 2 regulatory sub.	Heterodimer: A: catalytic + CaM binding B: Ca ²⁺ binding	Not known	Not known	Not known	Not known	Monomer
EFFECT OF CATIONS	Not known	Not known	Activated by Ca ²⁺	Not known	Not known	Not known	Ca ²⁺	Activated by high Mg ²⁺
ENDOGENOUS INHIBITORS	Phospho-Inhibitor-1, Phospho-DARPP32, Inhibitor-2 (P8218), NIPP, RIPP, CPI17, Phosphatidic acid (P9511)	I ₁ ^{PP2A} (P2118), I ₂ ^{PP2A} (P2243),	Cain, AKAP-79 ^a , DSCR1, ZAKI-4	Not known	Not known	Not known	Not known	Not known
PHARMACOLOGICAL INHIBITORS ^b	Calyculin A (C5552) >Microcystin LR (M2912) >Nodularin (N5148) >Tautomycin (86305) >Okadaic acid (O9381, O7760) >Cantharidin (C7632)	Nodularin >Microcystin LR (M2912) >Calyculin A (C5552) ~Okadaic acid (O9381, O7760) >Fostriecin (F4425) >Tautomycin (86305) >Cantharidin (C7632)	Cyclosporin A (C3662) ^c FK506 (F4679) ^d	Okadaic acid (O9381, O7760) >Microcystin LR (M2912) >Tautomycin (86305) >Calyculin A (C5552) >Fostriecin (F4425) >Cantharidin (C7632)	Microcystin LR (M2912) >Calyculin A (C5552) >Okadaic acid (O9381, O7760) >Tautomycin (86305)	Not known	Resistant to okadaic acid and related inhibitors	Not known
TISSUE EXPRESSION	Ubiquitous	Ubiquitous	Ubiquitous, high in brain	Ubiquitous, high in testis	Ubiquitous	Not known	Retina	Ubiquitous
PHYSIOLOGICAL FUNCTION	Many	Many	Many	Microtubule growth at centrosomes	Cell growth, stress response	Cell cycle regulation	Not known	Many
DISEASE RELEVANCE	Not known	Not known	Target of immunosuppressants	Not known	Not known	Not known	Not known	Not known

Abbreviations

AKAP-79: A kinase anchor protein 79

Cain: Calcineurin inhibitor

CaM: Calmodulin

CPI17: 17 kDa PKC-potentiated inhibitory protein of PPI

DARPP32: Dopamine and cAMP-regulated phosphoprotein

DSCR1: Down syndrome critical region 1

FKBP: FK506 binding protein

I₁^{PP2A}: Protein inhibitor 1 of protein phosphatase 2A

I₂^{PP2A}: Protein inhibitor 2 of protein phosphatase 2A

Inhibitor-2: Proteon phosphatase inhibitor-2

NIPP: Nuclear inhibitor of protein phosphatase 1

PP: Phosphoprotein phosphatase

PP1: Phosphoprotein phosphatase 1

PP2A: Phosphoprotein phosphatase 2A

PP2B: Phosphoprotein phosphatase 2B or calcineurin

PP2C: Phosphoprotein phosphatase 2C

PPM: Phosphoprotein phosphatase M family

PPP: Phosphoprotein phosphatase P family

RIPP: Ribosomal inhibitor of protein phosphatase 1

ZAKI-4: Down syndrome critical region 1-like 1

FOOTNOTES

a Binding protein, some inhibitory effect.

b Inhibitors are listed in order of decreasing potency.

c Combined with cyclophilin.

d Combined with FKBP.