Phosphoprotein Phosphatases

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 Ca2+ and Mg2+.

Molecular cloning revealed that serine/threonine phosphatases belong to two different families of about a dozen of genes each 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 I 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 Ca2+ binding to calcineurin B and binding of the Ca2+-calmodulin complex to calcineurin A. PP7 is also activated by Ca2+. 
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.

The Table below contains accepted modulators and additional information. For more information and a complete list of the related products, please click: Aladdin

<table>
<thead>
<tr>
<th>Gene Family</th>
<th>PPP</th>
<th>PPM</th>
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<tbody>
<tr>
<td>Type</td>
<td>PP1 PP2A PP2B PP4 PP5 PP6 PP7 PP2C</td>
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<tr>
<td>Alternate Names</td>
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<td>Endogenous Inhibitors</td>
<td>Phospho-Inhibitor-1 Phospho-DARPP32 Inhibitor-2 NIP RIPP CP17 Phosphatidic acid</td>
<td>Cain AKAP-79 DSCR1 ZAK1-4</td>
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<td>Pharmacological Inhibitors</td>
<td>Calycin A &gt;Microcystin LR &gt;Nodularin &gt;Tautomycin &gt;Okadaic acid &gt;Cantharidin Nodularin &gt;Microcystin LR &gt;Calcin A ~Okadaic acid &gt;Fostriecin &gt;Tautomycin &gt;Cantharidin Cyclosporin A FK506 Okadaic acid &gt;Microcystin LR &gt;Calcin A &gt;Okadaic acid &gt;Fostriecin &gt;Cantharidin</td>
<td>Microcystin LR &gt;Calcin A &gt;Okadaic acid &gt;Tautomycin</td>
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testis

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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
I1PP2A: Protein inhibitor 1 of protein phosphatase 2A
I2PP2A: 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

References


For more information and a complete list of the related products, please click: Aladdin