

PKC

Key References

Dekker, L.V. and Parker, P.J., Protein kinase C - a question of specificity., *Trends Biochem. Sci.*, **19**, 73-77 (1994).

Hug, H. and Sarre, T.F., Protein kinase C isoenzymes: Divergence in signal transduction?, *Biochem. J.*, **291**, 329-343 (1993).

Jaken, S., Protein kinase C isozymes and substrates., *Curr. Opin. Cell Biol.*, **8**, 168-173 (1996).

Mellor, H. and Parker, P.J., The extended protein kinase C superfamily., *Biochem. J.*, **332**, 281-292 (1998).

Mochly-Rosen, D., Localization of protein kinases by anchoring proteins: A theme in signal transduction., *Science*, **268**, 247-251 (1995).

Newton, A.C., Protein kinase C: Structure, function and regulation., *J. Biol. Chem.*, **270**, 28485-28498 (1995).

Newton, A.C., Regulation of the ABC kinases by phosphorylation: protein kinase C as a paradigm., *Biochem. J.*, **370**, 361-367 (2003).

Nishizuka, Y., Protein kinase C and lipid signaling for sustained cellular responses., *FASEB. J.*, **9**, 484-496 (1995).

Parekh, D.B., et al., Multiple pathways control protein kinase C phosphorylation., *EMBO J.*, **19**, 496-503 (2000).

Parker, P.J. and Murray-Rust, J., PKC at a glance., *J. Cell Sci.*, **117**, 131-132 (2004).

Poole, A.W., et al., PKC-interacting proteins: from function to pharmacology., *Trends Pharmacol. Sci.*, **25**, 528-535 (2004).

Webb, B.L.J., et al., Protein kinase C isoenzymes: A review of their structure, regulation and role in regulating airways smooth muscle tone and mitogenesis., *Br. J. Pharmacol.*, **130**, 1433-1452 (2000).

Overview

Protein kinase C (PKC) is an AGC kinase that phosphorylates serine and threonine residues in many target proteins. It was first identified in 1977 in bovine cerebellum by Nishizuka and co-workers as a protein kinase that phosphorylated histone and protamine. Since then, its involvement in many biological processes has been demonstrated, including development, memory, differentiation, proliferation and carcinogenesis. Once thought to be a single protein, PKC is now known to comprise a large family of enzymes that differ in structure, cofactor requirements and function. Ten isoforms of PKC have been identified, varying in tissue expression and cellular compartmentalization, allowing for specific interactions with substrates.

The PKC family has been divided into three groups, differing in the enzymes' cofactor requirements; conventional (c)PKC isoforms (comprising α , β_1 , β_{II} and γ), that require calcium and diacylglycerol (DAG) for activation; novel (n)PKC isoforms (comprising δ , ϵ , η [also known as PKC-L], and θ that require DAG; and atypical (a)PKC isoforms, namely ζ , and ι (also known as λ , the mouse homolog of human PKC ι) that require neither calcium nor DAG. Protein kinase D (PKD) is a distinct kinase family that was originally classified as a PKC subgroup (PKC μ , PKC ν). The PKC-related kinases (PRK/PKN) contain kinase domains homologous to PKC's. These are not closely related to the PKC family due to very different regulatory domains; however, they can be considered to be part of the PKC superfamily.

All PKCs possess a phospholipid-binding domain for membrane interaction. The general structure of a PKC molecule consists of a catalytic and a regulatory

domain, composed of a number of conserved regions, interspersed with regions of lower homology, the variable domains.

Activation of cPKCs involves translocation from the cytosol to the cell membrane by engaging the membrane-targeting modules. In the case of cPKCs, an increase in intracellular calcium first promotes the binding of the C2 domain to anionic lipids. The C1 domain binds DAG (or phorbol esters, functional DAG-analogs) and phosphatidylserine (PS), recruiting the conventional and novel PKCs to the membrane, where they can phosphorylate substrates. Specific anchoring proteins (immobilized at particular intracellular sites) localize the kinase to its site of action. These proteins include 'receptors for activated C-kinase' (RACKS), 'receptors for inactive C-kinase' (RICKS), 'A-kinase anchoring proteins' (AKAPS), and 'substrates that interact with C-kinase' (STICKS). In addition, nuclear localization signals (NLS) or nuclear export signals (NES) can send PKC into or out of the nucleus.

Some, if not all, PKC isoforms can be proteolytically cleaved at the hinge between the regulatory and catalytic domains by proteases such as the calcium-activated calpain, generating a free, cofactor-independent, catalytic subunit known as protein kinase M (PKM). This 'calpain product' should not be considered an 'unregulated' enzyme since its generation is, in fact, regulated by proteolysis. Cleavage is a physiologically relevant alternate activation mechanism for isozymes such as PKC δ , occurring in processes like apoptosis, where caspases appear to have important roles.

All PKCs, except the δ isoform, exhibit so-called PEST sequences, hydrophilic poly-

peptide segments enriched in proline (P), glutamic acid (E), serine (S) and threonine (T), which target proteins for degradation by the proteasome. An additional level of complexity is apparent following the observation that dephosphorylation of activated PKCs apparently predisposes them to ubiquitination and degradation. The downregulation of PKC is therefore also regulated by specific phosphatases and ubiquitin ligases.

PKC isoforms are processed by three ordered priming phosphorylations. The first phosphorylation is catalyzed by phosphoinositide-dependent kinase (PDK-1) and occurs at the activation loop (T500 in PKC β_{II}). This phosphorylation triggers two phosphorylations at the carboxy-terminus (T641 and S660 in β_{II}). Each phosphorylation event induces conformational changes in the PKC molecule that result in altered thermal stability, resistance to phosphatases and catalytic competency.

The first complete crystal structure of PKC was recently obtained for the novel isoform θ . Previous structural information was obtained from crystals of the regulatory domains, and by modeling the catalytic domain with protein kinase A. In addition to general biochemical information, the following chart lists several activators, inhibitors and substrates currently used to examine the roles of PKC in cellular processes.

PKC

FAMILY MEMBERS/ISOFORMS	α (P1782, P8311)	β_1 (P1787)	β_{II} (P3287)
OTHER NAMES	Conventional	Conventional	Conventional
MOLECULAR WEIGHT/ STRUCTURAL DATA	76.8 kDa (h) 672 aa (h)	76.7 kDa (h) 671 aa (h)	76.8 kDa (h) 673 aa (h)
SPECIES	Ubiquitous, e.g. human (h)	Ubiquitous, e.g. human (h)	Ubiquitous, e.g. human (h)
DOMAIN ORGANIZATION	N-terminal pseudosubstrate domain, C1A domain, C1B domain, C2 domain, catalytic domain, C-terminal domain	N-terminal pseudosubstrate domain, C1A domain, C1B domain, C2 domain, catalytic domain, C-terminal domain	N-terminal pseudosubstrate domain, C1A domain, C1B domain, C2 domain, catalytic domain, C-terminal domain
PHOSPHORYLATION SITES ^a	Thr ⁴⁹⁷ , Thr ⁶³⁸ , Ser ⁶⁵⁷ (r,m,h,rb)	Thr ⁵⁰⁰ , Thr ⁶⁴² , Ser ⁶⁶¹ (r,m,h,rb)	Thr ⁵⁰⁰ , Thr ⁶⁴¹ , Ser ⁶⁶⁰ (r,m,h)
TISSUE DISTRIBUTION	Many, e.g. CNS, heart, kidney, liver, lung	Many, e.g. CNS, heart, kidney, liver, lung	Many, e.g. CNS, heart, kidney, liver, lung
SUBCELLULAR LOCALIZATION	Cytosol, membrane	Cytosol, membrane	Cytosol, membrane
BINDING PARTNERS/ ASSOCIATED PROTEINS	All isoforms: many, e.g. RACKs, STICKs, AKAPs. See Reference ^b in Footnotes. e.g. 14-3-3		e.g. 14-3-3
UPSTREAM ACTIVATORS	Conventional and novel isoforms: G protein-coupled receptors, tyrosine kinase receptors, non-receptor tyrosine kinase receptors, and other agonists of phospholipid hydrolysis, atypical isoforms: binding proteins, e.g. p62/zip, par6		
DOWNSTREAM ACTIVATION ^c	MBP (M1891), Histones (eg. IIS) (H4524), EGFr, MARCKS, Protamine (P4505), AKAP79, GAP43, Pleckstrin, Adducin, Vinculin	MBP (M1891), Histone H3 (H4380), EGFr, MARCKS, Protamine (P4505), AKAP79, GAP43, Pleckstrin	MBP (M1891), Histone H3 (H4380), EGFr, MARCKS, Protamine (P4505), AKAP79, GAP43, Pleckstrin
SUBSTRATES	α Pseudosubstrate peptide, MBP peptide (P2186), Syntide 2 (S2525), EGFr peptide (L9905), PKC substrate (P5307, V2131), MARCKS peptide	α Pseudosubstrate peptide, MBP peptide (P2186), Syntide 2 (S2525), EGFr peptide (L9905), PKC substrate (P5307, V2131), MARCKS peptide	α Pseudosubstrate peptide, MBP peptide (P2186), Syntide 2 (S2525), EGFr peptide (L9905), PKC substrate (P5307, V2131), MARCKS peptide

FOOTNOTES

a Processing sites listed.

b For detailed list of binding partners, see Reference: Poole, A.W., et al. "PKC-interacting proteins: from function to pharmacology." *Trends Pharmacol Sci*, **25**, 528-535 (2004).

c PKC α pseudosubstrate site sequence RFARKGALRQKNVHEVKDH. PKC ϵ pseudosubstrate site sequence PRKRQGAVRRRVHQQVNGH (underlined are mutable sites for phosphorylatable residues). Substrates not determined on all isoforms.

d Specific lipid activator of α PKCs unknown.

e GF 109203X (Gö 6850 aka BIM 1) displays potency rank order of $\alpha > \beta > \epsilon > \delta > \zeta$. Bisindolylmaleimides (Ro compounds, BIM 1, Gö 6976) inhibit all PKCs in potency rank order of cPKCs > nPKCs > α PKCs (generally); Calphostin C inhibits DAG site in regulatory domain; BIM 1 and Ro compounds act at ATP site; Chelethrythrine chloride inhibits substrate site in catalytic domain.

PKC

ACTIVATORS ^d	Ca ²⁺ , DAG (D5156 , O6754), PDA (P9143), PDBu (P1269), PDD (P9018), PMA (P8139), PS (P5660 , P6641 , P7769)	Ca ²⁺ , DAG (D5156 , O6754), PDA (P9143), PDBu (P1269), PDD (P9018), PMA (P8139), PS (P5660 , P6641 , P7769)	Ca ²⁺ , DAG (D5156 , O6754), PDA (P9143), PDBu (P1269), PDD (P9018), PMA (P8139), PS (P5660 , P6641)
INHIBITORS ^e	Calphostin C (C6303), Ro 31-8220 (R136), GF109203X (G2911), Gö 6976, K252a, Ro 31-7549, Gö 6983 (G1918), Chelerythrine chloride (C2932), (-)-Balanol, UCN-01, CGP41251, CGP54345, CGP53506, aprinocarsen, CGP53506	Calphostin C (C6303), Ro 31-8220 (R136), GF109203X (G2911), Gö 6976, K252a, Ro 31-7549, Gö 6983 (G1918), Chelerythrine chloride (C2932), (-)-Balanol, UCN-01, CGP41251, LY333531, LY379196, LY317615, aprinocarsen	Calphostin C (C6303), Ro 31-8220 (R136), GF109203X (G2911), Gö 6976, K252a, Ro 31-7549, Gö 6983 (G1918), (-)-Balanol, UCN-01, CGP41251, LY333531, LY379196, LY317615
SELECTIVE ACTIVATORS	Not known	Not known	Not known
PHYSIOLOGICAL FUNCTION	Cell motility, migration, apoptosis	Cell growth, immune function, B-cell survival	Cell growth, immune function, B-cell survival, antiapoptotic
DISEASE RELEVANCE	Cardiac hypertrophy, heart failure, prostate cancer, breast cancer, chemotherapeutic resistance	Cardiac hypertrophy, heart failure, gastric cancer	Cardiac hypertrophy, heart failure, leukemia, colon cancer

FOOTNOTES

a Processing sites listed.

b For detailed list of binding partners, see Reference: Poole, A.W., et al. "PKC-interacting proteins: from function to pharmacology." *Trends Pharmacol Sci*, **25**, 528-535 (2004).

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PKC

FAMILY MEMBERS/ISOFORMS	γ (P9542)	δ (P8538)	ϵ (P1164)
OTHER NAMES	Conventional	Novel	Novel
MOLECULAR WEIGHT/ STRUCTURAL DATA	78.4 kDa (h) 697 aa (h)	77.7 kDa (h) 676 aa (h)	83.5 kDa (h) 737 aa (h)
SPECIES	Ubiquitous, including human	Ubiquitous, including human	Ubiquitous, including human
DOMAIN ORGANIZATION	N-terminal pseudosubstrate domain, C1A domain, C1B domain, C2 domain, catalytic domain, C-terminal domain	N-terminal C2 domain, pseudosubstrate domain, C1A domain, C1B domain, catalytic domain, C-terminal domain	N-terminal C2 domain, pseudosubstrate domain, C1A domain, C1B domain, catalytic domain, C-terminal domain
PHOSPHORYLATION SITES	Thr ⁵¹⁴ , Thr ⁶⁵⁵ , Thr ⁶⁷⁴ (r,m)	Thr ⁵⁰⁵ , Ser ⁶⁴³ , Ser ⁶⁶² (r,m,h), Thr ⁵⁶⁵ , Ser ⁷⁰⁹ , Ser ⁷²⁸ , (rb)	Thr ⁵⁶⁶ , Thr ⁷¹⁰ , Ser ⁷²⁹ (h,r)
TISSUE DISTRIBUTION	CNS	Many; e.g. CNS, heart, kidney, liver, lung	Many; e.g. CNS, heart kidney, liver, lung
SUBCELLULAR LOCALIZATION	Cytosol, membrane	Cytosol, membrane, mitochondria	Cytosol, membrane, Golgi
BINDING PARTNERS/ ASSOCIATED PROTEINS	All isoforms: many, e.g. RACKs, STICKs, AKAPs. e.g. 14-3-3	See Reference ^b in Footnotes. e.g. 14-3-3, connexin43	e.g. integrins, connexin43
UPSTREAM ACTIVATORS	Conventional and novel isoforms: G protein-coupled receptors, tyrosine kinase receptors, non-receptor tyrosine kinase receptors, and other agonists of phospholipid hydrolysis, atypical isoforms: binding proteins, e.g. p62/zip, par6		
DOWNSTREAM ACTIVATION	MBP (M1891), Histone H3 (H4380), EGFr, MARCKS, Protamine (P4505), GAP43, Pleckstrin, Connexin43	MBP (M1891), Histones (eg. IIS) (H4524), EGFr, Protamine (P4505), MARCKS, GAP43, Pleckstrin, STAT1, STAT3, Adducin	MBP (M1891), Histones (H4524), EGFr, Protamine (P4505), MARCKS, GAP43, Pleckstrin
SUBSTRATES	α Pseudosubstrate peptide, MBP peptide (P2186), Syntide 2 (S2525), EGFr peptide (L9905), PKC substrate (P5307, V2131), MARCKS peptide	α Pseudosubstrate peptide, ϵ Pseudosubstrate peptide, MBP peptide (P2186), EGFr peptide (L9905), PKC substrate (P5307, V2131), eEF-1 α , MARCKS peptide	α Pseudosubstrate peptide, ϵ Pseudosubstrate peptide (P4459), ϵ Substrate (P6114), MBP peptide (P2186), EGFr peptide (L9905), PKC substrate (P5307, V2131), MARCKS peptide

FOOTNOTES

a Processing sites listed.

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PKC

ACTIVATORS	Ca ²⁺ , DAG (D5156 , O6754), PDA (P9143), PDBu (P1269), PDD (P9018), PMA (P8139), PS (P5660 , P6641 , P7769)	DAG (D5156 , O6754), PDA (P9143), PDBu (P1269), PDD (P9018), PMA (P8139), PS (P5660 , P6641 , P7769)	DAG (D5156 , O6754), PDA (P9143), PDBu (P1269), PDD (P9018), PMA (P8139), PS (P5660 , P6641 , P7769)
INHIBITORS	Calphostin C (C6303), Ro 31-8220 (R136), GF109203X (G2911), Gö 6976, K252a, Ro 31-7549, Gö 6983 (G1918), Chelerythrine chloride (C2932), (–)-Balanol, UCN-01, CGP41251	Calphostin C (C6303), Gö 6983 (G1918), Chelerythrine chloride (C2932), LY333351, (–)-Balanol, Rottlerin	Calphostin C (C6303), GF109203X (G2911), Gö 6983 (G1918), LY333351, (–)-Balanol
SELECTIVE ACTIVATORS	Not known	Not known	Not known
PHYSIOLOGICAL FUNCTION	Nociceptive response, spatial learning, neuroplasticity	Proapoptotic, growth, differentiation, platelet granular secretion	Cell migration, antiapoptotic, nociceptive response, macrophage activation
DISEASE RELEVANCE	Spinocerebellar ataxia, lymphoma	Cardiac hypertrophy, cardiac ischemic injury, prostate cancer, leukemia	Cardiomyopathy, ischemic preconditioning, Alzheimer's disease, lung cancer, colorectal cancer, skin cancer, diabetes

FOOTNOTES

a Processing sites listed.

b For detailed list of binding partners, see Reference: Poole, A.W., et al. "PKC-interacting proteins: from function to pharmacology." *Trends Pharmacol Sci*, **25**, 528-535 (2004).

c PKC α pseudosubstrate site sequence RFARKGALRQKNVHEVKDH. PKC ϵ pseudosubstrate site sequence PRKRQGAVRRRVHQVNGH (underlined are mutable sites for phosphorylatable residues). Substrates not determined on all isoforms.

d Specific lipid activator of α PKCs unknown.

e GF 109203X (Gö 6850 aka BIM 1) displays potency rank order of $\alpha > \beta > \epsilon > \delta > \zeta$. Bisindolylmaleimides (Ro compounds, BIM 1, Gö 6976) inhibit all PKCs in potency rank order of cPKCs > nPKCs > α PKCs (generally); Calphostin C inhibits DAG site in regulatory domain; BIM 1 and Ro compounds act at ATP site; Chelerythrine chloride inhibits substrate site in catalytic domain.

FAMILY MEMBERS	η/L (P0540)	θ	ξ
OTHER NAMES	Novel	Novel	Atypical
MOLECULAR WEIGHT/ STRUCTURAL DATA	77.9 kDa (h) 680 aa (h)	81.9 kDa (h) 706 aa (h)	67.7 kDa (h) 592 aa (h)
SPECIES	Ubiquitous, e.g. human	Ubiquitous, e.g. human	Ubiquitous, e.g. human
DOMAIN ORGANIZATION	N-terminal C2 domain, pseudosubstrate domain, C1A domain, C1B domain, catalytic domain, C-terminal domain	N-terminal C2 domain, pseudosubstrate domain, C1A domain, C1B domain, catalytic domain, C-terminal domain	N-terminal PB1 domain, pseudosubstrate domain, atypical C1 domain, catalytic domain, C-terminal domain
PHOSPHORYLATION SITES	Thr ⁵¹² , Thr ⁶⁵⁵ , Ser ⁶⁷⁴ (h) Thr ⁵¹³ , Thr ⁶⁵⁶ , Ser ⁶⁷⁵ (r,m)	Thr ⁵³⁸ , Ser ⁶⁷⁶ , Ser ⁶⁹⁵ (m,h)	Thr ⁴¹⁰ , Thr ⁵⁶⁰ (r,m,h)
TISSUE DISTRIBUTION	Many; e.g. CNS, heart, lung, spleen	Many; e.g. CNS, heart, liver, airway smooth muscle, lung	Many; e.g. CNS, heart, kidney, liver, lung
SUBCELLULAR LOCALIZATION	Cytosol, membrane	Cytosol, membrane	Cytosol, membrane
BINDING PARTNERS/ ASSOCIATED PROTEINS	All isoforms: many, e.g. RACKs, STICKs, AKAPs. See Reference ^b in Footnotes. e.g. cdk2	e.g. IKKβ	e.g. p62/ZIP, Par6, mek5
UPSTREAM ACTIVATORS	Conventional and novel isoforms: G protein-coupled receptors, tyrosine kinase receptors, non-receptor tyrosine kinase receptors, and other agonists of phospholipid hydrolysis, atypical isoforms: binding proteins, e.g. p62/zip, par6 →		
DOWNSTREAM ACTIVATION	MBP (M1891), Histones (H4524), EGFr, Protamine (P4505), MARCKS, GAP43, Pleckstrin, Integrin βII	MBP (M1891), Histones (H4524), EGFr, Protamine (P4505), MARCKS, GAP43, Pleckstrin	MBP (M1891), Histones (H4524), EGFr, Protamine (P4505), Pleckstrin
SUBSTRATES	η Substrate (P2614), α Pseudosubstrate peptide, ε Pseudosubstrate peptide (P4459), MBP peptide (P2186), EGFr peptide (L9905), PKC substrate (P5307, V2131), MARCKS peptide	θ Substrate (P2489), α Pseudosubstrate peptide, MBP peptide (P2186), EGFr peptide (L9905), PKC substrate (P5307, V2131), MARCKS peptide	ε Substrate (P6114), ε Pseudosubstrate peptide (P4459), α Pseudosubstrate peptide, MBP peptide (P2186), EGFr peptide (L9905), PKC substrate (P5307, V2131)
ACTIVATORS	DAG (D5156, O6754), PDA (P9143), PDBu (P1269), PDD (P9018), PMA (P8139), PS (P5660, P6641, P7769)	DAG (D5156, O6754), PDA (P9143), PDBu (P1269), PDD (P9018), PMA (P8139), PS (P5660, P6641, P7769)	PS (P5660, P6641, P7769), p62/ZIP, Par6
INHIBITORS	Calphostin C (C6303), GF109203X (G2911), Gö 6983 (G1918), LY-333351, (–)-Balanol, η pseudosubstrate peptide (P1864, P2114), NPC 15437	Calphostin C (C6303), GF109203X (G2911), Gö 6983 (G1918), LY333351 (–)-Balanol, θ pseudosubstrate peptide (P1989, P1739)	Gö 6983 (G1918), ξ pseudosubstrate peptide (P1614)
SELECTIVE ACTIVATORS	Not known	Not known	Not known
PHYSIOLOGICAL FUNCTION	Antiapoptotic, cell cycle, differentiation, B-cell development	Immune function (T-cell signaling), cytoskeletal assembly, antiapoptotic	Immune function (B-cell signaling), cell polarity, antiapoptotic
DISEASE RELEVANCE	Glioblastoma, lung cancer, renal cancer, skin cancer, breast cancer	Gastrointestinal cancer, breast cancer, leukemia	Colon cancer, pancreatic cancer, renal cancer, leukemia

PKC

FAMILY MEMBERS/ISOFORMS	<i>ι/λ</i>
OTHER NAMES	Atypical
MOLECULAR WEIGHT/ STRUCTURAL DATA	67.3 kDa (h) 587 aa (h)
SPECIES	Ubiquitous, e.g. human
DOMAIN ORGANIZATION	N-terminal domain, PB1 domain, pseudosubstrate domain, atypical C1 domain, catalytic domain, C-terminal domain
PHOSPHORYLATION SITES	Thr ⁴¹² , Thr ⁵⁶⁴ (h)
TISSUE DISTRIBUTION	Many; e.g. CNS, heart, airway smooth muscle, liver, lung
SUBCELLULAR LOCALIZATION	Cytosol, membrane
BINDING PARTNERS/ ASSOCIATED PROTEINS	All isoforms: many, e.g. RACKS, STICKs, AKAPs. See Reference ^b in Footnotes. e.g. p62, ZIP5, mek5, LIP, Par6
UPSTREAM ACTIVATORS	Atypical isoforms: binding proteins, e.g. p62/ZIP, Par6
DOWNSTREAM ACTIVATION	MBP (M1891), Histones (H4524), EGFr, Protamine (P4505), Pleckstrin, MARCKS
SUBSTRATES	ϵ Pseudosubstrate peptide (P4459), α Pseudosubstrate peptide, MBP peptide (P2186 , M8184), EGFr peptide (L9905), PKC substrate (P5307 , V2131), MARCKS peptide
ACTIVATORS	PS (P5660 , P6641 , P7769), p62/ZIP, Par6
INHIBITORS	Gö 6983 (G1918)
SELECTIVE ACTIVATORS	Not known
PHYSIOLOGICAL FUNCTION	Cell polarity, antiapoptotic, insulin sensitivity
DISEASE RELEVANCE	Colon cancer, leukemia, diabetes

FOOTNOTES

a Processing sites listed.

b For detailed list of binding partners, see Reference: Poole, A.W., et al. "PKC-interacting proteins: from function to pharmacology." *Trends Pharmacol Sci*, **25**, 528-535 (2004).

c PKC α pseudosubstrate site sequence RFARKGALRQKNVHEVKDH. PKC ϵ pseudosubstrate site sequence PRKRQGAVRRRVHQVNGH (underlined are mutable sites for phosphorylatable residues). Substrates not determined on all isoforms.

d Specific lipid activator of aPKCs unknown.

e GF 109203X (Gö 6850 aka BIM 1) displays potency rank order of $\alpha > \beta > \epsilon > \delta > \zeta$. Bisindolylmaleimides (Ro compounds, BIM 1, Gö 6976) inhibit all PKCs in potency rank order of cPKCs > nPKCs > aPKCs (generally); Calphostin C inhibits DAG site in regulatory domain; BIM 1 and Ro compounds act at ATP site; Chelerythrine chloride inhibits substrate site in catalytic domain.

PKC

Abbreviations

r: Rat

h: Human

m: Mouse

rb: Rabbit

PS: Phosphatidylserine

AKAP: A-Kinase Anchoring Protein

Aprinocarsen: ISIS 3521

Cdk2: Cyclin dependent kinase 2

CGP41251: (PKC412): Staurosporine derivative

CGP54345: ATP analog

CGP53506: N-(3-Nitrophenyl)-4-(3-pyridyl)-2-pyrimidinamine

eEF-1 α : Eukaryotic elongation factor-1 α peptide, residues 422-443.

Gö 6976: 5,6,7,13-Tetrahydro-13-methyl-5-oxo-12H-indolo[2,3-a]pyrrolo[3,4-c]carbazole-12-propanenitrile

Gö 6983: 2-[1-(3-Dimethylaminopropyl)-5-methoxyindol-3-yl]-3-(1H-indol-3-yl)maleimide

GF 109203X: 3-[1-[3-(Dimethylamino)propyl]-1H-indol-3-yl]-4-(1H-indol-3-yl)-1H-pyrrole-2,5-dione (Gö6850)

LIP: PKC λ interacting protein to PKC λ interacting protein

LY-333531: 9-[(Dimethylamino)methyl]-6,7,10,11-tetrahydro-(9S)-NH,18H-5,21:12,15-dimetheno-

dibenzo[e,k]pyrrolo[3,4-h][1,4,13]oxadiazacyclohexadecine-18,20(19H)dione

K252a: Staurosporine-related alkaloid

MARCKS peptide: Myristoylated alanine-rich C-kinase substrate, Ac-phe-lys-lys-ser-phe-lys-leu-NH₂

MBP: Myelin basic protein

NPC 15437: S-2,6-Diamino-N-[[1'-(1'-oxotridecyl)-2'-piperidiny]]methyl]hexanamide dihydrochloride

PB1: Phox and Bem1p binding domain

PDA: Phorbol 12, 13-diacetate

PDBu: Phorbol 12, 13-dibutyrate

PDD: Phorbol 12, 13-didecanoate

Pleckstrin: Platelet and leukocyte C-kinase substrate protein

PMA: Phorbol 12-myristate 13-acetate

RACK: Receptors for Activated C-Kinase

Ro 31-7549: 2-[1-3(Aminopropyl)indol-3-yl]-3(1-methyl-1H-indol-3-yl)maleimide

Ro 31-8220: 2-{1-[3-(Amidinothio)propyl]-1H-indol-3-yl}-3-(1-methylindol-3-yl)-maleimide

STAT: Signal Transducers and Activators of Transcription

STICK: Substrates That Interact with C-Kinase

Syntide 2: H-pro-leu-ala-arg-thr-leu-ser-val-ala-gly-leu-pro-gly-lys-lys-OH

TPA: Tetra phorbol acetate

UCN-01: 7-Hydroxy-staurosporine

ZIP: PKC Zeta interacting protein

FOOTNOTES