Phospholipase C

Key References

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Overview

The hydrolysis of a minor membrane phospholipid, phosphatidylinositol 4,5-bisphosphate (PIP_2) by a specific phospholipase C (PLC) is one of the earliest key events in the regulation of various cell functions by more than 100 extracellular signaling molecules. This reaction produces two intracellular messengers, diacylglycerol (DAG) and inositol 1,4,5-trisphosphate (IP_3), which mediate the activation of protein kinase C and intracellular calcium release, respectively. Furthermore, a decrease in the amount of PIP_2 itself is likely an important signal because PIP_2 is an activator for phospholipase D and phospholipase A_2, modulates actin polymerization by interacting with various actin-binding proteins, and serves as a membrane-attachment site for many signaling proteins that contain pleckstrin homology (PH) domains. Consequently, the activity of PLC is strictly regulated in cells through several distinct mechanisms that link multiple PLC isoforms to various receptors.

The 12 mammalian PLC isozymes identified to date (excluding alternatively spliced forms) are all single polypeptides and can be divided into five types: β, γ, δ, ε and ζ, of which four PLC-β, two PLC-γ, four PLC-δ, one PLC-ε and one PLC-ζ proteins are known. Two regions of high sequence homology, designated X and Y, constitute the PLC catalytic domain. The β-, γ-, and δ-type isozymes all contain an NH_2-terminal PH domain, an EF-hand domain located between the PH and X domains, and a C2 domain, which is sometimes represented as part of an extended Y domain. Whereas PLC-β and PLC-δ isozymes contain a short sequence of 50 to 70 amino acids that separates the X and Y regions, PLC-γ isozymes have a long sequence of ~400 amino acids that contains Src homology (two SH2 and one SH3) domains. PLC-ε, differs from the other three types of isozymes in that it possesses an NH2-terminal Ras guanine nucleotide exchange factor (RasGEF)–like domain and one or two COOH-terminal Ras binding (RA) domains. PLC-ζ has domain features similar to PLC-δ, but lacks the PH domain.

The receptor-mediated activation of PLC-β isozymes is achieved mainly via the α subunits of the $G_{q/11}$ subfamily of heterotrimeric G proteins or the Gβγ dimers. The region of PLC-β that interacts with $G\alpha_{q/11}$ differs from that responsible for interaction with Gβγ. Binding of polypeptide growth factors (platelet-derived growth factor, epidermal growth factor, fibroblast growth factor) to their receptors results in activation of the intrinsic protein tyrosine kinase (PTK) activity that causes the phosphorylation of PLC-γ1 at tyrosines 771, 783 and 1254. Phosphorylation of tyrosine 783 was shown to be essential for the growth factor-dependent activation of PLC-γ1. Nonreceptor PTKs also phosphorylate and activate PLC-γ isozymes in response to the ligation of certain cell surface receptors listed in the table. These receptors, most of which comprise multiple polypeptide chains, do not themselves possess PTK activity, but activate a wide variety of nonreceptor PTKs such as the members of Src, Syk and Btk families.

The mechanism by which PLC-δ is coupled to membrane receptors remains unclear. PLC-ε can be activated by growth factors, $G\alpha_{12/13}$ via the small G proteins Ras, Rap or Rho, and by Gβγ. All PLC isozymes are activated by calcium *in vitro*, but PLC-δ isozymes are more sensitive to calcium compared with the other isozymes. Furthermore, PLC-δ can be tethered to PIP_2-containing membranes via its PH domain in the absence of other signals.

Phospholipase C

Subfamily Name	PLC-β	PLC-γ	PLC-δ	PLC-ε
Approximate Molecular Weight Unique Feature of Subfamily	150 kDa	145 kDa Presence of two SH2 and one SH3 domains	85 kDa Short carboxyl-terminal region following the Y-region	230 kDa RasGEF and RA Domain
Subfamily Members	PLC-β1, -β , -β3, and -β4	PLC-γ1 and -γ2	PLC-δ1, -δ2, -δ3 and -δ4	PLC-ε
Transducer 1	α subunit of the $G_{q/11}$ class G protein	Protein tyrosine kinase domain of the growth factor receptors; PIP_3	High molecular weight G protein and possibly PIP_2 **(P9763)** and Ca^{2+}	Ras **(R9894)**, G12
Receptors Coupled to Transducer 1	G protein-coupled receptors such as α_1-adrenoceptor and those for angiotensin, bombesin, bradykinin, histamine, muscarinic acetylcholine (M_1, M_3 and M_5), thrombin, thromboxane A_2, thyroid-stimulating hormone and vasopressin	Receptors for polypeptide growth factors such as platelet-derived growth factor, epidermal growth factor, nerve growth factor, fibroblast growth factor	α_1-adrenoceptor, oxytocin, thromboxane receptors	Not known
Transducer 2	βγ subunits of G proteins	Nonreceptor protein tyrosine kinases such as the members of Src, Syk and Btk families; PIP_3	Not known	Not known
Receptors Coupled to Transducer 2	G protein-coupled receptors such as those for muscarinic acetylcholine (M2) and interleukin 8	Membrane immunoglobulin M, T cell antigen receptor, high affinity IgE receptor, IgE receptors, and the receptors for cytokines such as ciliary neurotrophic factor, leukemia inhibitory factor, oncostatin M and interleukin 6	Not known	Not known
Non-Specific Inhibitors	Vinaxanthone ET-18-OCH3 **(E1779, O9262)** U-73,122 **(U6756)**	Vinaxanthone, ET-18-OCH3 **(E1779, O9262)**, U-73,122 **(U6756)**, Myristoylated peptide (Myr-GLYRKAMRLRYPV), Prenylated flavonoid from *Saccharomyces flavescense*	Vinaxathone, ET-18-OCH3 **(E1779)**, U-73,122 **(U6756)**	Not known
Tissue Expression	PLC-β1 and β3 are widely distributed PLC-β2 is mainly in hematopoietic tissues PLC-β4 is in retina and brain	PLC-γ1 is widely distributed. PLC-γ2 is in hematopoietic tissues, especially B cells	Widely distributed	Widely distributed
Physiological Function	Generates inositol trisphosphate which mobilizes intracellular Ca^{2+}. The resulting increase in Ca^{2+} induces many physiological responses.	Mediates part of growth factors action on growth and development	Not known	Not known

Abbreviations
ET-18-OCH3: 1-Octadecyl-2-methoxy-Sn-racglycero-3-phosphocholine
PIP_2: Phosphatidylinositol-4,5-bisphosphate
PIP_3: Phosphatidylinositol-1,4,5-trisphosphate
U-73,122: 1-(6-[([17b]-3-Methoxyestra-1,3,5[10]-trien-17-yl)-amino]hexyl)-1H-pyrrole-2,5-dione

Footnotes