Regulation of Phospholipase C Isozymes by Ras superfamily GTPases

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The physiological effects of many extracellular stimuli are mediated by receptor-promoted activation of phospholipase C (PLC). Inositol lipid signaling responses include the classically described conversion of PtdIns(4,5)P$_2$ to the Ca$^{2+}$-mobilizing second messenger Ins(1,4,5)P$_3$ and the protein kinase C-activating second messenger diacylglycerol as well as alterations in membrane association or activity of many proteins that harbor phosphoinositide binding domains. The PLC isozymes elaborate a minimal catalytic core typified by PLC-δ to confer multiple modes of regulation on their phospholipase activities. Although PLC-dependent signaling is prominently regulated by direct interactions with G$\alpha$- and G$\beta$$\gamma$-subunits of heterotrimeric G proteins and by tyrosine kinases, the existence of at least thirteen divergent PLC isozymes promises a diverse repertoire of regulatory mechanisms for this class of important signaling proteins. We recently have realized extensive and direct regulation of inositol lipid signaling by Ras superfamily GTPases. Cellular activity of mammalian PLC-ε is increased as a consequence of binding of Ras and Rap GTPases to conserved Ras-associating (RA) domains in the carboxy terminus. Rho GTPases also activate PLC-ε, but by a mechanism that does not require the carboxy terminal RA domains. We purified recombinant PLC-ε to homogeneity and illustrated direct GTP-dependent activation of this isozyme by purified RhoA. Results with intact cell analyses are consistent with the idea that activation of thrombin, lysophosphatidic acid, or other receptors results in sequential activation of G$\alpha$12/13, a Rho GEF, Rho, and PLC-ε. Rho family GTPases also are important regulators of certain PLC-β isozymes. Rac1, Rac2, and Rac3, but not RhoA, RhoB, or RhoC stimulate activity of PLC-β2 in vivo, and bind PLC-β2 and PLC-β3, but not PLC-β1, in vitro. Surface plasmon resonance studies identified the pleckstrin homology (PH) domain of PLC-β2 as the recognition site for Rac GTPases. We recently solved the crystal structure of a complex of PLC-β2 and GTP-bound Rac1 that defines the GTPase-interacting face of the PH domain of PLC-β2. It will be important to establish the physiological and pathophysiological roles played by PLC isozymes in Ras GTPase signaling pathways.

Profile: Kenan Professor, Journal of Biological Chemistry Editorial Board, former Editor, Molecular Pharmacology