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Review

Dynamic phospholipid signaling by G protein-coupled receptors

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Abstract

G protein-coupled receptors (GPCRs) control a variety of fundamental cellular processes by regulating phospholipid signaling pathways. Essential for signaling by a large number of receptors is the hydrolysis of the membrane phosphoinositide PIP_2 by phospholipase C (PLC) into the second messengers IP_3 and DAG. Many receptors also stimulate phospholipase D (PLD), leading to the generation of the versatile lipid, phosphatidic acid. Particular PLC and PLD isoforms take differential positions in receptor signaling and are additionally regulated by small GTPases of the Ras, Rho and ARF families. It is now recognized that the PLC substrate, PIP_2, has signaling capacity by itself and can, by direct interaction, affect the activity and subcellular localization of PLD and several other proteins. As expected, the synthesis of PIP_2 by phosphoinositide 5-kinases is tightly regulated as well. In this review, we present an overview of how these signaling pathways are governed by GPCRs, explain the molecular basis for the spatially and temporally organized, highly dynamic quality of phospholipid signaling, and point to the functional connection of the pathways.

Keywords: GPCR; Phospholipase C; Phospholipase D; PIP_2; Phosphoinositide 5-kinase; Small GTPase

Contents

Abbreviations: DAG, diacylglycerol; EGF, epidermal growth factor; ERK, extracellular signal-regulated kinase; GAP, GTPase-activating protein; GEF, guanine nucleotide exchange factor; GPCR, G protein-coupled receptor; GTPγS, guanosine 5′-*0*-(3-thio)-triphosphate; IP_3, inositol-1,4,5-trisphosphate; LPA, lysophosphatidic acid; PA, phosphatidic acid; PDGF, platelet-derived growth factor; PH, pleckstrin homology; PX, phox homology; PI3K, phosphoinositide 3-kinase; PIP5K, phosphoinositide 5-kinase; PIP_2, phosphatidylinositol-4,5-bisphosphate; PIP_3, phosphatidylinositol-3,4,5-trisphosphate; PKA, protein kinase A; PKC, protein kinase C; PLC, phospholipase C; PLD, phospholipase D; PTX, pertussis toxin; RA, Ras-binding domain; RGS, regulators of G protein signaling; RTK, receptor tyrosine kinase; SH, Src homology

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1. Introduction

GPCRs constitute a large group of membrane receptors known to modulate a wide range of biological responses, including cell growth, differentiation, migration, and inflammatory processes. Many cellular responses elicited by GPCRs are mediated by phospholipid signaling cascades, initiated by Gα and Gβγ subunits of heterotrimeric G proteins. The hydrolysis of membrane phospholipids leads to the formation of various bioactive lipid mediators, acting either as extracellular signaling molecules or as intracellular second messengers. A crucial second messenger-forming system is the stimulation of phosphoinositide-specific phospholipase C (PLC) isoforms. Upon activation, PLC enzymes hydrolyze phosphatidylinositol-4,5-bisphosphate (PIP_2) at the inner face of the plasma membrane and thereby generate the messengers, diacylglycerol (DAG) and inositol-1,4,5-trisphosphate (IP_3). These two signaling molecules lead to the activation of several protein kinase C (PKC) isoforms and the release of calcium from intracellular stores, respectively. It is now well established that PLC stimulation plays a major role in many early and late cellular responses to GPCR activation, including smooth muscle contraction, secretion, neuronal signaling as well as fertilization, cell growth and differentiation [1,2]. Phospholipase D (PLD) is a distinct, phospholipid-specific phosphodiesterase that hydrolyzes phosphatidylcholine to phosphatidic acid (PA) and choline. PLD is rapidly activated in response to extracellular stimuli, and the generation of PA is considered to mediate many of the biological functions attributed to PLD and to play important roles in the regulation of cell function and cell fate. Indeed, activation of PLD by GPCRs has now been established to modulate such a wide array of cellular responses as calcium mobilization, secretion, superoxide production, endocytosis, exocytosis, vesicle trafficking, glucose transport, rearrangements of the actin cytoskeleton, mitogenesis and apoptosis [3–6].

The phosphoinositide PIP_2 takes a pivotal point in cellular signaling by both PLC and PLD. PIP_2 serves as the major substrate for PLC enzymes and, at the same time, profoundly affects the subcellular localization and activity of PLD enzymes and many other proteins via specific interaction with unique phosphoinositide-binding domains, including pleckstrin homology (PH), phox homology (PX), ENTH, FERM, FYVE and tubby domains. In this way, PIP_2 (and other phosphoinositides) modulate a remarkable number of cellular processes, such as actin cytoskeletal dynamics, vesicle trafficking, ion channel activity, gene expression and cell survival [7,8]. The activity and localization of phosphoinositide 5-kinase (PIP5K) isoforms, which catalyze the formation of PIP_2, are tightly regulated by monomeric GTPases. The regulation of PIP5K by GTPases likely contribute to the spatial and temporal organization of PIP_2 metabolism and, thus, direct discrete and dynamic GPCR signaling by PLC and PLD. Consistent with their distinct structural organization, the PLC and PLD isoforms are susceptible to distinct modes of activation by membrane receptors and monomeric GTPases. This review will focus on

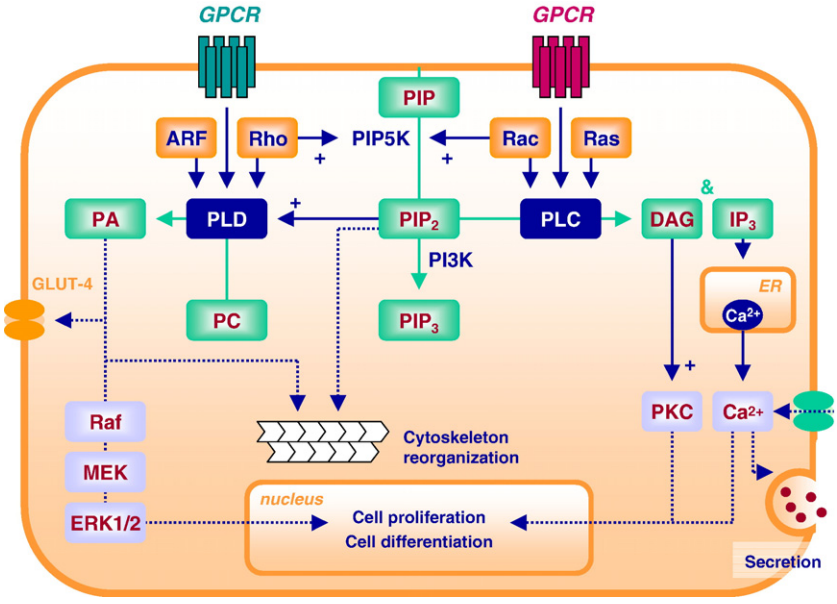

Fig. 1. Phospholipid signaling by GPCRs. GPCRs stimulate PLC isoforms that hydrolyze PIP_2 into the second messengers DAG and IP_3, leading to the activation of PKC isoforms and the release of Ca^{2+} from intracellular stores, respectively. PLC stimulation plays a major role in many cellular responses, including smooth muscle contraction, secretion, and cell proliferation and differentiation. Activation of PLD leads to the hydrolysis of phosphatidylcholine, and GPCR-induced PA generation modulates a wide array of cellular responses, including GLUT-4 translocation, actin cytoskeleton rearrangement, activation of the Raf/MEK/ERK1/2 signaling cascade, and mitogenesis. Stimulation of PLC and PLD enzymes by GPCRs involve monomeric GTPases of the Rho, Ras, and ARF families. PIP_2 takes a pivotal point in cellular signaling by both PLC and PLD: it serves as the major substrate for PLC enzymes, profoundly affects the subcellular localization and enzyme activity of PLD enzymes, can be further phosphorylated to the lipid mediator PIP_3 by PI3K, but also directly interacts with actin-remodeling proteins and ion channels. The synthesis of PIP_2 by PIP5K is regulated by Rho and ARF GTPases as well. PLC and PLD signaling is even more interconnected, as PLD activity is significantly regulated by PKC, and PA is a strong activator of PIP5K.