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Physiological functions of phospholipase C δ-type

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Introduction

Phosphoinositide metabolism is an important intracellular signaling system involved in a variety of cell functions, including secretion of hormones, transduction of neurotransmitters, growth factor signaling, membrane trafficking, and regulation of the cytoskeleton (Cockcroft and Carvou, 2007; Janetopoulos and Devreotes, 2006; Santarius et al., 2006). Phospholipase C (PLC) (PI-PLC; E.C.3.1.4.11) is one of the key enzymes in this system and hydrolyzes phosphatidylinositol 4,5-bisphosphate ($PI(4,5)P_2$) to generate two second messengers, inositol 1,4,5-trisphosphate (IP_3) and diacylglycerol (DAG). DAG mediates the activation of protein kinase C (PKC) (E.C.2.7.1.37), and IP_3 triggers release of Ca^{2+} from intracellular stores (Berridge and Irvine, 1984; Nishizuka, 1988).

In addition to the role of $PI(4,5)P_2$ as substrate for PLC, and PI 3-kinase (E.C.2.7.1.137), $PI(4,5)P_2$ directly regulates a variety of cell functions, including cytoskeletal reorganization, cytokinesis, membrane dynamics, nuclear events and channel activity (Clapham, 2003; Comer and Parent, 2007; Di Paolo and De Camilli, 2006; Fukami et al., 1992); therefore, strict regulation of $PI(4,5)P_2$ levels by PLC or other converting enzymes is necessary for homeostasis.

To date, 13 PLC isozymes have been identified and categorized into six classes, β, γ, δ, ε, ζ, and η-type, on the basis of structure and regulatory activation mechanisms (Fig. 1) (Fukami, 2002; Nakahara et al., 2005; Rhee, 2001). Each isozyme is composed of subtype-specific

Abbreviations: PLC, phospholipase C; $Ins(1,4,5)P_3$, *myo*-inositol 1,4,5-trisphosphate; DAG, diacylglycerol; $PI(4,5)P_2$, phospatidylinositol 4,5-bisphosphate; PH domain, pleckstrin homology domain; SH domain, src homology domain; RA domain, Ras-associating domain; RasGEF, Ras-GTPase exchange factor; PCR, polymerase chain reaction; FITC, fluorescent isothiocyanate; ZP, zona pellucida.

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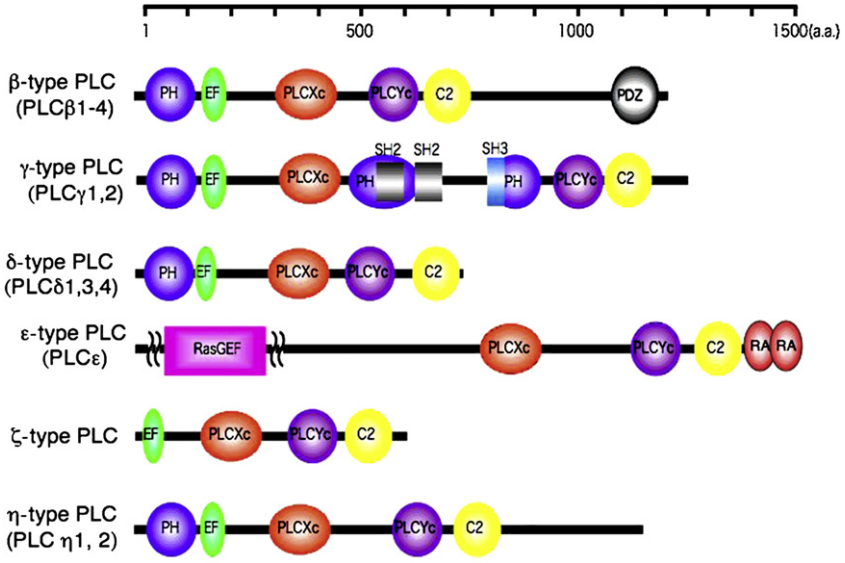

Fig. 1. Domain structure of each type PLC. Catalytic and regulatory domains are shown. PH: pleckstrin homology domain, EF: EF-hand domain, X and Y domain: PLC catalytic domain, C2: C2 domain, PDZ: PDZ-binding motif, SH: src homology domain, RasGEF: Ras-GTPase exchange factor-like domain, and RA: Ras-associating domain.

domains and conserved domains. All PLC isozymes contain catalytic X and Y domains as well as various regulatory domains, including the pleckstrin homology (PH) domain, EF-hand motif, and C2 domain. Subtype-specific domains contribute to the specific regulatory mechanisms. These domains include the src homology (SH) domain in PLCγ (Rhee, 2001) and the Ras-associating (RA) domain and Ras-GTPase exchange factor-like domain in PLCε (Kelley et al., 2001; Song et al., 2001).

The regulatory mechanisms of β-type and γ-type PLCs have been analyzed extensively. Association of heterotrimeric G proteins of the Gq family stimulates activity of β-type PLC (Offermanns et al., 1997), and γ-type isozymes are regulated primarily by receptor and cytosolic tyrosine kinases (Rhee, 2001; Rhee and Bae, 1997). In contrast, δ-type PLC isozymes are thought to be regulated by calcium (Kim et al., 1999). ε-Type PLC has been identified as an effector of Ras protein and is regulated by Ras in a GTP-dependent manner (Kelley et al., 2001; Song et al., 2001). However, the regulatory mechanism of the ζ-type PLC and η-type PLC remains unclear.

Among PLC family members, PLCδ is considered to be the most basic isoform because its structure is the simplest, comprising a PH domain (Essen et al., 1996; Ferguson et al., 1995), EF-hand motif, X and Y domains, and C2 domain. In addition, comparison of DNA sequences suggests an evolutionary relation in which PLCδ appeared in primitive eukaryotes.

PLCδ-type is composed of three isozymes, PLCδ1, δ3, and δ4 (Irino et al., 2004). We have generated these PLCδ gene-deficient (KO) mice. Here we focused on physiological functions of PLCδ-type by analyzing these KO mice. We have found that PLCδ4 is required for the acrosome reaction in fertilization (Fukami et al., 2001, 2003). We also found that PLCδ1 is essential for normal hair formation (Nakamura et al., 2003), and PLCδ1 KO mice displayed symptoms of skin inflammation (Ichinohe et al., 2007). Furthermore we found that double disruption of PLCδ1 and PLCδ3 results in embryonic lethality because of insufficient vascularization of the placenta (Nakamura et al., 2005).