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Review Article

The Contribution of Signaling to Unraveling the Natural History of Cancer. The Lesson of the Phosphoinositide-specific Phospholipase C Pathway

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Abstract

Signal transduction pathways represent the bases of physiological cell activities, and the disruption of one or more pathways is involved in several human diseases.

Phospholipases are well conserved enzymes identified in different organisms, including bacteria, yeast, plants, animals, and viruses. Phosphoinositide-specific Phospholipases C (PI-PLC) belongs to the inositide signaling pathways. In the structures of PI-PLC isozymes highly conserved domains as well as regulatory specific domains determine regulatory peculiarities. PI-PLC enzymes share a common mechanism, but each subtype plays a peculiar role and has a specific cell distribution related to a specific function. Many evidences indicated that the regulation of PI-PLCs is crucial in health and disease. PI-PLC-dependent molecular mechanisms were associated with the activation or inhibition of important physiological or pathological processes.

Keywords: Signal transduction pathways, Phosphoinositide-specific Phospholipases C, Cancer

Introduction

Many if not all human diseases result from abnormalities in one or more signaling pathways [1]. That moved to extensive research in order to unraveling the natural history of the disease and to develop therapies based on the interception of such abnormalities.

Many signal transduction pathways were studied in cancer as well as in degenerative diseases, including the wide Phosphoinositide signaling.

Phosphoinositide-specific Phospholipases C

The wide group of phospholipase enzymes comprises families found in animals, plants, bacteria, yeast, and viruses. The Phosphoinositide (PI)-specific Phospholipase C (PLC) family comprises different subtypes of enzymes that share a common basic activity, as PI-PLCs cleave the polar head group of phosphatidylinositol 4,5-bisphosphate (PIP2), producing two further signaling molecules, the inositol trisphosphate (IP3) and diacylglycerol (DAG) [2].

IP3 is water-soluble, and diffuses to the cytoplasm. In the endoplasmic reticulum (ER), IP3 binds IP3-gated calcium channels membrane promoting endoplasmic reticulum (ER) calcium release [2].

DAG, linked to the cell membrane using its fatty acid tails, can be cleaved into arachidonic acid [3], or can activate serine/threonine calcium-dependent protein kinases C (PKCs). Furthermore, the calcium increase due to IP3 allows PKC translate from the cytoplasm to the plasma membrane at the cytoplasmic face. The translocation activates and enables PKC to phosphorylate further target proteins [4,5].

Growing evidences indicate that the activity of PI-PLCs and related molecules are involved in a number of signal transduction pathways.

The PI-PLC family in mammals multi-domain enzymes includes six sub-families grouped depending on amino acid sequence, domain structure, and mechanism of recruitment: β(1-4), γ(1-2), δ(1, 3, 4), ε(1), ζ(1), and η(1-2) [5].

The structure of PI-PLC isozymes shows highly conserved domains, as the X and Y domains highly conserved regions. The C2, the EF-hand motif, and the pleckstrin homology (PH) domains represent regulatory domains different and specifically organized in depending on the PI-PLC subtype. Each PI-PLC isozyme bears a peculiar mix of X-Y and regulatory domains, acquiring different regulation, function, and tissue distribution.

PI-PLC enzymes are strictly cell-type specific [6-10], but the expression panel of PLCs in each cell type can vary in pathological conditions [11-19], as well as using specific stimuli [20-28] or inhibitors [6,7,12,13].

Also, the sub-cellular distribution of PLC enzymes influences the activity, suggesting that each isoform might play a specific role beside the basic cleavage of PIP2 [29-33].

A number of PI-PLC alternative splicing variants were described that might play an important role in the complex signaling cascades in human diseases, including cancer and degenerative diseases. PI-PLC family is thought to be essential to gain insights into the molecular mechanisms underlying both physiological processes and disease pathogenesis, also representing putative molecular targets in order to develop novel therapeutic approaches.

Mechanisms of Regulation of PI-PLC

One crucial point to understand and use PI-PLC signaling is represented by differences in the activation and regulation of these isozymes depending on subtype. PI-PLCβ enzymes can be activated by G protein-coupled receptors (GPCRs) by using different mechanisms. Although most PI-PLCβ enzymes may have a high guanosine triphosphatase activating protein (GAP) activity, PI-PLCβ1 has not. With the notable exception of PI-PLCβ4, PI-PLCβ isozymes can be activated by Gβγ dimers [34-38], with different sensitivity from that to Gqα subunits, with PI-PLCβ1 being the least sensitive to Gβγ [32,33,39-41].

PI-PLCβ1 has different regulatory mechanisms, as it can be regulated by a distinct binding region to phosphatidic acid (PA) or can be activated by MAPK, playing important roles in cell metabolism [39-42].

Interestingly, a nuclear cycle as described for PI-PLCβ1, can be activated by MAPK, translocate to the nucleus, where it is involved in specific signaling pathways involving inositol polyphosphate multikinase (IPMK) and gene promoter regulation.

PI-PLCγ subtypes can be activated by receptor tyrosine kinase (RTK), via SH2 domain-phospho-tyrosine interaction [43].

Regulation of PI-PLCγ1 involves polypeptide growth factor receptors that bind to RTKs. The SH2 domains of PI-PLC γ1 can mediate the link to auto-phosphorylated tyrosine residues in the intracellular region of the receptor [44]. PI-PLCγ1 can be activated downstream of a number of receptors lacking intrinsic tyrosine kinase activity [45-47].

PI-PLCγ2 can be activated downstream of immunoglobulin and adhesion receptors on immune cells, such as B cells, platelets, and mast cells, by non-receptor tyrosine kinases interacting with molecules belonging to other signaling pathways [48-50]. PI-PLCγ2 was demonstrated to play a critical role in B cells, via the B cell receptor (BCR) signaling, which induces the tyrosine phosphorylation of a variety of molecular substrates, including PI-PLCγ2 [51]. Lack of PI-PLCγ2 blocks the maturation of B cell from the transitional type 2 (T2) to follicular (FO) B cell transition. Deficiency of PI-PLCγ2 also impairs BCR-mediated calcium influx and NF-κB activation, crucial for B cell survival and function [48,52]. Moreover, PI-PLCγ2 is involved in the signaling of CD72, a type 2 membrane mostly expressed in B cells acting as a regulatory molecule important for B cell development [53]. In platelets, PI-PLCγ2 is involved signaling pathways acting during activation, especially in response to immobilized ligands like collagen and activated integrins, inducing calcium mobilization, cytoskeletal reorganization, and platelet activation [54]. In mast cells, PI-PLCγ2 acts crucially in activation and degranulation, triggering inflammation [53]. Activation of PI-PLCγ2 by cross-linking of FcεR (high-affinity IgE receptor) and FcγR (IgG receptor) increases intracellular calcium, essential for mast cell activation and degranulation. PI-PLCγ2 also contributes to the production of reactive oxygen species (ROS) and inflammatory cytokines, further enhancing the inflammatory response in mast cells [53].

PI-PLCδ subtypes are activated via a GPCR-mediated calcium mobilization. PI-PLCδ1 isozyme is one of the most sensitive enzymes to calcium, suggesting direct regulation by calcium [55,56].

PI-PLCε can be activated by both GPCR and RTK systems, with distinct activation mechanisms [57].

Different GPCR ligands can activate PI-PLCε. Moreover PI-PLCε can associate with Rap and translocate to the perinuclear area to interact with activated RTKs [58].

PI-PLCδ1 is thought to be involved in the positive feedback signal amplification of PI-PLC.

PI-PLCη1 can be activated via GPCR-mediated calcium mobilization, and specifically acts as a calcium sensor in the neuronal network [59].

Similarly to what described for PI-PLCδ1, PI-PLC η1 is involved in the positive feedback signal amplification of PI-PLC [57]. In fact, PI-PLC activity seems to be amplified and sustained by both intracellular calcium mobilization and extracellular calcium entry, taking advantage of either a negative or a positive feedback amplification of PI-PLC signaling [60-63].

PI-PLC β and PI-PLC γ isoenzymes are considered as primary PI-PLCs, activated by extracellular stimuli. Secondary PI-PLCs can be activated by Rho and Ras GTPases, while the activation of other secondary PI-PLCs (mainly PI-PLC δ1 and PI-PLC η1) might be enhanced by intracellular calcium mobilization that amplifies the PI-PLCs activity.

PI-PLCε isoenzymes can be activated by both GPCR and RTK systems, with distinct activation mechanisms.

The activation and regulatory mechanisms of sperm-specific PI-PLCζ are not fully understood, and the role interplays with the molecular activation of oocytes following fertilization in zygote interphase.

PI-PLC in Human Diseases

PI-PLC enzymes were involved in a number of human diseases, including different types of cancer [6-13].

The basic activity and/or accessory peculiar roles together with the chameleonic fine regulation probably explain why alterations affecting PI-PLC isozymes were identified in a number of human diseases originating in different tissues/organs [64-67].

PI-PLCβ1 plays a regulatory role in brain function, being highly expressed in olfactory bulb, hippocampus, amygdala, lateral septum, and cerebral cortex [68,69].

PI-PLC β1 is involved in the regulation of the cortical development and in synaptic plasticity, as it modulates hippocampal muscarinic acetylcholine receptor signaling. Abnormal expression of the *PLCB1* gene (OMIM *607120) and/or of PI-PLCβ1 enzyme was described in brain disorders [70].

Deletion of *PLCB1* in the orbito-frontal cortex [71] and abnormal expression pattern of PI-PLC β1 in specific brain areas of samples from human patients with schizophrenia and bipolar disorders [70] were described.

Enzymes belonging to the PI-PLCβ subfamily contribute to the differentiation and activation of immune cells involved both in the innate and adaptive immune system branches [72].

The contemporary lack of PI-PLCβ2 and PI-PLCβ3 was associated with abnormal T cell migration resulting from failure to increase intracellular calcium. In elderly people, human T cells show a reduced expression of PI-PLCβ2. This observation suggested that ageing immune suppression might be due to impairment of this PI-PLCβ2 enzyme in aged T lymphocytes [72,73].

Polarized macrophages play differently both in normal cells and in tumor cells. M1 macrophages are activated, typically by inflammatory stimuli, such as lipopolysaccharide (LPS) or Interferon (IFN)-γ, which induce the production of proinflammatory cytokines, phagocytosis, and initiation of the immune response [74,75]. Activated M1 macrophages also produce nitric oxide (NO) or reactive oxygen intermediates (ROI) which act as defense during infection. M2 macrophages are activated by exposure to selected cytokines, including Interleukin (IL)-4, IL-10, or IL-13 [75,76]. M2 macrophages will produce either polyamines to induce proliferation or proline to induce collagen production. These macrophages are associated with wound healing and tissue repair. In tumors, M1-polarized macrophages are considered to act as anti-tumor [75]. M2-polarized macrophages, considered tumor-associated macrophages (TAMs), contribute to many pro-tumorigenic outcomes in cancer, being involved in angiogenic and lymphangiogenic reorganization, immune suppression, hypoxia induction, cell proliferation, and metastasis progression [74]. Interestingly, in macrophages from murine models, the downregulation of PI-PLCβ2 plays an important role in M1-M2 differentiation and the activity of murine PI-PLCβ3 allow to promote macrophage survival. The last activity is crucial in atherosclerotic plaques, and PI-PLCβ3 might represent a putative molecular target in atherosclerosis mouse models [77]. Moreover, the pro-inflammatory molecule lipopolysaccharide (LPS) suppresses the expression of PI-PLCβ2 and PI-PLCβ1 in macrophages. The suppression of PI-PLCβ2 acts upon the M1/M2-like state switch [78,79], suggesting that this isoform is involved in macrophage polarization.

In murine macrophages, the deficiency of PI-PLCβ3 did not affect migration, adhesion, or phagocytosis, but resulted in increased sensitivity to apoptosis inducers via PKC-dependent upregulation of Bcl-XL [77].

Calcium is critical to T cell activation as a second messenger which rapidly activates further pathways. Calcium signaling networks a great number of signaling pathways inducing changes in gene expression and function in T cells [80]. Binding of antigens to the T cell antigen receptor (TCR) induces the mobilization of intracellular calcium which induces effective T cell activation. Thus, T cells showing defective calcium influx show defects in proliferation and cytokine production [80]. Due the growing importance of T cells in cancer immunotherapy, great interest arose about the possibility to monitor or manipulate calcium signaling in T cells both *in vitro* and *in vivo* [81].

Deletion of *PLCB1* was associated to myelodysplastic syndrome (MDS) progression toward acute myeloid leukemia (AML) [82].

Bone marrow and spleen of aged *Plcb3* null mice show increase of proliferating hematopoietic stem cells and myeloid progenitors with reduced apoptosis that have been molecularly associated with Stat5 inhibition [83].

The molecular interaction between enzymes belonging to the PI-PLCβ subfamily and G proteins inducing PI-PLCβ enzymes to localize in the cytosol or at the nuclear level can be determined by the intervention of translin-associated protein X (TRAX), a nuclease involved in RNA interference [84]. Enzymes belonging to the PI-PLCγ subfamily can play a specific key role in cancer cell migration and invasion. PI-PLCγ enzymes regulate cell metabolism, representing another putative molecular target in order to develop new therapeutic strategy. PI-PLCε was specifically linked to tumor suppression [85,86], mainly in colorectal cancer, where its reduction is associated with a more aggressive disease [87].

Great interest arose around PI-PLC ε as its regulation is strictly related to G protein signalling.

PI-PLC enzymes are involved in cancer, as well as in degenerative disorders and in male infertility, with special regard to PI-PLCζ isoform [88].

The fusion of the gametes is followed by a series of intracellular calcium oscillations in the zygote, which modulate molecular processes called "oocyte activation", which is crucial for the early embryonic development. These complex processes are triggered and regulated by calcium release resulting from PI-PLCζ activity. Recently, literature data reported abnormalities of the expression, structure, localization, and function of PI-PLCζ in the human sperm of infertile males resulting in impaired oocyte activation [89].

Enzymes belonging to the PI-PLCδ subfamily play several roles in different tissues and organs. PI-PLCδ1 and PI-PLCδ3 share a high sequence homology, so that they can play redundant roles in various tissues. PI-PLCδ1 is crucial in the maintenance of skin homeostasis. PI-PLCδ3 regulates enterocytes in the formation of microvilli and in the cerebral cortex of the developing brain the radial migration of neurons. Contemporary loss of PI-PLCδ1 and PI-PLCδ3 in mice induces embryo lethality due to placental vascular defects [90].

Conclusions

PI-PLC family enzymes play a basic role and further peculiar roles all essential in cell metabolism, by regulating calcium and other intracellular signaling pathways involved in cell proliferation and differentiation. PI-PLC enzymes act in physiological processes, as well as are involved in several pathological conditions. Thus, knowledge of the regulation of PI-PLC enzymes and related pathways can allow understand the cell physiology and also can help to outline the pathogenesis and the natural history of a number of diseases, that might open the way to develop innovative therapy strategies based upon the comprehension of molecular processes underlying the diseases.

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