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Nuclear phosphoinositide signaling

Keqiang Ye[1], Jee-Yin Ahn[2]

[1]Department of Pathology and Laboratory Medicine, Emory University School of Medicine, 615 Michael Street, Atlanta, GA 30322, USA, [2]Department of Molecular Cell Biology, Center for Molecular Medicine, Samsung Biomedical Research Institute, Sungkyunkwan University School of Medicine, Suwon 440-746, Korea

TABLE OF CONTENTS

1. Abstract
2. Introduction
3. Nuclear phosphoinositides ; PI3P, PI4P, and PI5P
3.1. Nuclear PI3P
3.2. Nuclear PI4P
3.3. Nuclear PI5P
4. Nuclear phosphoinositides ; PI3,4P_2, and PI4,5P_2
4.1. Nuclear PI3,4P_2
4.2. Nuclear PI4,5P_2
5. Nuclear phosphoinositides, PI(3,4,5)P_3
6. Phosphoinositide-phospholipase C (PI-PLC)
7. Perspective
8. Acknowledgements
9. References

1. ABSTRACT

Nuclear lipid metabolism performs a pivotal function in multiple signaling networks that mediate a variety of cellular events, including proliferation, differentiation and cell survival. The presence of phosphoinositides in the nuclei of mammalian cells is no longer in any doubt, and this has been corroborated by the detection of the enzymes responsible for phosphoinositide metabolism, phosphoinositide kinases and phosphatases in the nucleus. The nuclear phosphoinositide pool exists independently of the cytosolic pool, thereby showing a distinctive feature of nuclear lipid signaling as opposed to its cytosolic counterpart. The principal objective of this review is to summarize our updated knowledge regarding nuclear phosphoinositides and to discuss the current theories about the roles of the nuclear phosphoinositides.

2. INTRODUCTION

Among phospholipids, the phosphoinositides are generally considered to function as lipid second messengers, which act as key players in a number of cellular signaling events, including cell proliferation, differentiation, apoptosis, vesicle trafficking, insulin action, cytoskeleton changes, and motility (1), although they constitute only approximately 10% of membrane lipids, and their dysregulation is commonly observed in neoplasms and other diseases (2).

Phosphoinositide signaling primarily occurs at the plasma membrane, where phosphoinositides respond to stimuli and generate inositol phospholipid second messengers, which activate signal transduction within the cells. Nonetheless, phosphoinositides also exist in the

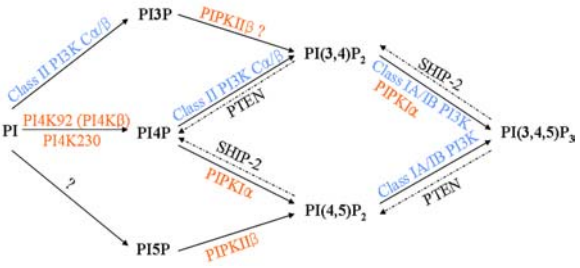

Figure 1. Major metabolism of phosphoinositide in the nucleus. The identified various kinases and phosphathase involved in the nuclear PI pathways are only depicted here.

nucleus of mammalian cells. Instead of the nuclear membrane, nuclear phosphoinositides reside within the nucleus and especially, associate with nuclear speckles domain. Initially, people believed that the nuclear membrane was the place where nuclear phosphoinositides are synthesized (3). However, extensive studies have demonstrated that isolated membrane free-nuclei from mouse erythroleukemia (MEL) cells remain the capability to synthesize phosphoinositides: PI4P and $PI(4,5)P_2$, and also that the quantity of nuclear $PI(4,5)P_2$ depends on the cellular differentiation state, although the total population of $PI(4,5)P_2$ does not appear to vary (4). The stimulation of Swiss 3T3 fibroblasts with insulin-like growth factor (IGF)-1 regulates nuclear phosphoinositides in a manner different from that observed in cytoplasmic lipid metabolism (5, 6). These early observations indicated that signaling by inositol lipids occurs within the nucleus, and that nuclear phosphoinositide metabolism and the relevant regulatory mechanisms operate independently from their cytoplasmic counterparts. Indeed, accumulating evidence demonstrates the presence of the enzymes involved in classical PI generation in the nuclei, including $PI(4,5)P_2$ kinase and phospholipase C as well as diacylglycerol kinase (DGK) (7, 8, 9, 10, 11). A great deal of literature documents the nuclear phosphoinositide metabolism, and recent reviews have updated our knowledge about subnuclear localization and nuclear phospholipid metabolism, as well as the kinases responsible for nuclear phospholipid metabolism (12, 13, 14, 15) (Figure 1).

It is now generally accepted that nuclear phosphoinositides exist independently of the nuclear membrane, and regulate a broad array of cellular events via association with their effectors and/or the formation of proteolipid complexes, for example, as was observed with $PI(4,5)P_2$ in association with the cytoskeleton. In this review, we will summarize the current wisdom regarding the role of nuclear phosphoinositides in major cellular events. We will also discuss their potential nuclear targets and the impact of these phenomena on cell biology.

3. NUCLEAR PIPS

To date, among seven different phosphorylated derivatives of phosphatidylinositol (PI), which are collectively referred to as "Ptdlns", the simplest of the inositol phospholipids include the phosphatidylinositol phosphates (PIPs), PI3P, PI4P, and PI5P. The PIPs are not only intermediates in PIP_2 and PIP_3 synthesis, but also involve in a variety of cellular processes (16).

3.1. Nuclear PI3P

PI3P can be generated via the phosphorylation of the D-3 position of the inositol head group by a family of PI3-kinases. It has been suggested that PI3P may play roles in both membrane trafficking and early endosomal dynamics in the cytoplasm (17, 18). Using a high-affinity PI3P specific - double-FYVE probe, Gillooly *et al.* (2000) detected PI3P within the nucleolus in human fibroblasts and BHK cells via electron microscopy. This observation is consistent with the fact that several types of PI3-kinases and their kinase activities occur in the nucleus (19, 20, 21, 22), suggesting that PI3P may perform some functions in nuclear processes or nucleolar activity. Moreover, one of the class II PI3-kinases C is activated during the G2/M phase and induces an elevation of nuclear PI3P (23), indicating that PI3P may play some role in the regulation of the cell cycle.

3.2. Nuclear PI4P

PI4P can be generated either by synthesis from PI via the phosphorylation of the D-4 position by PI4-kinase, or via the dephosphorylation of $PI(3,4)P_2$ by PTEN (phosphatase and tensin homologue deleted on chromosome 10), which acts as a 3' phosphatase on the inositol ring. In the cytoplasm, PI4P has been proposed to play a major role in golgi secretory functions (17, 24).

Previous study suggests that PI 4-kinase activity occur within the nucleus (25). The kinase responsible for the activity, namely PI4K beta was identified in the nuclei of native NIH3T3 fibroblasts and CHO cells. Additionally, the transfected PI4K beta accumulated in the nucleus of Cos-1 cells after the blockage of nuclear export by leptomycin B (LMB) (26). PI4K beta was also detected in the nuclei of yeast (27). Very recently, the phosphorylation specific forms of PI4K92 (Ser-496 and Thr-504) were also detected in the nuclear speckles (28), fitting with the previous observations regarding the nuclear distribution of other enzymes of the phosphoinositol cycle as well as the lipid products. For example, PIPKs type I and type II isoforms, as well as their products, $PI(4,5)P_2$ (29, 11); PI3-Kinase class 2alpha and 2beta (30, 31); and SHIP-2 (32, 33) were detected in the nuclear speckles. Moreover, microinjection of anti-pSer-496 antibody into the nucleus resulted in cell death (28), implying that PI4K92 plays a pivotal role in cell survival. In addition, another PI 4-kinase isoform, PI4K230, was detected in the nucleoli and the nucleoplasm of neural and nonneural cells. Both *Si*RNA for PI4K230 and DNase or RNase treatment disrupts the nucleolar localization of PI4K230 (34). Although there were some early observations that PI4P levels vary during the progression of the cell cycle (35), suggesting some role in cell proliferation, nuclear PI4P is believed to function principally as a precursor of $PI(4,5)P_2$ (14).

Specific subnuclear localization of different PI4-kinases may result in restricted production of PI4P in different nuclear compartments and lead to the formation of a distinct pool of $PI(4,5)P_2$, coincident with PI4P5-kinase,

which is associated with nuclear structures such as the speckle components (29) or regulatory proteins including the retinoblastoma protein (36). However, the possibility should not be dismissed that PI4P itself may be involved directly in the regulation of cell proliferation, survival, and nucleolar activity, operating via a distinct mechanism. The exact functions of PI4P in the nucleus remain largely unknown, and the biological significance of different nuclear compartment pools of PI4P awaits further clarification as well.

3.3. Nuclear PI5P

PI5P is the third PIP identified in the nuclei of mammalian cells, nuclear PI5P levels increase 20-fold during the G1 phase of the cell cycle (35), although the molecular mechanism of how PI5P levels are regulated remains to be determined. Both PI5P-Kinases (or type I PIPKs) and PIKfyve have been suggested to be able to convert PI to PI5P *in vitro* (37, 38, 39, 40), and PIKfyve has actually been determined as an enzyme responsible for the production of PI5P in mammalian cells (41). Emerging evidence suggests that the PHD finger motif of ING2, a putative tumor suppressor protein, is a nuclear receptor for PI5P, and a nuclear pool of this lipid has been shown to play a critical role in the response to DNA damage (42). In experiments conducted with overexpressed PIKIIbeta, which employed PI5P as a substrate for the production of $PI(4,5)P_2$, altered ING2 subcellular localization *in vivo* and ING2-association with the chromatin/nuclear matrix were observed, thereby indicating that the association of ING2 with chromatin is regulated by binding to PI5P. In addition, the interruption of PI5P and ING2 binding resulted in an attenuation of the ING2-mediated regulation of p53 acetylation and apoptosis (42). These results suggest that nuclear PI5P signaling may impinge on the levels within the nucleus, modulating p53 activity and cell death via interactions with chromatin-associated ING2. However, further study will be required in order to elucidate the manner in which nuclear PI5P is synthesized, as no unique PI5-kinase has been discovered within the nucleus.

4. NUCLEAR PIP_2s

Up to now, there is no report of $PI(3,5)P_2$ in the nucleus of mammalian cells. While its possible precursors, PI3P and PI5P, can be converted to $PI(3,5)P_2$ *in vitro*, the kinase responsible for the transformation in the nucleus remains elusive. In addition, the phosphatases SHIP-2 and PTEN, which can dephosphorylate specific 5'inositol phospholipids and 3' inositol phospholipids respectively from $PI(3,4,5)P_3$ to create $PI(3,4)P_2$ and $PI(4,5)P_2$, are identified at specific sites within the nucleus, whereas no specific 4' ipid phosphatase has ever been identified in the nucleus. Thus, although we cannot exclude the presence of $PI(3,5)P_2$ in the nuclear compartment, in this review, we will focus two well identified PIP_2s.

4.1. Nuclear $PI(3,4)P_2$

$PI(3,4)P_2$ can be generated via the dephosphrylation of $PI(3,4,5)P_3$ by the 5' lipid phosphatase SHIP1/2 (Src Homology domain-containing Inositol Phsophatase 1/2) (43, 44) or via the phosphorylation of PI4-P (45). $PI(3,4)P_2$, as well as $PI(3,4,5)P_3$, bind to the PH domain of Akt/PKB (protein kinase B), consequently recruiting Akt to the plasma membrane, where it is phosphorylated for full activation. Activated Akt regulates a variety of cellular signaling protocols, including cell proliferation, tumorigenesis, and cell survival, which suggests that $PI(3,4)P_2$ may be an important second messenger for cellular life.

Very little is known about nuclear $PI(3,4)P_2$. Although it is not clear whether $PI(3,4)P_2$ is present inside the nucleus, $PI(3,4)P_2$ has been detected in the nuclear membrane, using a specific $PI(3,4)P_2$ monoclonal antibody (46). The monomeric enzyme Class II PI3K (C2alpha, beta, gamma) exhibits a profound preference for PI4P as a substrate and produces $PI(3,4)P_2$, but also generates PI3P from PI. C2alpha has been detected both in the nucleus and in the nuclear speckles, whereas C2beta has been observed only in membrane-stripped nuclei, but not in the speckles (30), thus suggesting that $PI(3,4)P_2$ may play a role in pre-mRNA splicing. Moreover, the results of *in vitro* studies have revealed that SHIP1 employs both $Ins(1,2,4,5,)P_4$ and $PI(3,4,5)P_3$ as substrates (47, 48) whereas SHIP2 utilizes only $PI(3,4,5)P_3$ as a substrate (49). Thus far, only SHIP2, but not SHIP1 has been shown to be expressed and activated in the nuclei of vascular smooth muscle cells (32), particularly in the nuclear speckles. These findings imply that $PI(3,4)P_2$, may itself play a fundamental role in nuclear signaling events including transcriptional regulation, apoptosis, and the processing of mRNA splicing, rather than functioning only as a precursor for $PI(3,4,5)P_3$.

PTEN is a tumor suppressor gene, however, there is little evidence to date implicating that SHIP2 in the regulation of PI3K-dependent proliferation or cell death pathways that control tumorigenesis. Overexpression of SHIP2 inhibits insulin-stimulated PI3K dependent signalings (44). Depletion of *SHIP2* gene in mice results in an obesity-resistant phenotype. The animals show normal insulin and glucose tolerance but are highly resistant to weight gain on high fat diet (50). Thus, SHIP2 might be a significant therapeutic target for treatment of both obesity and type 2 diabetes. Nuclear PTEN does not dephosphorylate the nuclear pool of PIP3 (51). It remains unknown whether nuclear SHIP2 also lose its capability to hydrolyze $PI(3,4,5)P_3$ into $PI(3,4)P_2$.

4.2. Nuclear $PI(4,5)P_2$

$PI(4,5)P_2$ is the predominant regulatory molecule in the cytosolic phosphoinositide cycle. It is generated from PIP by the PIP kinases. Among the three types of PIP kinases, the type I and type II families of PIP kinases are known to generate $PI(4,5)P_2$, although they differ with regard to their substrate preferences (52, 53). The type I PI4P 5-Kinase (PIPKIalpha) and the type II PI5P 4-Kinase (PIPKIIbeta) exist within the nucleus, evidencing an association with the nuclear matrix. However, it remains to be determined whether PIPKIIbeta is localized in the nucleus or not (29, 54).

$PI(4,5)P_2$, as well as PIPKIalpha and PIPKIIbeta, can be found in electron-dense intranuclear

particles (29, 55), and recognized on the basis of nuclear speckle morphology as the result of changing transcriptional activity under immunofluorescence microscopy, demonstrating its co-localization with small nuclear ribonucleoprotein particles (snRNP) (29). The localization of $PI(4,5)P_2$ and its responsible kinase in the nuclear speckles is suggestive of a role in some aspect of mRNA processing. Osborne *et al.*, in 2001, demonstrated that $PI(4,5)P_2$ co-localizes with the splicing factor SC35, and hyperphosphorylates RNA pol II, as well as the Sm protein, a snRNP component, which is a known marker for nuclear speckles during interphase, but not during mitosis. Moreover, $PI(4,5)P_2$ was co-immunoprecipitated with snRNP as well as RNA pop II, suggesting that $PI(4,5)P_2$ probably exists as a lipid-protein-nucleic acid complex within the nucleus. Furthermore, the immunodepletion of $PI(4,5)P_2$ disrupted mRNA splicing, but the addition of $PI(4,5)P_2$ to nuclear extracts of Hela cells resulted in no detectable effects on the splicing rate *in vitro*. This may be attributable to the failure of exogenous $PI(4,5)P_2$ to be incorporated precisely into the nuclear compartment, where it should be. However, it remains to be determined whether or not the involvement of $PI(4,5)P_2$ in mRNA processing occurs directly, or indirectly, in conjunction with some other component of the nuclear matrix. Another factor also exists; namely, syntenin-2, which harbors a PDZ (Postsynaptic density protein, Disc large, Zona occludens) domain that co-localizes with $PI(4,5)P_2$ and binds to $PI(4,5)P_2$ in the nuclear speckles. The knockdown of this protein in MCF-7 and U2OS cells by S*i*RNA altered the localization of $PI(4,5)P_2$ in the nuclear speckles (56). Conceivably, syntenin-2 modulates $PI(4,5)P_2$ metabolism and regulates its translocation or sequestration into the nucleus, because syntenin-2 is targeted to the plasma membrane by $PI(4,5)P_2$, and is also co-localized with $PI(4,5)P_2$ in the nuclear speckles.

$PI(4,5)P_2$ is capable of binding to histones H1 and H3 and attenuating histone H1 transcriptional inhibition via the release of H1 from the DNA. This has been suggested as a mechanism for the regulation of $PI(4,5)P_2$ in chromatin remodeling (57). Another possible way that $PI(4,5)P_2$ may be involved in the regulation of chromatin remodeling involves the activation of T-lymphocytes, during which $PI(4,5)P_2$ may augment or facilitate the interaction of the chromatin remodeling complex, Brahma-related gene associated factor (BAF) with the nuclear matrix (58). During T-cell activation, the BAF complex is translocated from a soluble to an insoluble nuclear fraction via interaction with chromatin. The addition of $PI(4,5)P_2$ to the resting stage of the T-cells facilitated the association between BAF and the nuclear matrix (58) and $PI(4,5)P_2$ binds to BRG-1, which is known as an actin binding subunit of the BAF complex, and then stabilizes the nuclear matrix protein, actin (59), thereby augmenting the association of BAF with the nuclear matrix (60). Additionally, the retinoblastoma protein, Rb, which is a tumor suppressor that functions via the recruitment of the BAF complex to the transcription site, can interact with and activate PIPKIalpha (36, 61). This finding not only constitutes a significant step toward the determination of the mechanism by which $PI(4,5)P_2$ production occurs at sites where it influences BAF function, but also raises the possibility that pRB is an effective regulator of nuclear $PI(4,5)P_2$ levels, by virtue of its ability to stimulate the kinase activity of PIPKIalpha.

The emerging link between $PI(4,5)P_2$ and chromatin remodeling and transcriptional regulation leads to the supposition that $PI(4,5)P_2$ may perform a pivotal function in the regulation of these events. In fact, nuclear PIPKIα binds to Rb, which is involved in transcriptional regulation and chromatin remodeling, resulting in a recruitment of the PIPKIalpha to these complexes in which PI(4,5) can be generated. Another pool of nuclear $PI(4,5)P_2$, which is generated by PIPKIIbeta, implies the reduction of the nuclear level of PI5P, which binds to ING2 (42) as described above. ING2 levels were, in turn, reduced in the chromatin and nuclear matrix fraction in the PIPKIIbeta-overexpressd cells, suggesting that the generation of $PI(4,5)P_2$ at specific chromatin locations might result in an inhibition of the localized activation of ING2, via a reduction in PI5P production. This differential localization pool of $PI(4,5)P_2$ may influence the stability or activity of nuclear structural protein complexes, such as the chromatin remodeling complex or the splicing apparatus in the nuclear speckles.

5. $PI(3,4,5)P_3$

Compelling evidence has been accumulated in the past few years suggesting that nuclear $PI(3,4,5)P_3$ is linked to a variety of cellular events, including cell cycle progression, differentiation, proliferation, and cell survival. Nuclear $PI(3,4,5)\ P_3$ metabolism appears to be at least as complex as it could be in the cytoplasm. In the nucleus, the level of $PI(3,4,5)P_3$ can be regulated via generation by the class I PI 3-kinases, and degradation by two specific phosphatases-3' phosphatase (PTEN) and 5'phosphatase (SHIP-2).

$PI(3,4,5)P_3$ can be generated by the class IA PI3-kinases, which prefer $PI(4,5)P_2$ as a major substrate, consists of a p110 catalytic subunit (p110alpha,beta,delta) and one of a number of regulatory subunits derived from the alternative spicing of the p85, or p55 genes. p85/p110 PI3-kinase has been demonstrated to be active in the nuclei of rat liver cells (19), in human hepatocarcinoma HepG2 cells (62), osteoblast-like MC3T3-E1 cells (9) and HL-60 human promyelocytic leukemia cells (63). In addition, the class IB PI3-kinases, which consist of a p110gamma catalytic subunit and a 101 regulatory subunit, were detected in the nucleus (64).

HL-60 cells are differentiated into granulocytes following retinoid stimulation, whereas vitamin D3 has been shown to induce the differentiation of HL-60 cells into monocytes. Indeed, during the maturation of HL-60 cells into either granulocytes or monocytes, a marked increase in $PI(3,4,5)P_3$ synthesis and an upregulation of nuclear PI3-kinase activity have been shown to occur. Moreover, the treatment of these cells with specific PI3-kinase inhibitors or antisense PI3-kinase has been shown to disrupt its differentiation after retinoic acid treatment (65).

Furthermore, during the differentiation of erythroleukemia K562 cells, nuclear PI3-kinase activity was shown to be elevated and treatment with specific PI3-Kinase inhibitor or antisense PI3-kinase blocked cell differentiation (63). These findings clearly link PI(3,4,5) and nuclear PI3-Kinase to the process of differentiation.

It has been demonstrated that the rapid translocation of PI3-kinase into the nuclei of PC12 cells occurs in response to treatment with nerve growth factor (NGF) (66). Consistent with the detection of $PI(3,4,5)P_3$ in the nucleus, Tanaka *et al.* (1999) (67) found that the $PI(3,4,5)P_3$ binding protein (PIP_3BP), which contains a zinc finger motif and two PH domains, is localized within the nucleus and is abundant in the brain, thereby implying that PI(3,4,5) may be involved in the functioning of nerve systems. Moreover, as the result of NGF treatment applied to PC12 cells, the nuclear translocation of protein kinase C (PKC)-zeta was found to be dependent on $PI(3,4,5)P_3$ synthesis via enhanced nuclear PI3-Kinase activity (20), thus suggesting that the level of nuclear $PI(3,4,5)P_3$ may control the nuclear PKC-zeta pool.

The emerging link between nuclear PI(3,4,5) and anti-apoptotic signaling has become the focus of intense study. We have determined that nuclear PI3-Kinase performs a pivotal function in the prevention of caspase-3 activity and DNA fragmentation by DFF40/CAD, as the result of an *in vitro* DNA fragmentation assay using cell-free apoptotic solution, consisting of the cytosolic fraction of HEK293 cells supplemented with purified activated caspase-3 (68). $PI(3,4,5)P_3$, but no other PIP or PIP_2, mimicked the anti-apoptotic effects of NGF in the PC12 cells. When the isolated nuclei from NGF-treated PC12 cells were preincubated with PTEN or SHIP, which is expected to dephosphorylate $PI(3,4,5)P_3$ to $PI(4,5)P_2$ or $PI(3,4)P_2$, the nuclei evidenced obvious DNA fragmentation (68), indicating the loss of the anti-apoptotic effects of NGF. This suggests the involvement of nuclear $PI(3,4,5)P_3$ in the protective effects of NGF. In this connection, we identified B23/Nucleophosmin as a nuclear $PI(3,4,5)P_3$ binding protein using a $PI(3,4,5)P_3$ column and NGF-treated PC12 nuclear extract (69). The interaction between $PI(3,4,5)P_3$ and B23 is regulated by exposure to NGF, and B23 mutants that lose binding affinity for $PI(3,4,5)P_3$ fail to prevent apoptosis, thereby demonstrating that they cannot bind to DFF40/CAD, while the wild-type B23 resists apoptosis, evidencing robust DFF40/CAD-binding ability in apoptotic cells. These findings establish that $PI(3,4,5)P_3$ mediates the anti-apoptotic effects of NGF via binding to B23, which inhibits DNA fragmentation via the prevention of DFF40/CAD activity. Interestingly, nuclear Akt is necessary, but not sufficient, to mediate the anti-apoptotic activity of NGF. In fact, Akt is the best characterized downstream target protein of $PI(3,4,5)P_3$ in the cytoplasm, and it is now clear that Akt also exists within the nucleus. However, it appears not to be a target of $PI(3,4,5)P_3$ in the nucleus.

Despite its well-defined role in signaling at the plasma membrane, PTEN is found in the nucleus in a number of different normal and tumor cell types. Recent studies demonstrate that nuclear PTEN contribute to its tumor suppressive activity (70). In addition, it also regulates chromosomal stability (71). Interestingly, ubiquitination of PTEN regulates its nuclear translocation (72, 73). Surprisingly, Lindsay *et al.*, recently show that nuclear PTEN does not dephosphorylate nuclear $PI(3,4,5)P_3$ (51). Although the interesting results were reported with regard to the expression of nuclear PTEN during the progression of the cell cycle (74, 32), the function of nuclear $PI(3,4,5)P_3$ in cell cycle progression remains to be clearly elucidated. Further, PI3K inhibitors, overexpressed PTEN or SHIP2 was shown to downregulate the CDK inhibitory protein, $p27^{KIP}$, and to interrupt the G1 phase of the cell cycle (75, 76, 77). Thus, these data demonstrate that nuclear PTEN also implicates in cell cycle, however, whether it depends on the phosphatase function of nuclear PTEN awaits further clarification.

6. PI-PLC

Nuclear $PI(4,5)P_2$ is also substrate of another important enzyme, phosphoinositide-phospholipase C (PI-PLC), which is responsible for the generation of diacylglycerol (DAG) and inositol 1,4,5-triphosphste (IP_3). There are 13 isoforms of PI-PLC, some of which can be detected in the nucleus, but most of attention has been focused on PI-PLCbeta1 because this isoform is predominant in the nucleus (78, 79) and contains C-terminus nuclear localization signal (NLS) (80). Moreover, recent studies have showed that PI-PLCbeta1and $PI(4,5)P_2$ are associated to electron dense particle in the nuclear speckles (81), strengthen the possibility that $PI(4,5)P_2$ play important role in mRNA processing.

Stimulation of Swiss 3T3 fibroblasts cells by insulin-like growth factor 1(IGF-1) has firstly evidenced the activation of PI-PLC by a decrease in nuclear PI4P and $PI(4,5)P_2$ mass and a corresponding increase of DAG mass, with a translocation of PKC to the nucleus (6). Later, it has been demonstrated that PI-PLCbeta1 is responsible for IGF-1- induced the increase of nuclear DAG in the nucleus of Swiss 3T3 cells (78), as inhibition of PI-PLCbeta1 expression with antisense RNA reduces the DAG mass increase by IGF-1, but not by platelet-derived growth factor (PDGF) (82). Similarly, blocking of IGF-1 induced nuclear DAG production with a selective pharmacological inhibitors of PI-PLCbeta1elicited no translocation of PKC alpha to the nucleus, and the failure of S phase entry in response to IGF-1 in Swiss 3T3 cells (83), indicating that nuclear DAG recruit PKC alpha to the nucleus, which is essential in the mitogenic signaling exerted by IGF-1. How PKC alpha affect the proliferation rate has shown with the experiment that in NIH 3T3 mouse fibroblasts which were treated with tumor promoter 12- myristate 13-acetate (PMA), PKC alpha and PKC epsilon activate the cyclin D1 and cyclin E promoter, resulting in increase of the level of both cyclins, and thus elevate proliferation rates (84).

There is another evidence for PI-PLCbeta1 role in nuclear signaling. Erythroid differentiation of MEL cells is accompanied by a decrease in nuclear PI-PLCbeta1 activity and DAG mass (85, 79). In contrast, differentiation of C2C12 rat myoblasts was corresponded with a marked

increase of PI-PLCbeta1 activity and expression (86). Moreover, the expression of PI-PLCbeta1 mutant that is lacking of NLS suppressed C2C12 cell differentiation. One possible explanation that encompasses the opposite result from MEL and C2C12 cells is provided the observation of PKC isoforms, depending on the timing of activation in the G1 phase, either positively or negatively regulates cell cycle (63), along with different subcellular expression of PI-PLCbeta1 isoforms (87).

A new role for nuclear PI-PLCbeta1 has arisen from the hints at nuclear PI-PLCbeta1 as a key signaling molecule in the normal cell progression. Using specific probe of the PI-PLCbeta1 gene, fluorescence *in situ* hybridization (FISH) analysis has revealed monoallelic deletion of PI-PLCbeta1 gene allowing rearrangement of the chromosome 20 or other chromosome among MDS (myelodysplastic syndrome), which constitutes a group of hematological disorders characterized by peripheral blood cytopenias, secondary to bone marrow dysfunction, and AML (acute promyelocytic leukemia), which is characterized by an uncontrolled proliferation of blasts, patients (88, 89, 90, 91), implying that PI-PLCbeta1 could be involved in the progression of the disease.

7. PERSPECTIVE

Despite the vast amounts of research regarding nuclear lipid signaling conducted over the last two decades, relatively little useful information is currently available, especially compared to the great deal knowledge about cytosolic lipid signaling. We continue to be faced with the most basic questions. In what physical form do the nuclear phosphoinositides exist? Precisely where in the nucleus are they generated? And, finally, why is the subnuclear localization of nuclear phosphoinositides restricted?

However, the availability of useful new tools for phosphoinositides research has ushered in many important discoveries in the study of nuclear lipids. With better tools for the study of individual nuclear phosphoinositides, the inscrutable process of nuclear lipid signaling, about which we know so little thus far, will be greatly accelerated.

The findings reviewed here demonstrate that nuclear lipid signaling may be responsible for a multitude of cellular events, including differentiation, proliferation, cell cycle progression, RNA processing, and cell survival. However, our current understanding of nuclear phosphoinositide signaling is quite limited at present, with many questions left to be answered. The identification of specific nuclear targets of phosphoinositides and a greater insight into the role of phosphoinositides *in vivo* might provide us with a more detailed understanding of the functions of the nuclear phosphoinositides.

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9. REFERENCES

1. Toker, A.: Phosphoinositides and signal transduction. *Cell Mol Life Sci*, 59, 761-779 (2002)
2. Payrastre, B., K. Missy, S. Giuriato, S. Bodin, M. Plantavid & M. Gratacap: Phosphoinositides: key players in cell signalling, in time and space. *Cell Signal*, 13, 377-387 (2001)
3. Smith, C. D. & W. W. Wells: Phosphorylation of rat liver nuclear envelopes. II. Characterization of *in vitro* lipid phosphorylation. *J Biol Chem*, 258, 9368-9373 (1983)
4. Cocco, L., R. S. Gilmour, A. Ognibene, A. J. Letcher, F. A. Manzoli & R. F. Irvine: Synthesis of polyphosphoinositides in nuclei of Friend cells. Evidence for polyphosphoinositide metabolism inside the nucleus which changes with cell differentiation. *Biochem J*, 248, 765-770 (1987)
5. Cocco, L., A. M. Martelli, R. S. Gilmour, A. Ognibene, F. A. Manzoli & R. F. Irvine : Rapid changes in phospholipid metabolism in the nuclei of Swiss 3T3 cells induced by treatment of the cells with insulin-like growth factor I. *Biochem Biophys Res Commun*, 154, 1266-1272 (1988)
6. Divecha, N., H. Banfic & R. F. Irvine: The polyphosphoinositide cycle exists in the nuclei of Swiss 3T3 cells under the control of a receptor (for IGF-I) in the plasma membrane, and stimulation of the cycle increases nuclear diacylglycerol and apparently induces translocation of protein kinase C to the nucleus. *Embo J*, 10, 3207-3214 (1991)
7. D'Santos, C. S., J. H. Clarke & N. Divecha : Phospholipid signalling in the nucleus. Een DAG uit het leven van de inositide signalering in de nucleus. *Biochim Biophys Acta*, 1436, 201-232 (1998)
8. Martelli, A. M., L. Cocco, R. Bareggi, G. Tabellini, R. Rizzoli, M. D. Ghibellini & P. Narducci: Insulin-like growth factor-I-dependent stimulation of nuclear phospholipase C-beta1 activity in Swiss 3T3 cells requires an intact cytoskeleton and is paralleled by increased phosphorylation of the phospholipase. *J Cell Biochem*, 72, 339-348 (1999)
9. Martelli, A. M., G. Tabellini, R. Bortul, L. Manzoli, R. Bareggi, G. Baldini, V. Grill, M. Zweyer, P. Narducci & L. Cocco : Enhanced nuclear diacylglycerol kinase activity in response to a mitogenic stimulation of quiescent Swiss 3T3 cells with insulin-like growth factor I. *Cancer Res*, 60, 815-821 (2000)
10. Cocco, L., A. M. Martelli, O. Barnabei & F. A. Manzoli: Nuclear inositol lipid signaling. *Adv Enzyme Regul*, 41, 361-384 (2001)
11. Irvine R. F.: Nuclear lipid signalling. *Nat Rev Mol Cell Biol*, 4, 349-360 (2003)
12. Martelli, A.M., G. Tabellini, P. Borgatti, R. Bortul, S. Capitani & L. M. Neri: Nuclear lipids: new functions for old molecules? *J Cell Biochem*, 88, 455-461 (2003)
13. Cocco, L., A. M. Martelli, R. Fiume, I. Faenza, A. M. Billi & F. A. Manzoli: Signal transduction within the nucleus: revisiting phosphoinositide inositide-specific phospholipase Cbeta1. *Adv Enzyme Regul*, 46, 2-11 (2006)
14. Gonzales, M. L. & R. A. Anderson: Nuclear phosphoinositide kinases and inositol phospholipids. *J Cell Biochem*, 97, 252-260 (2006)

15. Martelli, A. M., C. Evangelist, A. M. Billi, L. Manzoli, V. Papa & L. Cocco: Intranuclear 3'-phosphoinositide metabolism and apoptosis protection in PC12 cells. *Acta Biomed*, 78 Suppl 1, 113-119 (2007)
16. Clarke, J. H.: Lipid signalling: picking out the PIPs. *Curr Biol*, 13, R815-R817 (2003)
17. Odorizzi, G., M. Babst & S. D. Emr: Phosphoinositide signaling and the regulation of membrane trafficking in yeast. *Trends Biochem Sci*, 25, 229-235 (2000)
18. Gillooly, D. J., I. C. Morrow, M. Lindsay, R. Gould, N. J. Bryant, J. M. Gaullier, R. G. Parton & H. Stenmark: Localization of phosphatidylinositol 3-phosphate in yeast and mammalian cells. *Embo J*, 19, 4577-4588 (2000)
19. Lu, Y., B. Cuevas, S. Gibson, H. Khan, R. LaPushin, J. Imboden & G. B. Mills: Phosphatidylinositol 3-kinase is required for CD28 but not CD3 regulation of the TEC family tyrosine kinase EMT/ITK/TSK: functional and physical interaction of EMT with phosphatidylinositol 3-kinase. *J Immunol*, 161, 5404-5412 (1998)
20. Neri, L. M., R. Bortul, M. Zweyer, G. Tabellini, P. Borgatti, M. Marchisio, R. Bareggi, S. Capitani & A. M. Martelli: Influence of different metal ions on the ultrastructure, biochemical properties, and protein localization of the K562 cell nuclear matrix. *J Cell Biochem*, 73, 342-354 (1999)
21. Ye, K., K. J. Hurt, F. Y. Wu, M. Fang, H. R. Luo, J. J. Hong, S. Blackshaw, C. D. Ferris & S. H. Snyder: Pike. A nuclear gtpase that enhances PI3kinase activity and is regulated by protein 4.1N. *Cell*, 103, 919-930 (2000)
22. Xia, X., A. Cheng, D. Akinmade & A. W. Hamburger: The N-terminal 24 amino acids of the p55 gamma regulatory subunit of phosphoinositide 3-kinase binds Rb and induces cell cycle arrest. *Mol Cell Biol*, 23, 1717-1725 (2003)
23. Visnjic, D., J. Curic, V. Crljen, D. Batinic, S. Volinia & H. Banfic: Nuclear phosphoinositide 3-kinase C2beta activation during G2/M phase of the cell cycle in HL-60 cells. *Biochim Biophys Acta*, 1631, 61-71 (2003)
24. Wang, Y. J., J. Wang, H. Q. Sun, M. Martinez, Y. X. Sun, E. Macia, T. Kirchhausen, J. P. Albanesi, M. G. Roth & H. L. Yin: Phosphatidylinositol 4 phosphate regulates targeting of clathrin adaptor AP-1 complexes to the Golgi. *Cell*, 114, 299-310 (2003)
25. Payrastre, B., M. Nievers, J. Boonstra, M. Breton, A. J. Verkleij & P. M. Van Bergen en Henegouwen: A differential location of phosphoinositide kinases, diacylglycerol kinase, and phospholipase C in the nuclear matrix. *J Biol Chem*, 267, 5078-5084 (1992)
26. de Graaf, P., E. E. Klapisz, T. K. Schulz, A. F. Cremers, A. J. Verkleij & P. M. van Bergen en Henegouwen: Nuclear localization of phosphatidylinositol 4-kinase beta. *J Cell Sci*, 115, 1769-1775 (2002)
27. Strahl, T., H. Hama, D. B. DeWald & J. Thorner: Yeast phosphatidylinositol 4-kinase, Pik1, has essential roles at the Golgi and in the nucleus. *J Cell Biol*, 171, 967-979 (2005)
28. Szivak, I., N. Lamb & L. M. Heilmeyer: Subcellular localization and structural function of endogenous phosphorylated phosphatidylinositol 4-kinase (PI4K92). *J Biol Chem*, 281, 16740-16749 (2006)
29. Boronenkov, I.V., J. C. Loijens, M. Umeda & R. A. Anderson: Phosphoinositide signaling pathways in nuclei are associated with nuclear speckles containing pre-mRNA processing factors. *Mol Biol Cell*, 9, 3547-3560 (1998)
30. Didichenko, S. A., & M. Thelen: Phosphatidylinositol 3-kinase c2alpha contains a nuclear localization sequence and associates with nuclear speckles. *J Biol Chem*, 276, 48135-48142 (2001)
31. Sindic, A., A. Aleksandrova, A. P. Fields, S. Volinia & H. Banfic: Presence and activation of nuclear phosphoinositide 3-kinase C2beta during compensatory liver growth. *J Biol Chem*, 276, 17754-17761 (2001)
32. Deleris, P., D. Bacqueville, S. Gayral, L. Carrez, J. P. Salles, B. Perret & M. Breton-Douillon: SHIP-2 and PTEN are expressed and active in vascular smooth muscle cell nuclei, but only SHIP-2 is associated with nuclear speckles. *J Biol Chem*, 278, 38884-38891 (2003)
33. Radu, A., V. Neubauer, T. Akagi, H. Hanafusa & M. M. Georgescu : PTEN induces cell cycle arrest by decreasing the level and nuclear localization of cyclin D1. *Mol Cell Biol*, 23, 6139-6149 (2003)
34. Kakuk, A., E. Friedlander, G. Jr. Vereb, A. Kasa, A. Balla, T. Balla, L. M. Jr. Heilmeyer, P. Gergely & G. Vereb: Nucleolar localization of phosphatidylinositol 4-kinase PI4K230 in various mammalian cells. *Cytometry A*, 69, 1174-1183 (2006)
35. Clarke, J. H., A. J. Letcher, C. S. D'Santos, J. R. Halstead, R. F. Irvine & N. Divecha: Inositol lipids are regulated during cell cycle progression in the nuclei of murine erythroleukaemia cells. *Biochem J*, 357, 905-910 (2001).
36. Divecha, N., M. Roefs, A. Los, J. Halstead, A. Bannister A & C. D'Santos: Type I PIPkinases interact with and are regulated by the retinoblastoma susceptibility gene product-pRB. *Curr Biol*, 12, 582-587 (2002)
37. Tolias, K. F., L. E. Rameh, H. Ishihara, Y. Shibasaki, J. Chen, G. D. Prestwich, L. C. Cantley & C. L. Carpenter: Type I phosphatidylinositol-4-phosphate 5-kinases synthesize the novel lipids phosphatidylinositol 3,5-bisphosphate and phosphatidylinositol 5-phosphate. *J Biol Chem*, 273, 18040-18046 (1998)
38. Shisheva, A., D. Sbrissa & O. Ikonomov: Cloning, characterization, and expression of a novel Zn2+-binding FYVE finger-containing phosphoinositide kinase in insulin-sensitive cells. *Mol Cell Biol*, 19, 623-634 (1999)
39. Sbrissa, D., O. C. Ikonomov & A. Shisheva A: PIKfyve, a mammalian ortholog of yeast Fab1p lipid kinase, synthesizes 5-phosphoinositides. Effect of insulin. *J Biol Chem*, 274, 21589-21597 (1999)
40. Shisheva A.: PIKfyve: the road to PtdIns 5-P and PtdIns 3,5-P (2). *Cell Biol Int*, 25, 1201-1206 (2001)
41. Sbrissa, D., O. C. Ikonomov & A. Shisheva: Phosphatidylinositol 3-phosphate-interacting domains in PIKfyve. Binding specificity and role in PIKfyve. Endomenbrane localization. *J Biol Chem*, 277, 6073-6079 (2002)
42. Gozani, O., P. Karuman, D. R. Jones, D. Ivanov, J. Cha, A. A. Lugovskoy, C. L. Baird, H. Zhu, S. J. Field, S. L. Lessnick, J. Villasenor, B. Mehrotra, J. Chen, V. R. Rao , J. S. Brugge, C. G. Ferguson, B. Payrastre, D. G. Myszka, L. C. Cantley, G. Wagner, N. Divecha, G. D. Prestwich & J. Yuan: The PHD finger of the chromatin-associated protein ING2 functions as a nuclear phosphoinositide receptor. *Cell*, 114, 99-111 (2003)

43. Woscholski, R. & P. J. Parker: Inositol lipid 5-phosphatases--traffic signals and signal traffic. *Trends Biochem Sci*, 22, 427-431 (1997)
44. Backers, K., D. Blero, N. Paternotte, J. Zhang & C. Erneux: The termination of PI3K signalling by SHIP1 and SHIP2 inositol 5-phosphatases. *Adv Enzyme Regul*, 43, 15-28 (2003)
45. Leevers, S. J., B. Vanhaesebroeck & M. D. Waterfield: Signalling through phosphoinositide 3-kinases: the lipids take centre stage. *Curr Opin Cell Biol*, 11, 219-225 (1999)
46. Yokogawa, T., S. Nagata, Y. Nishio, T. Tsutsumi, S. Ihara, R. Shirai, K. Morita, M. Umeda, Y. Shirai, N. Saitoh & Y. Fukui: Evidence that 3'-phosphorylated polyphosphoinositides are generated at the nuclear surface: use of immunostaining technique with monoclonal antibodies specific for PI 3,4-P (2). *FEBS Lett*, 473, 222-226 (2000)
47. Lioubin, M. N., P. A. Algate, S. Tsai, K. Carlberg, A. Aebersold & L. R. Rohrschneider: p150Ship, a signal transduction molecule with inositol polyphosphate-5-phosphatase activity. *Genes Dev*, 10, 1084-1095 (1996)
48. Giuriato, S., B. Payrastre, A. L. Drayer, M. Plantavid, R. Woscholski, P. Parker, C. Erneux & H. Chap: Tyrosine phosphorylation and relocation of SHIP are integrin-mediated in thrombin-stimulated human blood platelets. *J Biol Chem*, 272, 26857-26863 (1997)
49. Wisniewski, D., A. Strife, S. Swendeman, H. Erdjument-Bromage, S. Geromanos, W. M. Kavanaugh, P. Tempst & B. Clarkson: A novel SH2-containing phosphatidylinositol 3,4,5-trisphosphate 5-phosphatase (SHIP2) is constitutively tyrosine phosphorylated and associated with src homologous and collagen gene (SHC) in chronic myelogenous leukemia progenitor cells. *Blood*, 93 (8), 2707-2720 (1999)
50. Sleeman, M. W., K. E. Wortley, K. M. Lai, L. C. Gowen, J. Kintner, W. O. Kline, K. Garcia, T. N. Stitt, G. D. Yancopoulos, S. J. Wiegand & D. J. Glass: Absence of the lipid phosphatase SHIP2 confers resistance to dietary obesity. *Nat Med*, 11, 199-205 (2005)
51. Lindsay, Y., D. McCoull, L. Davidson, N. R. Leslie, A. Fairservice, A. Gray, J. Lucocq & C. P. Downes: Localization of agonist-sensitive PtdIns (3,4,5)P3 reveals a nuclear pool that is insensitive to PTEN expression. *J Cell Sci*, 119, 5160-5168 (2006)
52. Anderson, R. A., I. V. Boronenkov, S. D. Doughman, J. Kunz & J. C. Loijens: Phosphatidylinositol phosphate kinases, a multifaceted family of signaling enzymes. *J Biol Chem*, 274 (15), 9907-9910 (1999)
53. Rameh, L. E., K. F. Tolias, B. C. Duckworth & L. C. Cantley: A new pathway for synthesis of phosphatidylinositol-4,5-bisphosphate. *Nature*, 390, 192-196 (1997)
54. Ciruela, A., K. A. Hinchliffe, N. Divecha & R. F. Irvine: Nuclear targeting of the beta isoform of type II phosphatidylinositol phosphate kinase (phosphatidylinositol 5-phosphate 4-kinase) by its alpha-helix 7. *Biochem J*, 346 Pt 3, 587-591 (2000)
55. Osborne, S. L., C. L. Thomas, S. Gschmeissner & G. Schiavo: Nuclear PtdIns (4,5)P2 assembles in a mitotically regulated particle involved in pre-mRNA splicing. *J Cell Sci*, 114, 2501-2511 (2001)
56. Mortier, E., G. Wuytens, I. Leenaerts, F. Hannes, M. Y. Heung, G. Degeest, G. David & P. Zimmermann: Nuclear speckles and nucleoli targeting by PIP2-PDZ domain interactions. *Embo J*, 24, 2556-2565 (2005)
57. Yu, H., K. Fukami, Y. Watanabe, C. Ozaki & T. Takenawa: Phosphatidylinositol 4,5-bisphosphate reverses the inhibition of RNA transcription caused by histone H1. *Eur J Biochem*, 251, 281-287 (1998)
58. Zhao, K., W. Wang, O. J. Rando, Y. Xue, K. Swiderek, A. Kuo, G. R. Crabtree: Rapid and phosphoinositol-dependent binding of the SWI/SNF-like BAF complex to chromatin after T lymphocyte receptor signaling. *Cell*, 95, 625-636 (1998)
59. Pederson T.: Half a century of "the nuclear matrix". *Mol Biol Cell*, 11, 799-805 (2000)
60. Rando, O. J., K. Zhao, P. Janmey & G. R. Crabtree: Phosphatidylinositol-dependent actin filament binding by the SWI/SNF-like BAF chromatin remodeling complex. *Proc Natl Acad Sci U S A*, 99, 2824-2829 (2002)
61. Kang, H., K. Cui & K. Zhao: BRG1 controls the activity of the retinoblastoma protein via regulation of p21CIP1/WAF1/SDI. *Mol Cell Biol*, 24, 1188-1199 (2004)
62. Kim S. J.: Insulin rapidly induces nuclear translocation of PI3-kinase in HepG2 cells. *Biochem Mol Biol Int*, 46 (1), 187-196 (1998)
63. Neri, L. M., R. Bortul, P. Borgatti, G. Tabellini, G. Baldini, S. Capitani & A. M. Martelli: Proliferating or differentiating stimuli act on different lipid-dependent signaling pathways in nuclei of human leukemia cells. *Mol Biol Cell*, 13, 947-964 (2002)
64. Metjian, A., R. L. Roll, A. D. Ma & C. S. Abrams: Agonists cause nuclear translocation of phosphatidylinositol 3-kinase gamma. A Gbetagamma-dependent pathway that requires the p110gamma amino terminus. *J Biol Chem*, 274, 27943-27947 (1999)
65. Bertagnolo, V., L. M. Neri, M. Marchisio, C. Mischiati & S. Capitani : Phosphoinositide 3-kinase activity is essential for all-trans-retinoic acid-induced granulocytic differentiation of HL-60 cells. *Cancer Res*, 59, 542-546 (1999)
66. Neri, L. M., D. Milani, L. Bertolaso, M. Stroscio, V. Bertagnolo & S. Capitani: Nuclear translocation of phosphatidylinositol 3-kinase in rat pheochromocytoma PC 12 cells after treatment with nerve growth factor. *Cell Mol Biol (Noisy-le-grand)*, 40, 619-626 (1994)
67. Tanaka, K., K. Horiguchi, T. Yoshida, M. Takeda, H. Fujisawa, K. Takeuchi, M. Umeda, S. Kato, S. Ihara, S. Nagata & Y. Fukui: Evidence that a phosphatidylinositol 3,4,5-trisphosphate-binding protein can function in nucleus. *J Biol Chem*, 274, 3919-3922 (1999)
68. Ahn, J. Y., R. Rong, X. Liu & K. Ye: PIKE/nuclear PI 3-kinase signaling mediates the antiapoptotic actions of NGF in the nucleus. *Embo J*, 23, 3995-4006 (2004)
69. Ahn, J. Y., X. Liu, D. Cheng, J. Peng, P. K. Chan, P. A. Wade & K. Ye: Nucleophosmin/B23, a nuclear PI (3,4,5)P (3) receptor, mediates the antiapoptotic actions of NGF by inhibiting CAD. *Mol Cell*, 18**,** 435-445 (2005)
70. Lian, Z. & A. Di Cristofano: Class reunion: PTEN joins the nuclear crew. *Oncogene*, 24, 7394-7400 (2005)
71. Shen, W. H., A. S. Balajee, J. Wang, H. Wu, C. Eng, P. P. Pandolfi & Y. Yin: Essential role for nuclear PTEN in maintaining chromosomal integrity. *Cell*, 128, 157-170 (2007)

72. Trotman, L. C., X. Wang, A. Alimonti, Z. Chen, J. Teruya-Feldstein, H. Yang, N. P. Pavletich, B. S. Carver, C. Cordon-Cardo, H. Erdjument-Bromage, P. Tempst, S. G. Chi, H. J. Kim, T. Misteli, X. Jiang & P. P. Pandolfi: Ubiquitination regulates PTEN nuclear import and tumor suppression. *Cell*, 128, 141-5677 (2007)
73. Wang, X., L. C. Trotman, T. Koppie, A. Alimonti, Z. Chen, Z. Gao, J. Wang, H. Erdjument-Bromage, P. Tempst, C. Cordon-Cardo, P. P. Pandolfi & X. Jiang: NEDD4-1 is a proto-oncogenic ubiquitin ligase for PTEN. *Cell*, 128, 129-139 (2007)
74. Ginn-Pease, M. E. & C. Eng: Increased nuclear phosphatase and tensin homologue deleted on chromosome 10 is associated with G0-G1 in MCF-7 cells. *Cancer Res*, 63, 282-286 (2003)
75. York, J. D. & P. W. Majerus: Nuclear phosphatidylinositols decrease during S-phase of the cell cycle in HeLa cells. *J Biol Chem*, 269, 7847-7850 (1994)
76. Volinia, S., R. Dhand, B. Vanhaesebroeck, L. K. MacDougall, R. Stein, M. J. Zvelebil, J. Domin, C. Panaretou & M. D. Waterfield: A human phosphatidylinositol 3-kinase complex related to the yeast Vps34p-Vps15p protein sorting system. *Embo J*, 14, 3339-3348 (1995)
77. Simonsen, A., R. Lippe, S. Christoforidis, J. M. Gaullier, A. Brech, J. Callaghan, B. H. Toh, C. Murphy, M. Zeria & H. Stenmark: EEA1 links PI (3)K function to Rab5 regulation of endosome fusion. *Nature*, 394 (6692), 494-498 (1998)
78. Martelli, A. M., R. S. Gilmour, V. Bertagnolo, L. M. Neri, L. Manzoli & L. Cocco: Nuclear localization and signalling activity of phosphoinositidase C beta in Swiss 3T3 cells. *Nature* 358, 242-245(1992)
79. Divecha, N., A. J. Letcher, H. H. Banfic, S. G. Rhee & R. F. Irvine: Changes in the components of a nuclear inositide cycle during differentiation in murine erythroleukaemia cells. *Biochem J*, 312 (Pt 1), 63-67 (1995)
80. Kim, C. G., D. Park & S. G. Rhee: The role of carboxyl-terminal basic amino acids in Gqalpha-dependent activation, particulate association, and nuclear localization of phospholipase C-beta1. *J Biol Chem*, 271, 21187-21192 (1996)
81. Tabellini, G., R. Bortul, S. Santi, M. Riccio, G. Baldini, A. Cappellini, A. M. Billi, R. Berezney, A. Ruggeri, L. Cocco & A. M. Martelli: Diacylglycerol kinase-theta is localized in the speckle domains of the nucleus. *Exp Cell Res*, 287, 143-154 (2003)
82. Manzoli, L., A. M. Billi, S. Rubbini, A. Bavelloni, I. Faenza, R. S. Gilmour, S. G. Rhee & L. Cocco: Essential role for nuclear phospholipase C beta1 in insulin-like growth factor I-induced mitogenesis. *Cancer Res*, 57, 2137-2139 (1997)
83. Neri, L. M., P. Borgatti, S. Capitani & A. M. Martelli: Nuclear diacylglycerol produced by phosphoinositide-specific phospholipase C is responsible for nuclear translocation of protein kinase C-alpha. *J Biol Chem*, 273, 29738-29744 (1998)
84. Soh, J. W. & I. B. Weinstein: Roles of specific isoforms of protein kinase C in the transcriptional control of cyclin D1 and related genes. *J Biol Chem*, 278, 34709-34716 (2003)
85. Martelli, A. M., A. M. Billi, R. S. Gilmour, L. M. Neri, L. Manzoli, A. Ognibene & L. Cocco: Phosphoinositide signaling in nuclei of Friend cells: phospholipase C beta down-regulation is related to cell differentiation. *Cancer Res*, 54, 2536-2540 (1994)
86. Faenza, I., A. Bavelloni, R. Fiume, G. Lattanzi, N. M. Maraldi, R. S. Gilmour, A. M. Martelli, P. G. Suh, A. M. Billi & L. Cocco: Up-regulation of nuclear PLCbeta1 in myogenic differentiation. *J Cell Physiol*, 195, 446-452 (2003)
87. Faenza, I., A. Bavelloni, R. Fiume, P. Santi, A. M. Martelli, A. Maria Billi, V. R. Lo Vasco, L. Manzoli & L. Cocco: Expression of phospholipase C beta family isoenzymes in C2C12 myoblasts during terminal differentiation. *J Cell Physiol*, 200, 291-296 (2004)
88. Lo Vasco, V. R., G. Calabrese, L. Manzoli, G. Palka, A. Spadano, E. Morizio, P. Guanciali-Franchi, D. Fantasia & L. Cocco: Inositide-specific phospholipase c beta1 gene deletion in the progression of myelodysplastic syndrome to acute myeloid leukemia. *Leukemia*, 18, 1122-1126 (2004)
89. Calabrese, G., L. Stuppia, P. G. Franchi, R. Peila, E. Morizio, A. M. Liberati, A. Spadano, R. Di Lorenzo, E. Donti & A. Antonucci *et al*: Complex translocations of the Ph chromosome and Ph negative CML arise from similar mechanisms, as evidenced by FISH analysis. *Cancer Genet Cytogenet*, 78, 153-159 (1994)
90. Mori, A., H. Wada, M. Okada, H. Takatsuka, A. Tamura, Y. Fujimori, T. Okamoto, Y. Takemoto, A. Kanamaru & E. Kakishita: Acute promyelocytic leukemia with marrow fibrosis at initial presentation: possible involvement of transforming growth factor-beta (1). *Acta Haematol*, 103, 220-223 (2000)
91. Cocco, L., L. Manzoli, G. Palka & A. M. Martelli: Nuclear phospholipase C beta1, regulation of the cell cycle and progression of acute myeloid leukemia. *Adv Enzyme Regul*, 45, 126-135 (2005)

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Send correspondence to: Dr Jee-Yin Ahn, Department of Molecular Cell Biology, Center for Molecular Medicine, Samsung Biomedical Research Institute, Sungkyunkwan University School of Medicine, Suwon 440-746, Korea, Tel: 82-31-299-6134, Fax: 82-31-299-6139, E-mail: jyahn@med.skku.ac.kr

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