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IPMK: A versatile regulator of nuclear signaling events

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ABSTRACT

Inositol-derived metabolites (e.g., phosphoinositides and inositol polyphosphates) are key second messengers that are essential for controlling a wide range of cellular events. Inositol polyphosphate multikinase (IPMK) exhibits complex catalytic activities that eventually yield water-soluble inositol polyphosphates (e.g., IP_4 and IP_5) and lipid-bound phosphatidylinositol 3,4,5-trisphosphate. A series of recent studies have suggested that IPMK may be a multifunctional regulator in the nucleus of mammalian cells. In this review, we highlight the novel modes of action of IPMK in transcriptional and epigenetic regulation, and discuss its roles in physiology and disease.

Contents

1. Introduction

Inositol phosphates are signaling messengers that are involved in mediating diverse biological events such as growth, proliferation, and metabolic homeostasis (Chakraborty et al., 2010; Hatch and York, 2010; Wilson et al., 2013; Shears, 2015). Inositol polyphosphate multikinase (IPMK) is an enzyme essential for the synthesis of IP_4 [both Ins(1,3,4,5)P_4 and Ins(1,4,5,6)P_4] and IP_5 [Ins(1,3,4,5,6)P_5] (Saiardi et al., 1999; Frederick et al., 2005) (Fig. 1). The 6-kinase activity of IPMK makes this enzyme the sole factor capable of converting IP_3 into Ins(1,4,5,6)P_4 (one of only two IP_4 molecules). IPMK is also the only enzyme that can produce IP_5, placing it upstream of both the inositol hexakisphosphate kinases (IP6Ks) and the diphosphoinositol pentakisphosphate kinases (PPIP5Ks). IPMK depletion nearly eliminates intracellular IP_6 as well as inositol

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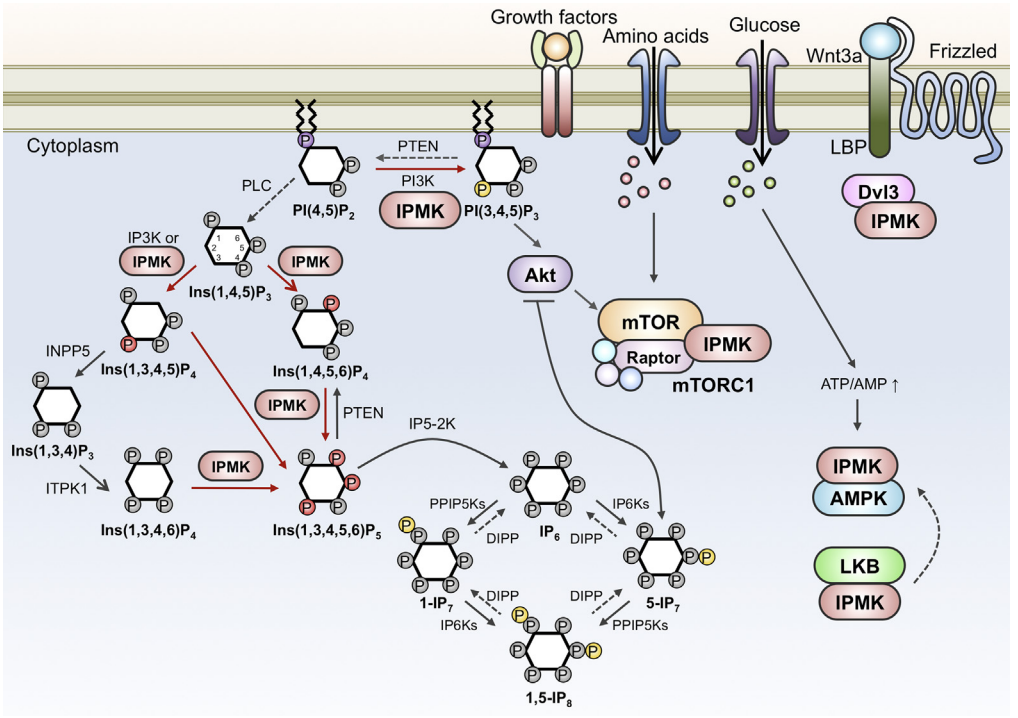

Fig. 1. Cytoplasmic IPMK functions in coordinating various signaling events. IPMK is essential for the production of various IPs like Ins(1,3,4,5)P_4, Ins(1,4,5,6)P_4, as well as Ins(1,3,4,5,6)P_5. As a PI3-kinase, IPMK also produces PIP_3, thus activating Akt signaling pathway in response to insulin and growth factors. Acting in a non-catalytic manner, IPMK binds, stabilizes, and mediates the activation of mTORC1 in response to amino acids. Depending on the cellular energy level, IPMK appears to control AMPK phosphorylation via direct protein interaction. IPMK-LKB1 binding may act as a critical event for determining metformin-dependent LKB1-AMPK signaling actions. Dishevelled-3 seems critical for the translocation of cytosolic IPMK into the plasma membrane where IPMK can regulate Wnt3a-Frizzled pathway.

pyrophosphates IP_7, proposing that IPMK is indispensable for the generation of all highly phosphorylated IP species (Frederick et al., 2005). IPMK appears to act upon an extraordinarily broad range of substrates, as it can also function as an inositol phospholipid kinase to phosphorylate PIP_2 at the 3 position, thereby producing phosphatidylinositol 3,4,5-trisphosphate (PIP_3) (Resnick et al., 2005). Snyder and his colleagues revealed that deletion of IPMK in mouse embryonic fibroblasts significantly decreased PIP_3 levels by up to 50% and subsequently attenuated growth-factor-induced PIP_3-dependent activation of Akt, indicating that IPMK is physiologically relevant as a major PI3-kinase (Maag et al., 2011). Moreover, IPMK can act in a catalysis-independent manner to mediate the amino-acid-stimulated activation of mammalian target of rapamycin (mTOR) via protein–protein interaction (Kim et al., 2011). Other IPMK-binding signaling molecules include AMP-activated protein kinase (AMPK), liver kinase B1 (LKB), and dishevelled segment polarity protein 3 (Dvl3) (Bang et al., 2012, 2014; Dailey and Kim, 2012; Wang and Wang, 2012). Collectively, these findings strongly indicate that IPMK is involved in coordinating major growth and energy metabolism signaling networks (Lee et al., 2012). IPMK is also present in the nuclear compartment, prompting keen research interest into the functional significance of nuclear IPMK (Nalaskowski et al., 2002).

This review discusses recent evidence indicating that IPMK is a key player in mediating various nuclear events in mammalian cells. We first summarize recent findings regarding the functional significance of IPMK-dependent nuclear PIP_3. We then review the evidence supporting a link between epigenetic control and Ins(1,4,5,6)P_4. Next, we highlight discoveries regarding the targets of IPMK-binding nuclear proteins and the modes of regulation that do not involve the catalytic activities of IPMK. Finally, we highlight some yet-unanswered questions in this area of cellular and molecular biology, and discuss future research directions.

2. IPMK acting as a nuclear PI3-kinase

Steroidogenic factor 1 (SF-1; also known as NR5A1) is a nuclear receptor that interacts with PIP_2 to control the expression levels of steroidogenic enzymes and peptide hormones, such as anti-Mullerian hormone (AMH) (De Santa Barbara et al., 1998) and steroidogenic acute regulatory protein (StAR) (Parker and Schimmer, 1997). The binding of PIP_2 to SF-1 appears to be critical for the transcriptional activity of the latter, as the PIP_2-binding-defective mutant of SF-1 lacks activity (Biason-Lauber and Schoenle, 2000; Sablin et al., 2009). IPMK was recently shown to be the only enzyme to physically interact with the SF-1–PIP_2 complex and phosphorylate SF-1–bound PIP_2 to generate PIP_3 (Blind et al., 2012; Blind, 2013) (Fig. 2). Classical PI3-

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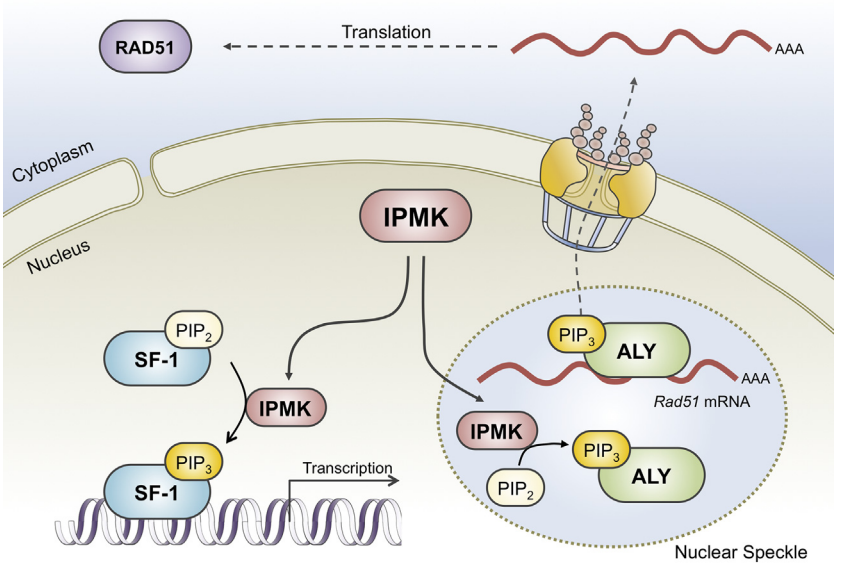

Fig. 2. IPMK actions as a nuclear PI3-kinase. IPMK can bind and phosphorylate transcription factor SF-1–bound PIP_2 to PIP_3 which is important for SF-1 mediated transcriptional control. Nuclear PIP_3 produced by IPMK is also critical for the ALY function in the recognition of specific mRNA species, which triggers the export of nuclear mRNA. For example, in the absence of IPMK, homologous recombination protein, Rad51 thus cannot be appropriately translated by DNA damage.

kinases (e.g., p110 PI3-kinase) failed to replace the function of wild-type IPMK in SF-1–PIP_2 phosphorylation. Interestingly, IPMK prefers SF-1–PIP_2 to PIP_2 as a substrate in micelles. Moreover, the IPMK-dependent phosphorylation of SF-1–PIP_2 has a functional impact on the activation of SF-1. In HEK293 cells, IPMK depletion was shown to impair the induction of SF-1 target genes. This phenotype was fully rescued by overexpression of wild-type IPMK, whereas expression of catalytically inactive IPMK or *Arabidopsis thaliana* IPMK (deficient in PI3-kinase activity) failed to restore SF-1 activity. These findings suggest that IPMK-dependent PIP_3 production is functionally significant in the activation of SF-1–specific transcription.

The importance of IPMK as a key nuclear PI3-kinase is further emphasized by its involvement in the export of nuclear mRNA to the cytoplasm, which is a critical step in the translation of eukaryotic mRNAs (Carmody and Wente, 2009; Tutucci and Stutz, 2011). The RNA-binding adaptor protein, ALY, is a TREX (transcription-export) complex component that plays a key role in releasing spliced mRNAs from nuclear speckle domains into the cytosol. An interaction between ALY and PIP_3 has been suggested to be required for the localization of ALY in the nuclear speckle domain, and to thereby regulate mRNA export activity. Interestingly, poly(A)$^+$ RNA species were found to accumulate in the nuclear speckles of IPMK-deficient human cancer cells, which is similar to the phenotype generated by ALY deficiency (Wickramasinghe et al., 2013). Genome-wide analyses further revealed that IPMK depletion downregulates the export of specific mRNA transcripts, most of which are involved in the DNA damage response pathway [e.g., homologous recombination (HR) proteins such as RAD51, BRCA1, FANCD2, and CHK1 (Fig. 2)]. In the absence of IPMK, human cancer cells exhibit severe defects in DNA repair responses, such as RAD51 recombinase assembly. Similar to the effects of IPMK depletion, overexpression of catalytically inactive IPMK mutants in cancer cells resulted in the aberrant accumulation of nuclear mRNAs and reduced assembly of the RAD51 complex in response to DNA damage. In the absence of IPMK, ALY no longer recognizes the RAD51 3′-UTR sequence, which is a critical event for the export of target mRNAs into the cytosol. Importantly, the addition of exogenous PIP_3 to IPMK-depleted cell extracts successfully restored the binding between ALY and the RAD51 3′-UTR. These findings clearly suggested that IPMK, acting as a PI3-kinase, crucially regulates the transcript-selective mRNA export pathway by controlling the homeostasis of nuclear PIP_3. Signaling relationship among IPMK and other PI-metabolizing enzymes in the fine control of nuclear phosphoinositides await further investigation (Keune et al., 2011; Balla, 2013; Bulley et al., 2014).

3. Ins(1,4,5,6)P_4 and epigenetic regulation

Histone deacetylase (HDAC) is a major epigenetic regulator that detaches acetyl groups from lysine residues in histone tails, and thereby regulates chromosomal condensation and gene expression. The Class I HDACs (e.g., HDAC1, HDAC2, and HDAC3) are distinct among the four classes of mammalian HDACs in that corepressor proteins recruit them into specific transcriptional repression complexes (Grunstein, 1997; Struhl, 1998; Shogren-Knaak et al., 2006). More specifically, HDAC1 and HDAC2 are activated by specific corepressor complexes that include Sin3A (Laherty et al., 1997), CoREST (Humphrey et al.,

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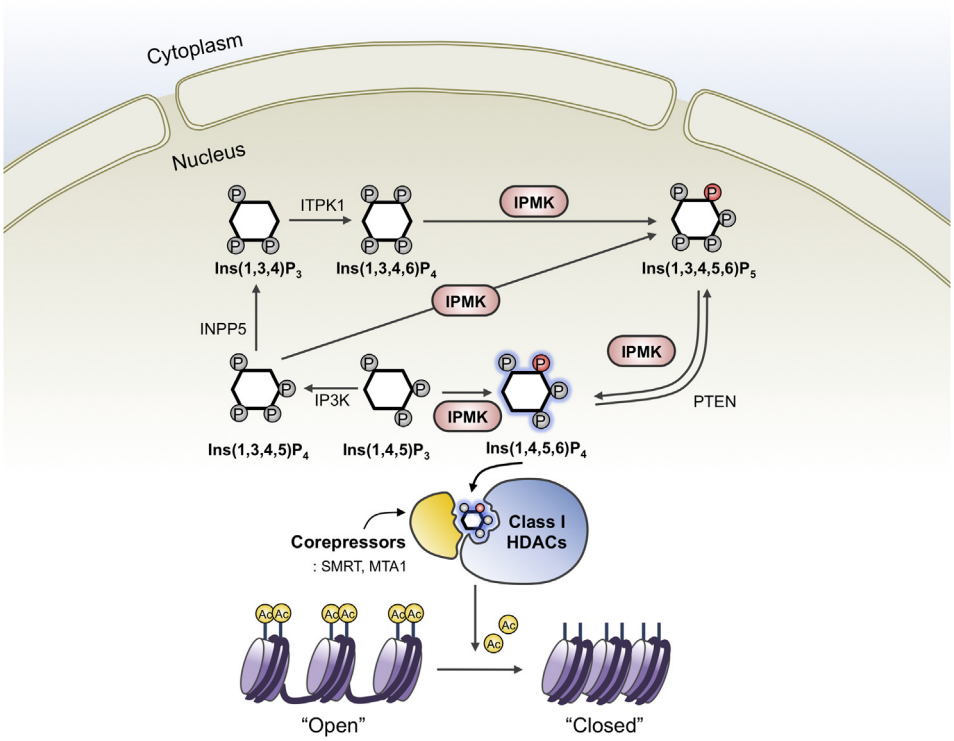

Fig. 3. Ins(1,4,5,6)P_4 and HDAC regulation. Ins(1,4,5,6)P_4 can bind to the basic interface present between class I HDAC and its repressors, thereby allosterically regulating the catalytic activity of the class I HDAC complexes. IPMK's IP kinase activity is essential for Ins(1,4,5,6)P_4 biosynthesis which can be controlled by IPMK-dependent phosphorylation of Ins(1,4,5)P_3. The other route for Ins(1,4,5,6)P_4 production is PTEN-dependent dephosphorylation of Ins(1,3,4,5,6)P_5 that is also linked to IPMK activity.

2001), and NuRD (Xue et al., 1998; Zhang et al., 1999). HDAC3, on the other hand, is recruited to the SMRT complex by interaction with a conserved DAD motif, and is subsequently activated by the formation of this multi-subunit protein complex (Guenther et al., 2000; Li et al., 2000; Wen et al., 2000; Zhang et al., 2002; Yoon et al., 2003; Oberoi et al., 2011). In 2012, Watson et al. reported the crystal structure of the HDAC3-bound SMRT-DAD domain complex, which was successfully purified from mammalian HEK293 cells but not from bacterial cells (Watson et al., 2012). Interestingly, Ins(1,4,5,6)P_4 was discovered to be tightly bound at the highly basic interface between HDAC3 and SMRT-DAD (Fig. 3). A subsequent study showed that when the longer form of the SMRT protein was purified and constitutively tethered to HDAC3, its deacetylase activity was lost in the absence of Ins(1,4,5,6)P_4 and was restored by the addition of exogenous Ins(1,4,5,6)P_4 (Millard et al., 2013). The general allosteric action of Ins(1,4,5,6)P_4 in the activation of class I HDACs was supported by a study showing that, consistent with the results obtained using HDAC3, incubation of Ins(1,4,5,6)P_4 with the HDAC1-MTA1 complex significantly increased HDAC1 activity. These structural studies clearly suggested that the interactions of HDAC1 and HDAC3 with their cognate corepressors, MTA1 and SMRT, play a common role in fully activating the HDACs via an interaction with Ins(1,4,5,6)P_4. Considering that IPMK is the only enzyme capable of governing the synthesis of Ins(1,4,5,6)P_4, we speculate that nuclear IPMK may be the main point of control for the activities of the class I HDACs in mammalian cells. Moreover, the other route for Ins(1,4,5,6)P_4 biosynthesis, which occurs via PTEN-dependent dephosphorylation of Ins(1,3,4,5,6)P_5, can be also intimately linked to the unique 6-kinase activity of IPMK and its ability to determine Ins(1,3,4,5,6)P_5 levels inside the cell.

4. IPMK as a transcriptional coactivator

In addition to the enzymatic role of IPMK in the biosynthesis of inositol polyphosphates and PIP_3, it also has a non-catalytic, scaffolding function that was first elucidated in yeast biology. Yeast IPMK (called Arg82/ArgRIII) was identified as a key determinant required for nutrient-sensitive cell growth with arginine as the sole nitrogen source (Bechet et al., 1970; Bercy et al., 1987; Dubois et al., 1987; Odom et al., 2000). Yeast IPMK is one of four components (Mcm1, Arg80, Arg81, and Arg82) of the Mcm1-ArgR transcription complex, which is responsible for transcriptional control in response to environmental arginine levels. Mechanistically, yeast IPMK non-catalytically assembles and stabilizes the transcriptional complex by directly binding to Mcm1 (Dubois et al., 2000; El Alami et al., 2003; Bosch and Saiardi, 2012). The kinase-dependent regulation of yeast IPMK also appears to be necessary for transcriptional control, suggesting that the IPMK-mediated production of IP_4/IP_5 is sufficient to complement the non-catalytic transcriptional function of IPMK (Odom et al., 2000).

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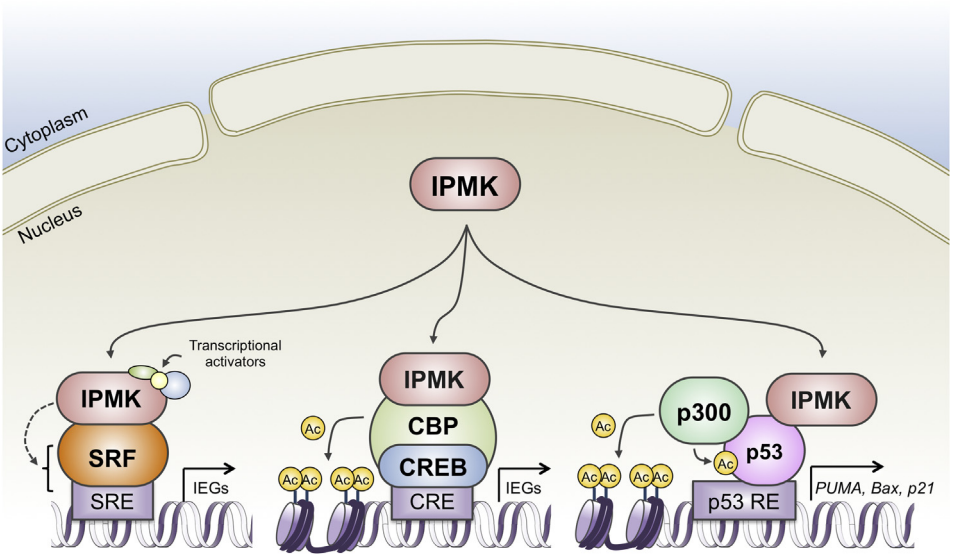

Fig. 4. Kinase activity independent actions of IPMK in the control of gene expression. Independent of its catalytic activity, IPMK has been known as a transcriptional coactivator in the nucleus. IPMK interacts with SRF and stabilizes SRF binding to its promoter (SRE), thereby regulating a wide range of immediate early gene (IEG) expression. Epigenetic control of IEGs can be further controlled by IPMK which can directly bind and recruit CREB-binding protein, CBP, to the promoter region of IEGs. IPMK is also known as a critical factor for p53 functions. Interaction between IPMK and p53 appears to enhance the binding between p53 and p300 acetyl transferase, thereby increasing p53-dependent transcription.

SRF (serum response factor), a mammalian ortholog of Mcm1, is a key transcription factor essential for the expression of a wide range of immediate early genes (IEGs), such as *c-jun* and *c-fos* (Hill and Treisman, 1995). IEGs are a family of rapidly inducible genes that are transcriptionally activated in response to various stimuli, including serum (Curran and Morgan, 1985; Hunt et al., 1987; Cole et al., 1989, 1995; Hope et al., 1992). To define the functional significance of nuclear IPMK in mammals, Kim et al. investigated its transcriptional role in regulating SRF-dependent gene expression (Kim et al., 2013) (Fig. 4). Under serum stimulation, the depletion of IPMK from mouse embryonic fibroblasts triggered the down-regulation of numerous SRF target genes and markedly diminished the protein levels of Jun and Fos. Interestingly, overexpression of a catalytically inactive IPMK mutant in IPMK-knockout cells rescued the defects in SRF-dependent transcription to wild-type levels, indicating that the transcriptional regulation of IPMK is independent of its catalytic activity. SRF directly binds to IPMK via regions containing inositol phosphate-binding and kinase domains. IPMK-SRF complex formation was not altered by serum stimulation, suggesting that there is a stable interaction between IPMK and SRF. Importantly, the absence of IPMK abolished the binding of SRF to its promoter SRE (serum response element). Overexpression of a dominant-negative peptide that interfered with the binding of IPMK and SRF decreased the SRE-binding affinity of SRF and inhibited its transcriptional activity. Genetic deletion of IPMK in excitatory neurons reduced both the SRF-SRE interaction and the function of SRF *in vivo*. These findings collectively suggest that the interaction between nuclear IPMK and SRF provides a physiological scaffold for the stable binding of SRF to the SRE, thereby regulating the induction of IEGs.

Another action of IPMK as a transcriptional coactivator was identified in a study showing that the histone acetyl transferase, CREB-binding protein (CBP), is an IPMK-binding protein (Xu et al., 2013a). Neural stimulus-induced IEGs (e.g., *c-fos, c-jun, egr2* and *egr3*), which are controlled by CBP and SRF, are critical to synaptic plasticity and its associated cognitive regulation (Bourtchuladze et al., 1994; Yin et al., 1994; Bartsch et al., 1998; Silva et al., 1998; Kandel, 2001; Matynia et al., 2002). Indeed, the genetic deletion of these IEGs often leads to deficits in the encoding and consolidation of long-term memory (Plath et al., 2006; Alberi et al., 2011; Ramamoorthi et al., 2011). For the expression of IEGs, cyclic-AMP response-element-binding protein (CREB) is phosphorylated, triggering the recruitment of CBP and the subsequent transcriptional activation of IEGs (Bourtchuladze et al., 1994; Wu et al., 2008). Xu et al. observed that the hippocampal mRNA levels of IEGs are substantially decreased in the neuron-specific IPMK-null animal model elicited by electroconvulsive shock (ECS) (Fig. 4). Similar transcriptional defects were detected in response to diverse stimuli, including potassium chloride, forskolin, nerve growth factor, brain-derived neurotrophic factor, bicuculline (a GABA antagonist), and kainic acid (a glutamate agonist). IPMK-knockout mice also display spatial memory defects and exhibit longer escape latencies. Interaction between IPMK and CBP appears dynamically induced by neuronal stimulation. Mechanistically, IPMK appears to recruit the CBP enzyme to the promoter regions of IEGs; when IPMK is depleted, CBP-dependent histone H3 and H4 acetylation is incomplete. As in the case of IPMK-SRF signaling, these transcriptional defects are restored by the expression of a catalytically inactive IPMK mutant.

A loss-of function screening in primary human fibroblasts identified IPMK as a candidate gene that could be essential for the control of p53 (Drost et al., 2010). As a tumor suppressor, p53 senses diverse stress signals and regulates the expression levels of genes involved in cell cycle arrest, cellular senescence, and apoptosis (Chen et al., 2005; Collado et al., 2005; Vousden

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and Prives, 2009; Brady and Attardi, 2010). Studies examining the possible role of IPMK in regulating p53 showed that IPMK binds p53 and modulates p53-dependent gene expression (Xu et al., 2013b) (Fig. 4). Depletion of IPMK in mouse embryonic fibroblasts decreased p53-dependent transcription, whereas overexpression of IPMK enhanced the expression levels of p53-dependent target genes (e.g., *PUMA, Bax* and *p21*). IPMK is recruited by and co-localizes with p53 on the promoters of the *PUMA, Bax*, and *p21* in cells undergoing cell death. IPMK seems to stimulate the transcriptional activity of p53 by enhancing the acetylations of p53 and histone via the histone acetyl transferase, p300; IPMK apparently stimulates the binding of p53 to p300, increasing the acetylation of the former. In IPMK-null cells, the binding of p300 to the promoter of p21 was significantly reduced under cell death conditions, increasing cell survival and decreasing apoptosis. The catalytic function of IPMK is unnecessary for its ability to activate p53. Taken together, these findings suggest that IPMK is a transcriptional coactivator of p53, and that it regulates cell death in a catalysis-independent fashion. Interestingly, IP6K2 (which acts in the same IP biosynthesis pathway) is also a p53-binding regulatory protein (Koldobskiy et al., 2010). Unlike IPMK, this function of IP6K2 requires its catalytic product, 5-IP_7, and affects subsets of p53 target genes involved in apoptosis but not cell cycle arrest. In the future, it will be important to examine the complex interplay among IPMK, IP6K2, and p53.

5. Concluding remarks

The idea that inositol polyphosphates and IPMK control transcription, which was introduced in 2000 and based on studies performed in *Saccharomyces cerevisiae*, is now widely accepted and has been broadly extended to various nuclear events in mammalian cells (Odom et al., 2000). The findings discussed in this review clearly suggest that mammalian IPMK and/or its catalytic products play multiple functions in the nucleus, as shown by the following lines of evidence: (*i*) As a nuclear PI3-kinase, IPMK was identified as a critical enzyme that produces ALY-activating PIP_3, thereby promoting the export of specific nuclear mRNAs (e.g., those encoding DNA damage-sensitive recombination proteins). IPMK-mediated PIP_3 production was also shown to be required for the full transcriptional activation of the nuclear hormone receptor, SF-1. (*ii*) The unique product of IPMK, Ins(1,4,5,6)P_4, was revealed as a ligand required for activating class I HDAC-corepressor complexes. (*iii*) In a catalytic activity-independent manner, IPMK acts as a transcriptional coactivator for different transcription factors, including SRF, CBP, and p53. IPMK not only stabilizes the interaction between SRF and the SRF-binding DNA sequence, it also recruits transcriptional activating factors (e.g., acetyltransferases) into CREB-CBP- and p53-containing transcription complexes. The IPMK-dependent control of IEG expression was further validated *in vivo* using conditional IPMK-knockout mouse models. The selective loss of neuronal IPMK was shown to markedly decrease the DNA binding affinity of SRF and abrogate the ability of CBP to be appropriately recruited to CREB in response to neural stimulation. These molecular alterations appear to decrease the induction of IEGs, leading to behavioral defects in spatial memory. However, most of the other findings described in this review were established using *in vitro* or mammalian cell culture settings, and should thus be examined *in vivo* in the future.

Recently, a germline deletion mutation in IPMK was discovered among familial and sporadic small intestinal carcinoid patients (Sei et al., 2015). This autosomal dominant mutation truncates the IPMK protein to a version that lacks the nuclear localization signal and the kinase domain, and thus the mutant protein shows nuclear localization defects and a lack of kinase activity. B lymphoblasts from carcinoid patients with mutant IPMK show misregulation of p53 activity in the nucleus, suggesting that intestinal carcinoid tumorigenesis could be promoted by insufficient p53-mediated control of genes related to apoptosis and cell-cycle arrest. Further comprehensive studies will be needed to fully elucidate how the other proposed nuclear functions of IPMK contribute to pathological dysregulation.

In addition to defining the roles of IPMK in physiological and pathological conditions, future studies should test the stoichiometric relationship of IPMK in the nuclear and cytoplasmic compartments. Further investigations are also warranted to examine the regulatory mechanisms responsible for the dynamic nucleocytoplasmic shuttling of IPMK and the fine control of IPMK-dependent catalytic products in the nucleus. It would be interesting to identify more nuclear target proteins that can interact with IPMK and its products (e.g., PIP_3 and IP_4). Overall, an in-depth investigation of how IPMK functions in multiple catalytic and non-catalytic manners will be an important research theme. Finally, drugs that selectively perturb the effects of nuclear IPMK on major signaling targets (e.g., p53, HDAC, and SRF) may prove useful in treating cancer, type 2 diabetes, and psychiatric diseases.

Conflict of interest statement

The authors declare no conflict of interest.

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