Inositol phosphates are water-soluble intracellular signaling molecules found in eukaryotes from yeasts to mammals, which are synthesized by a complex network of enzymes including inositol phosphate kinases. Among these, inositol polyphosphate multikinase (IPMK) is a promiscuous enzyme with broad substrate specificity, which phosphorylates multiple inositol phosphates, as well as phosphatidylinositol 4,5-bisphosphate. In addition to its catalytic actions, IPMK is known to non-catalytically control major signaling events via direct protein-protein interactions. In this review, we describe the general characteristics of IPMK, highlight its pleiotropic roles in various physiological and pathological conditions, and discuss future challenges in the field of IPMK signaling pathways.

**Keywords:** cell signaling, disease, inositol phosphate, inositol polyphosphate multikinase

**INTRODUCTION**

Inositol phosphates (IPs) are a group of cytosolic metabolites derived from myo-inositol. Myo-inositol, a key nutrient in the human diet, is a glucose isomer with one axial and five equatorial hydroxyl groups (Holub, 1986). Inositols are found in the cell in two distinct forms, as either the membrane-anchored phosphatidylinositol (PI) or water-soluble IP. Inositol 1,4,5-trisphosphate (IP3) is the classic type of IP and acts as a second messenger to induce calcium release from the endoplasmic reticulum, thereby increasing cytosolic calcium concentrations (Berndige et al., 2000). IP3 biosynthesis is catalyzed by the activated form of phospholipase C (PLC), which hydrolyzes phosphatidylinositol 4,5-bisphosphate (PIP2). Since the discovery of IP3, the complexity of IP metabolism has been gradually elucidated by cloning series of enzymes such as IP kinases and phosphatases (Hatch and York, 2010). Combined actions of specific and selective IP kinases phosphorylate the six carbons of inositol to generate IP6. Additional phosphorylation of IP6 generates inositol pyrophosphates (e.g., 5-IP7), which contain high-energy phosphoanhydride bonds and perform multiple biological functions (Lee et al., 2020c; Park et al., 2018; Shears, 2015). However, IP synthesis is not entirely dependent on PLC-mediated PIP2 hydrolysis. Alternatively, glucose can be directly isomerized into IP1, which is further phosphorylated by ITPK1 and other IP kinases to produce IP species with multiple phosphate moieties (Desfougères et al., 2019). In this review, we will summarize the newly-discovered roles of inositol polyphosphate multikinase (IPMK) in homeostasis control, as well as in the pathogenesis of diseases.

**BROAD SUBSTRATE SPECIFICITY OF IPMK**

IPMK was initially cloned from yeast as a transcriptional regulator of arginine-sensitive genes and was originally named Arg82, which is now referred to as Ipk2 or yeast IPMK (Be-
IPMK Signaling in Health and Disease
Boah Lee et al.

In 1999, the mammalian IPMK was first characterized as an essential factor for the synthesis of IP4 [both Ins(1,3,4,5)P$_4$ and Ins(1,4,5,6)P$_4$] and IP5 [Ins(1,3,4,5,6)P$_5$] (Odom et al., 2000; Saiardi et al., 1999) (Fig. 1). Particularly, the inositol 6-kinase activity of IPMK makes this enzyme a unique factor for IP5 synthesis. IPMK deletion in mouse embryonic fibroblasts (MEFs) and many other mammalian cells markedly reduces the cellular levels of IP5 and downstream IPs, such as IP7 (Frederick et al., 2005). Furthermore, IPMK can produce phosphatidylinositol 3,4,5-trisphosphate (PIP3) by phosphorylating PIP2 at the C-3 position. In response to growth stimuli, such as serum or growth factors, IPMK-deficient MEFs produced approximately 50% less PIP3 and underwent significantly less PIP3-dependent Akt phosphorylation than wild-type MEFs, suggesting that IPMK acts as a PI3-kinase in mammalian cells (Maag et al., 2011).

**ACTION MODES OF THE IPMK SIGNALING**

The discovery of the involvement of IP3 and its corresponding receptor in the control of cytosolic calcium levels has led to the discovery of a wide and complex IPs that act as second messengers, which might mediate diverse cellular events. IPMK, the key mediator of IP metabolism, is known to control signaling events via its IP products (Table 1). For example, Ins(1,4,5,6)P$_4$ has been found to tightly intercalate between histone deacetylase 3 (HDAC3) and the SMRT-DAD domain of an HDAC3-interacting protein (Watson et al., 2012). Further, the deacetylase activity of HDAC3 depends on this inositol (Millard et al., 2013; Watson et al., 2016). In addition to the direct products of IPMK, its downstream IP products, including IP6, have been suggested to mediate cellular signaling. For example, in IPMK knock-out (KO) murine B cells, reductions in the level of IP6, a cofactor required for Btk kinase activation, impaired Btk activation and B-cell receptor signaling (Kim et al., 2019). The lipid-kinase activity of IPMK (i.e., a PI3-kinase) expands the signaling role of IPMK in mammals (Table 1). For instance, IPMK directly interacts with the nuclear receptor SF-1–PIP2 complex and phosphorylates PIP2, converting it into PIP3, which is a key regulatory step for the induction of SF-1 target genes (Blind et al., 2012).

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**Fig. 1.** The multiple catalytic functions of IPMK in inositol biosynthesis pathway. IPMK possesses the activity of phosphorylating IP3 to IP4 as well as IP4 to IP5. IPMK also acts as a PI3-kinase.
Furthermore, IPMK-dependent SF1-PIP3 signaling was found to mediate ataxia telangiectasia and Rad3 related (ATR) recruitment upon DNA damage, suggesting the involvement of nuclear PI3-kinase activity of IPMK in the control of DNA repair (Wang et al., 2017). Apart from its catalytic functions, IPMK appears to non-catalytically modulate target proteins and signaling events through different mechanisms (Table 1). For example, IPMK can stabilize protein complexes, such as mTORC1 (Kim et al., 2011b). Additionally, recent research suggests that IPMK-TRAF6 interaction is critical to protect TRAF6 from ubiquitination-dependent degradation (Kim et al., 2017b). IPMK also acts as a transcriptional coactivator by interacting with various transcription factors such as serum response factor (SRF) (Kim et al., 2013) and controls gene expression presumably through conformational changes or recruitment of other regulatory factors.

**PHYSIOLOGICAL ROLES OF IPMK SIGNALING**

Considering the complex roles of IPMK in catalysis and cellular signaling, our primary objective was to define in vivo relevance of IPMK signaling. Whole-body KO of IPMK in mice resulted in embryonic lethality at day 9.5 post-coitum due to growth and neural-tube defects, thus demonstrating the essential role of IPMK (Frederick et al., 2005). Therefore, conditional and cell-type–specific IPMK KO in mice has provided substantial insights into the biological roles of IPMK.

### Table 1. Modes of IPMK-mediated signaling actions in mammals

| Signaling targets | Mode of actions | Biological events | References |
|------------------|----------------|-------------------|------------|
| HIF1α            | IP5            | HIF1α hydroxylation | Fu et al., 2018 |
| Btk              | IP6            | Btk activation in B cell receptor signaling | Kim et al., 2019 |
| MLKL             | IP6            | MLKL-dependent necroptosis | Dovey et al., 2018; McNamara et al., 2019 |
| HIV capsid       | IP5, IP6       | HIV viral assembly and life cycle | Dick et al., 2018; Mallery et al., 2019; Sowd et al., 2021 |
| Akt              | PIP3           | Akt activation in mouse embryonic fibroblasts and U87MG cells/ Akt activation in striatal neuron | Ahmed et al., 2015; Maag et al., 2011 |
| ALY              | PIP3           | Homologous recombination | Wickramasinghe et al., 2013 |
| SF1              | PIP3           | SF1-dependent gene expression/ ATR recruitment for DNA repair | Blind et al., 2012; Wang et al., 2017 |
| mTOR             | Direct binding | mTORC1 activation in response to amino acid | Kim et al., 2011b |
| AMPK             | Direct binding | Phosphorylation of AMPK in response to glucose/ AMPK-mediated autophagy | Bang et al., 2012; Guha et al., 2019 |
| CBP              | Direct binding | CBP-mediated histone acetylation/ Immediate early gene induction | Xu et al., 2013a |
| p53              | Direct binding | p53 activation | Xu et al., 2013b |
| SRF              | Direct binding | SRF-dependent transcription/ Immediate early gene induction | Kim et al., 2013 |
| LKB              | Direct binding | Metformin-mediated AMPK activation | Guha et al., 2019 |
| Mutant Huntingtin| Direct binding | Regulation of IPMK stability | Ahmed et al., 2015 |
| TRAF6            | Direct binding | Control of TRAF6 degradation | Kim et al., 2017b |
|ULK1              | Direct binding | ULK1-mediated autophagy | Guha et al., 2019 |
| TFEB             | Direct binding | TFEB-dependent autophagy | Chen et al., 2020 |

**Neural control**

The brain is among the organs with the highest IPMK levels. Deletion of IPMK in murine neuroprogenitor cells by outcrossing the transgenic nestin-Cre and floxed ipmk mouse lines severely impaired the induction of the immediate early genes (IEGs) (e.g., c-jun, c-fos, and egr2) that mediate complex neural processes, such as learning and memory (Xu et al., 2013a). Mechanistically, this neural IEG induction failure can be explained by the nuclear actions of IPMK as a transcriptional coactivator. IPMK directly binds to the histone acetyltransferase CREB-binding protein (CBP), which consequently binds to the promoter regions of IEGs (Xu et al., 2013a). As expected, this IPMK KO mouse model exhibits characteristic neurological phenotype such as long-term spatial memory deficiencies.

In contrast, postnatal deletion of Ipmk in excitatory neurons using CaMKII-Cre transgenic mice resulted in no apparent deficits of novel-object recognition or spatial memory (Park et al., 2019). Interestingly, these conditional IPMK KO mice exhibited normal cued fear conditioning but displayed an enhanced fear extinction, which was accompanied by facilitated hippocampal long-term potentiation. Further analyses revealed that the mechanistic target of rapamycin (mTOR) regulatory enzyme p85 S6 kinase 1 is selectively activated in the amygdala of these mice following fear extinction (Park et al., 2019). Nonetheless, the specific roles of IPMK-dependent
catalytic products or IPMK-interacting signaling target proteins in the fear extinction circuitry remain to be elucidated.

Immunity
Kim et al. (2017b) demonstrated that IPMK deletion in myeloid cells protects mice against polymicrobial septic shock and lipopolysaccharide-induced inflammation. IPMK KO macrophages in culture exhibit defective Toll-like receptor (TLR) signaling, which is tightly controlled to protect hosts from microorganisms. The regulatory role of IPMK depends largely on the interaction between IPMK and tumor necrosis factor receptor–associated factor 6 (TRAF6), the key member of the TLR signaling pathway. IPMK depletion in macrophages decreases the TRAF6 level, thus decreasing TLR-induced signaling and pro-inflammatory cytokine production (Kim et al., 2017b). IPMK is a key determinant in stabilizing TRAF6 by preventing the ubiquitination-dependent proteasomal degradation of this TLR signaling factor, thereby influencing the TLR-induced innate immunity.

Bacterial polysaccharides and the repetitive epitopes of viral particles can activate B cells independently of T cells via cross-linking of the antigen receptors (Kim et al., 2019). This process triggers a rapid and robust antibody response to bacterial infection. Conditional deletion of IPMK in B cells resulted in reduced activation of Bruton’s tyrosine kinase (Btk) and the downstream effector PLCγ2, thus abolishing the calcium influx. Consequently, the IPMK KO B cells exhibited substantially lower cell proliferation in response to T cell-independent antigens. The main signaling role of IPMK in Btk activation appears to be mediated by IP6, as cell-permeable IP6 treatment can successfully restore Btk activation and signaling in IPMK KO B cells (Kim et al., 2019). These studies clearly demonstrate the crucial role of IPMK in B cells to produce IP6, an allosteric metabolite required for full Btk activation (Wang et al., 2015).

Angiogenesis
Angiogenesis is the physiological process by which new blood vessels are formed, which is principally promoted by vascular endothelial growth factor (VEGF). Fu et al. (2018) reported that Ipmk deletion in MEFs induces tube formation accompanied by increased VEGF mRNA and protein levels. Serum VEGF levels were significantly elevated in the brain of IPMK KO mice. Moreover, IPMK KO fibroblasts and brain tissues exhibited an increased hypoxia-inducible factor-1α (HIF-1α) activity, which in turn upregulated the expression of its target genes. These abnormalities high serum VEGF levels in the brain of IPMK KO mice appeared to decrease pericyte coverage, suggesting a disruption in the blood-brain barrier. This signaling role of IPMK relies on the activity of IP kinases. IP5, the catalytic product of IPMK, promotes HIF-1α prolyl hydroxylation, which in turn increases the von Hippel–Lindau protein (pVHL)-dependent degradation of HIF-1α. In the absence of IPMK, the stabilized HIF1-α upregulates VEGF production to induce angiogenesis (Fu et al., 2018). Therefore, the roles of IPMK and its product (IP5) in the control of hypoxia-mediated pathological events such as tumor angiogenesis must be further investigated.

Metabolic organs
Early studies on cell lines identified IPMK as a key factor for the biosynthesis of several metabolic sensors such as AMPK and mTOR (Bang et al., 2012; Kim et al., 2011b), suggesting that IPMK contributes to the homeostatic control of metabolic organs. Guha et al. (2019) recently characterized the roles of IPMK in the control of autophagy in hepatocytes and hepatocyte-specific IPMK KO mouse models. Importantly, the authors found that the lipophagic activity of the liver was markedly impaired in these conditional IPMK KO mice after overnight starvation. Moreover, these mice exhibited more severe carbon-tetrachloride-induced hepatic damage and an approximately 50% decrease in hepatic regeneration potential compared to wild-type mice, in addition to displaying signs of increased inflammation, apoptosis, and serum ALT levels. The autophagic control of IPMK in the liver appears to be predominantly mediated by AMPK activation. AMPK is known to activate autophagy through the phosphorylation of Unc-51-like autophagy-activating kinase (ULK) followed by the recruitment of the beclin1 complex and activation of Vps34 (Kim et al., 2011a). IPMK non-catalytically binds to both AMPK and ULK, thus efficiently phosphorylating both these proteins. IPMK also promotes the transcription of autophagic genes via AMPK-mediated histone deacetylation (Guha et al., 2019). However, additional studies are needed to validate whether the role of IPMK in autophagy induction also applies to other tissues and autophagy-associated diseases. A recent study using Caenorhabditis elegans and human cancer cell lines as model systems demonstrated that IPMK depletion stimulates autophagy via TFEB targeting, which is a key transcriptional factor that governs autophagy (Chen et al., 2020). According to a model developed by Chen et al. (2020), nuclear AMPK acts as a chaperone to bind and suppress the liquid-liquid separation of TFEB. This, in turn, inhibits TFEB transcriptional activity, which is needed to induce autophagy and lysosomal biogenesis. Therefore, comparative research is required to gain insights into the specific cellular and physiological functions of IPMK and its involvement in autophagy control.

Inositol pyrophosphates, such as 5-IP7, are known to modulate whole-body energy homeostasis (Chakraborty et al., 2011). Particularly, conditional deletion of IP6K1 (which is responsible for 5-IP7 production) in the adipose tissue resulted in the reprogramming of the mechanisms that control energy metabolism (Zhu et al., 2016). Recently, Lee et al. (2020b) generated an adipocyte-specific IPMK KO mouse model but observed no apparent metabolic phenotypes in associated with fat accumulation, glucose homeostasis, or insulin sensitivity when the animals were fed with a regular-chow or high-fat diet. Moreover, the loss of adipose IPMK had no major impact on thermogenesis in response to cold exposure. These findings collectively suggest that adipocyte IPMK is dispensable for adipose tissue homeostasis, adipose-related physiological functions, and whole-body metabolism. Therefore, IP metabolism plays complex roles in the regulation of adipose tissue, and other IP kinases such as ITPK1 may participate in these IP pathways.
**IPMK SIGNALING IN HUMAN DISEASES**

**Cancer**
Considering the pleiotropic signaling activity of IPMK, it is assumed that IPMK contributes to various aspects of tumorigenesis and cancer progression. A germ-line mutation in *Ipmk* has been identified in patients with familial small intestinal carcinoids (Sei et al., 2015). The causative *Ipmk* truncation mutation impairs IP kinase activity and reduces the nuclear localization of IPMK. The resulting haploinsufficiency appears to cause diminished p53 signaling and increases cell survival, suggesting that IPMK has a tumor-suppressive role in intestinal epithelial tumorigenesis.

Necroptosis is generally considered a "double-edged sword" in the context of cancer control (Najafov et al., 2017). Specifically, the dual role of necroptosis in both promoting and inhibiting tumor growth has been reported in various forms of cancer. A genetic screening to identify mixed lineage kinase domain-like pseudokinase (MLKL)-mediated necroptosis factors identified IPMK and ITPK1, both of which are critical for IP metabolism (Dovey et al., 2018). Deletion of IPMK in HT-29 colorectal cancer cell line impaired MLKL oligomerization and membrane localization. This defective necroptosis can be explained by the specific interaction between MLKL and IP6, the downstream product of IPMK. Mechanistically, IP6 acts as a molecular glue to regulate the full activation of MLKL and necroptosis (Dovey et al., 2018; McNamara et al., 2019). Therefore, the involvement of IPMK's IP-kinase activity in controlling cancer cell death should be further assessed using variety of cancer models.

IPMK was recently found to mediate the DNA damage response, which is among the primary events involved in carcinogenesis. In addition to the PI3K activity of IPMK in ATR recruitment as discussed above, IPMK has also been found to mediate transcript-selective nuclear export (Wickramasinghe et al., 2013). For instance, IPMK deletion selectively inhibits the nuclear export of mRNAs (e.g., Rad51) responsible for homologous recombination. IPMK is needed to transport *Rad51* transcripts via the ALY mRNA export factor. The PI3K homologous recombination. IPMK is needed to transport the nuclear export of mRNAs (e.g., Rad51) responsible for et al., 2013). For instance, IPMK deletion selectively inhibits the full activation of MLKL and necroptosis (Dovey et al., 2018; McNamara et al., 2019). Therefore, the involvement of IPMK's IP-kinase activity in controlling cancer cell death should be further assessed using variety of cancer models.

IPMK was recently identified as a key element of metformin-mediated cellular migration (Tu-Sekine et al., 2019). Treatment of metformin, a drug used to treat diabetes, decreased the levels of IPMK and integrin β1 in MEFs and primary mouse hepatocytes. IPMK has been found to control the modulation of integrin β1 and focal adhesion kinase activity suggesting the potential role of IPMK in the adhesion signal-ing pathway. Considering the value of metformin as a potential anticancer drug (Pernicova and Korbonits, 2014), the loss of IPMK by metformin treatment and associated defects in adhesion and migration should be further investigated to assess the impact of IPMK signaling on metformin-treated cancer cells.

**Huntington’s disease**
The involvement of IPMK in neuropathological conditions is exemplified by Huntington’s disease (HD), a neurodegenerative disorder characterized by motor abnormalities and caused by the expansion of glutamine repeats in the mutant huntingtin (mHtt) gene. IPMK levels have been found to be substantially lower in the striata of HD patients and mouse models (Ahmed et al., 2015). The loss of IPMK in HD tissues appears to be caused by mutant-huntingtin-induced impairment of COUP-TF-interacting protein 2, which is a striatal-enriched transcription factor that regulates IPMK expression. In the pathogenesis of HD, neuronal IPMK’s PI3K activity was decreased due to the IPMK deficiency. This reduction of IPMK and its product PIP3 in HD cells appears to lower the activity of Akt, a guardian of neuronal survival (Ahmed et al., 2015). Consequently, the neuronal survival is impaired, resulting in increased neuronal loss. These observations suggest that the PI3K activity of IPMK is necessary to produce the pro-survival signal for striatral neurons (Ahmed et al., 2015). Whether IPMK is linked to other neurodegenerative diseases needs to be further investigated.

**PERSPECTIVES**
In the past 20 years, growing evidence has established IPMK as a multifunctional component of cellular signaling networks in mammals (Fig. 2; Kim et al., 2017a). In addition to the recent findings reviewed herein, more actions of IPMK have been suggested from studies involving cell lines. For example, IPMK depletion in T cells can control the HIV viral life cycle (Sowd and Aiken, 2021). Moreover, given that IP5 and IP6 have been found to stimulate the assembly of both immature and mature HIV-1 particles (Dick et al., 2018; Mallery et al., 2019), IP kinases have been targeted to control HIV. When IPMK was depleted in T-cell lines, the HIV-1 propagation in the cells decreased due to defects in intracellular HIV-1 assembly and virion maturation (Sowd and Aiken, 2021).

Therefore, additional cell-type-specific IPMK KO mouse models are needed to dissect the physiological roles of IPMK. Moreover, identifying novel pharmacological agents to control IPMK catalysis is also critical. Recently, Lee et al. (2020a) performed a structure-based virtual screening of compounds approved by the U.S. Food and Drug Administration and discovered that the antidepressant vilazodone is an IPMK inhibitor. Vilazodone treatment of fibroblasts and cancer cells reduced the activities of IPMK as well as Akt phosphorylation, indicating the selective activities of vilazodone against IPMK-dependent catalytic steps in the IP biosynthesis pathway and Akt activation. More studies on the structure of human IPMK and its catalysis (Gu et al., 2019; Seacrist and Blind, 2018) will be useful to design IPMK inhibitors and modulate the IPMK signaling pathway quantitatively and dynamically, with the
IPMK Signaling in Health and Disease
Boah Lee et al.

The ultimate goal of targeting IPMK-dependent pathological conditions.

Recently, genetic variations of human IPMK have been identified as potential factors involved in Alzheimer’s disease, inflammation, and the control of longevity (Dato et al., 2021; De Rango et al., 2019; Yokoyama et al., 2016). Therefore, additional studies on Ipmk mutations and single-nucleotide polymorphisms will improve our understanding of the role of IPMK signaling. Thus, our future studies will focus on identifying a link between IPMK and clinical findings to translate fundamental findings into diagnostic and therapeutic strategies. We strongly believe that our continuous effort to dissect IPMK-mediated signaling networks will provide critical insights into the intricacies of IP metabolism, as well as a theoretical basis for the development of strategies to treat related diseases.

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AUTHOR CONTRIBUTIONS

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CONFLICT OF INTEREST

The authors have no potential conflicts of interest to disclose.

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