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ROLES OF INOSITOL PHOSPHATES AND INOSITOL PYROPHOSPHATES IN DEVELOPMENT, CELL SIGNALING AND NUCLEAR PROCESSES

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INTRODUCTION

Upon agonist stimulation, phospholipase C metabolizes phosphatidylinositol 4,5-bisphosphate into the intracellular second messengers 1,2-diacylglycerol (DAG) and inositol 1,4,5-trisphosphate (IP_3) (Berridge, 1993; Hokin, 1985; Majerus, 1992; Mikoshiba, 1997; Nishizuka, 1986). The PLC-generated second messenger DAG is well known as an activator of protein kinase C, while IP_3 regulates cellular calcium flux by binding to IP_3 receptors and subsequently induce the release of Ca^{2+} from internal stores. IP_3 is metabolized to form a number of more polar inositol phosphates (IPs) and diphosphoryl inositol phosphates (PP-IPs), also commonly referred to as inositol pyrophosphates (Irvine and Schell, 2001; Majerus, 1992; Shears, 1998; York, 2006). In the last fifteen years, there has been a rapid accumulation of knowledge defining the metabolic pathways of these molecules, the enzymes involved in their production, and their biological roles (Figure 1). Four kinases have been identified as conserved in nearly all eukaryotes from budding yeast to man, and two additional enzymes have been found in selected metazoans and plants. These gene products may be categorized into two classes: 1) kinases that produce inositol phosphomonoesters and 2) those that produce inositol diphosphates. The cloning and cellular studies of these gene products has led to significant increases in our knowledge of the metabolic pathways of these molecules and their biological roles in eukaryotes from budding yeast *Saccharomyces cerevisiae* to man. Here we discuss a subset of recent advances that highlight roles for IP and PP-IP molecules in cellular processes and organism development.

ENZYME REGULATION OF IP AND PP-IP SYNTHESIS IN BUDDING YEAST

For simplicity, we will begin our discussion of the routes of inositol phosphate metabolism in the single cell eukaryote, *S. cerevisiae*. The budding yeast genome encodes four kinases responsible for synthesizing an array of IP and PP-IP species (Figure 1) (Mulugu et al., 2007; Odom et al., 2000; Saiardi et al., 2000a; Saiardi et al., 2000b; York et al., 1999). In the budding yeast, Ipk2 is the first enzyme required for PLC dependent synthesis of IPs, and is a dual-specificity IP_3/IP_4 6-/3-kinase that converts inositol 1,4,5-trisphosphate [$I(1,4,5)P_3$ or

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IP_3] to inositol 1,3,4,5,6-pentakisphophate [I(1,3,4,5,6)P_5 or IP_5] via the intermediate inositol 1,4,5,6-tetrakisphosphate [I(1,4,5,6)P_4 or IP_4]. IP_5 is subsequently metabolized by another kinase Ipk1, an IP_5 2-kinases, to inositol 1,2,3,4,5,6-hexakisphosphate [I(1,2,3,4,5,6)P_6 or IP_6]. Inositol pyrophosphates [PP- IP_4, PP-IP_5 (IP_7), PP_2-IP_3 and PP_2-IP_4 (IP_8)] are generated by two kinases called Kcs1 and Vip1 in yeast. Kcs1 and Vip1 function as both inositol hexakisphosphate (IP6K) and inositol heptakisphosphate kinases (PPIP5K). They generate different IP_7 isomers: Kcs1 make 5-IP_7 and Vip1 makes 1/3-IP_7 (Lin et al., 2009) – 1/3 designates enantiomers that have not yet been resolved and it is possible that Vip1 makes 1-, 3- or both isomers of IP_7. Kcs1 and Vip1 collectively work together to generate IP_8 from IP_6.

Except for Vip1, the enzymes involved in IPs and PP-IPs can be found in the nucleus. Yeast PLC1 has been shown to associate with the kinetochore, and nuclear PLC isoforms have been identified in mammals (Cocco et al., 1996; Lin et al., 2000; Manzoli et al., 1995; Maraldi et al., 1995). Ipk2 in yeast and other organisms is predominantly nuclear (Bercy et al., 1987; Fujii and York, 2005; Nalaskowski et al., 2002; Odom et al., 2000; Seeds et al., 2004; Xia et al., 2003). Yeast Ipk1 resides in the nuclear envelope (York et al., 1999). Kcs1 and its mammalian homologs IP6Ks have both nuclear and cytoplasmic distributions (Luo et al., 2002; Saiardi et al., 2000a; Saiardi et al., 2000b). The nuclear presence of these enzymes suggests IPs and PP-IPs have nuclear functions; indeed studies in yeast demonstrated they are involved in diverse nuclear processes such as transcriptional control, mRNA export and telomere length regulation (Alcazar-Roman and Wente, 2008; York, 2006; York et al., 2001). In recent years, much progress has been made in understanding the biology of IPs and PP-IPs in other organisms by employing a reverse genetics approach.

METABOLISM OF IP AND PP-IP SPECIES IN PLANTS, FLIES AND MAMMALS

The genes involved in IPs and PP-IPs synthesis are evolutionary conserved from yeast to man, however in mammals there are two additional classes of kinase as well as gene duplications for several of the six kinases (Figure 1). In eukaryotic species examined to-date, all appear to require a Ipk2 homolog (also known as inositol phosphate multi-kinase, IPMK) and a Ipk1 homolog to produce IP_5 and IP_6 (Chang et al., 2002; Frederick et al., 2005; Fujii and York, 2005; Nalaskowski et al., 2002; Saiardi et al., 2001; Seeds et al., 2004; Stevenson-Paulik et al., 2005; Stevenson-Paulik et al., 2002; Verbsky et al., 2005a; Verbsky et al., 2005b; Verbsky et al., 2002; Xia et al., 2003). However, additional IPKs are identified in higher organisms, which represent alternative biosynthetic routes to IP_6. In plants and human cells, I(1,3,4)P_3 5/6-kinases have been identified and disruption of these 5/6-kinases decreased IP_6 levels in maize and human cells (Shi et al., 2003; Verbsky et al., 2005b; Wilson and Majerus, 1997). I(1,3,4)P_3 5/6-kinase (alias ITPK1) has also been shown to regulate chloride channel activity via novel 1-kinase activity towards I(3,4,5,6)P_4 and I(1,3,4,5,6)P_5 1-phosphatase (Ho et al., 2002; Yang and Shears, 2000). The structures of I(1,3,4)P_3 5/6-kinase/ITPK1 have illuminate the bases for these activities (Chamberlain et al., 2007; Miller et al., 2005). On the other hand, I(1,4,5)P_3 3-kinases have been identified in mammals and *Drosophila*. There is no evidence that these 3-kinases are required for IP_6 synthesis in mouse cells or *Drosophila* (Leyman et al., 2007; Seeds et al., 2004). However, an alternative route to generate IP_6 involving 5/6-kinase and 3-kinase has been elucidated in human cells (Majerus, 1992; Menniti et al., 1993; Verbsky et al., 2005b). In this pathway, I(1,4,5)P_3 is first phosphorylated by IP_3 3-kinase to I(1,3,4,5)P_4, which is then dephosphorylated by 5-Ptase to I(1,3,4)P_3. I(1,3,4)P_3 is subsequently metabolized to I(1,3,4,6)P_4 by IP_3 5/6-kinase. I(1,3,4,6)P_4 is sequentially phosphorylated by Ipk2 and Ipk1 to make IP_5 and finally IP_6. In slime mold and duckweed, an inositol lipid-independent pathway of IP_6 synthesis has been proposed (Biswas et al., 1978; Brearley and Hanke, 1996;

Stephens and Irvine, 1990), in which I(3)P is generated from glucose 6-phosphate by inositol 3-phosphate synthase (MIPS). I(3)P is successively phosphorylated to $I(3,4)P_2$, $I(3,4,6)P_3$, $I(3,4,5,6)P_4$, $I(1,3,4,5,6)P_5$ and finally to IP_6. The enzymology involved in this pathway is not fully understood at this point. The existence of multiple biosynthetic routes to IP_6 may increase signaling versatility and redundancy in higher organisms.

BIOLOGICAL ROLES OF IP AND PP-IP MOLECULES IN YEAST

A major role of Ipk2 and its products, IP_4 and IP_5, is transcriptional regulation in response to changes in environmental and nutritional cues. *IPK2* is allelic to *ARG82*, and is a component of the arginine responsive ArgR-Mcm1 complexes. Ipk2 and its kinase activity have been shown to be required for formation of the active ArgR-Mcm1 complexes which controls the transcription regulation of arginine responsive genes that are required for the utilization of arginine or ornithine as the only nitrogen source in budding yeast (Bechet et al., 1970; El Alami et al., 2003; Messenguy and Dubois, 1993; Odom et al., 2000). On the other hand, Ipk2 has been shown to be required for the induction of transcription of some phosphate responsive genes (e.g. Pho5) by modulation of the chromatin remodeling complexes SWI/SNF and INO80, under high phosphate conditions (El Alami et al., 2003; Steger et al., 2003). In vitro, IP_4 and IP_5 have been shown to stimulate nucleosome mobilization by the yeast SWI/SNF complex (Shen et al., 2003). Recently, Vancura's group showed that Plc1 and IPs are involved in regulation of activity of the kinetochore by facilitating recruitment of another chromatin remodeling complex, RSC, which stands for Remodels Structure of Chromatin. RSC has been shown to be required for maintaining the structure of the centromere and for proper kinetochore function (Cairns et al., 1996; Desai et al., 2009).

The yeast Ipk1 was first identified as a regulator of mRNA export in a synthetic lethal screen with the *gle1-2* mutant, where Gle1 is an essential factor associated with the nuclear pore complex (NPC) required for mRNA export (Murphy and Wente, 1996; York et al., 1999). It was subsequently shown that the product of IPK1, IP_6, and Gle1 regulates mRNA export through the binding to and synergistic activation of the RNA-dependent ATPase activity of a nuclear pore-associated DEAD-box protein Dbp5, which is essential for RNA export (Alcazar-Roman et al., 2006; Snay-Hodge et al., 1998). Recently, it has also been proposed that IP_6, Gle1 and DbP5 cooperate to control translation termination (Bolger et al., 2008).

KCS1 was initially identified as a suppressor of mutation of the protein kinase C gene (Huang and Symington, 1995). *kcs1* null cells have small and fragmented vacuoles (Saiardi et al., 2000b) and is required for resistance to salt stress, cell wall integrity and vacuole morphogenesis (Dubois et al., 2002). These phenotypes maybe due to the defect in endocytosis observed in the *kcs1* mutant (Saiardi et al., 2002). In addition, Kcs1 activity modulates telomere homeostasis such that loss and gain of $PP\text{-}IP_4$ in cells increase and decrease average telomere length, respectively (Saiardi et al., 2005; York et al., 2005). The affect of $PP\text{-}IP_4$ on telomere length requires the presence of Tel1 but does not depend on Ku70. It is not clear whether or not these pathways mechanistically overlap with a putative role of Kcs1 in regulating of DNA hyper-recombination (Luo et al., 2002).

Vip1 was identified by a biochemical approach to look for the enzyme responsible for the remaining IP_6 kinase activity in the *kcs1 ddp1* double mutant cells (Mulugu et al., 2007; York et al., 2005). In addition to a kinase domain, Vip1 harbors a C-terminal phosphatase domain of unidentified function (Fridy et al., 2007; Mulugu et al., 2007). In the budding yeast, Vip1-generated $1(3)\text{-}IP_7$, but not Kcs1-gerenated $5\text{-}IP_7$, acts as a signaling molecule regulating the yeast phosphate (Pi)-responsive (PHO) signaling pathway (Lee et al., 2007). $1(3)\text{-}IP_7$ binds to the CDI-Cyclin-CDK complex Pho81-Pho80-Pho85 and promote Pho81-

dependent inactivation of Pho80-Pho85, leading to dephosphorylation and nuclear accumulation of the transcription factor of Pho4 and subsequent transcription of the PHO genes (Lee et al., 2008; York and Lew, 2008). On the other hand, in the fission yeast *S. pombe*, the homolog of Vip1, Asp1, has been suggested to play a role in regulating actin-related protein complexes (ARP) (Feoktistova et al., 1999). Over-expression of a kinase only mutant of Asp1 is toxic to the cells and the toxicity can be alleviated in an *arp3* mutant background, strongly suggesting Vip1 generated 1(3)-IP_7 functionally interact with the Arp complex (Mulugu et al., 2007).

PP-IPs have also been proposed to be phosphate donor in non-enzymatic phosphorylation of proteins in eukaryotic cells (Bhandari et al., 2007; Draskovic et al., 2008; Saiardi et al., 2004). It is thought that the beta-phosphate from 5-PP-IP_5 is non-enzymatically donated to a "pre-primed" phosphoserine residue on the recipient protein thereby generating a protein-serine-pyrophosphate and IP_6 as products (Bhandari et al., 2007). A wide range of proteins have been implicated as recipients (Azevedo et al., 2009). Elucidation of the biological roles of this pathway is an area of active research, although to our knowledge it has not yet been shown by physical methods that serine-pyrophosphate modified recipient proteins exist in cells.

ROLES OF IP MESSENGERS IN STRESS/HORMONE SIGNALING AND DEVELOPMENT IN PLANTS

In the plant *Arabidopsis thaliana*, two homologs of the yeast Ipk2 has been identified to-date, i.e. *At*Ipk2α and *At*Ipk2β (Stevenson-Paulik et al., 2005; Stevenson-Paulik et al., 2002; Xia et al., 2003). *Different genes located on chromosome 5 encode AtIpk2α and AtIpk2β*. Despite their low overall sequence identities to the yeast Ipk2 (12-18%), purified recombinant *At*IPK2α and *At*Ipk2β are inositol phosphate 6/3/5-kinases, capable of generating I(1,3,4,5,6)P_5 (IP_5) from I(1,4,5)P_3 (IP_3) predominately through an I(1,4,5,6)P_4 (IP_4) intermediate. Expression of either *At*Ipk2 can restore IP_4 and IP_5 synthesis in the *ipk2* null yeast strain and complement its temperature sensitivity, indicating *At*Ipk2α and *At*Ipk2β are true functional homologs of the yeast Ipk2 (Stevenson-Paulik et al., 2002).

Both *At*Ipk2α and *At*Ipk2β are ubiquitously expressed in the leaves, stem, roots, siliques and flowers in adult plants by semi-quantitative PCR (Stevenson-Paulik et al., 2002). In addition, using a reporter of *At*Ipk2α expression in which the 1.5kb 5' upstream region of the gene is fused to the E. coli GUS reporter gene, the Xue lab found that *At*Ipk2α is also expressed in the emerging seedlings, seedlings at different developmental stages, roots, pollen grains and growing pollen tubes (Xia et al., 2003; Xu et al., 2005). Also, a strong expression is detected in anthers and the stigma in flowers using the GUS reporter. When expressed in onion epidermal cells, *At*Ipk2α-GFP localizes in the nucleus as well as the plasma membrane, suggesting nuclear roles for this protein. Transgenic plants expressing an *At*Ipk2α anti-sense using its own promoter were made which results in a strong reduction in expression of *At*Ipk2α while the transcript level of *At*Ipk2β is unaffected. Interestingly, the homozygous *At*Ipk2α anti-sense transgenic plants exhibit higher germination frequencies, increase in pollen tube lengths and enhanced root growth and early seedling growth, consistent with the expression of *At*Ipk2α in these tissues. These data indicated *At*Ipk2α impacts on plant development by acting as negative regulator of pollen germination and root growth. As the Xue group has shown that exogenous application of IP_3 can enhance root growth, the phenotypic consequences of inhibition of *At*Ipk2α may in part due to an accumulation of IP_3 in addition to depletion of IP_4 and IP_5.

The expression of the other plant Ipk2 homolog, *At*Ipk2β, can be induced by abiotic stress (Yang et al., 2008). Transcript levels of *At*Ipk2β increase when subject to cold or drought

stress, and decrease upon high salt or ABA addition, and *At*Ipk2β protein levels increase in response to mannitol. In order to investigate the role of *At*Ipk2β in stress signaling in plants, the Zhang's lab generated transgenic tobacco plants constitutively expressing the *At*Ipk2β gene. Expression of *At*Ipk2β does not cause any discernable change in plant morphology. However, the *At*Ipk2β -expressing plants exhibit an enhanced tolerance to various kinds of stress: they are more resistant to root and seedlings growth retardation caused by high salt concentrations, osmotic stress induced by PEG, drought conditions, H_2O_2-induced damage and short term -20°C treatment. The observed increase tolerance can partly be explained by an increase in proline levels in the transgenic plant. Proline was reported to be involved in free radical scavenger (Hong et al., 2000) and in protection of macromolecules from dehydration (Yancey, 2005). Also, elevation of catalase activity in the transgenic plant can offer addition protection from stress-induced reactive oxygen species. More importantly, the constitutive expression of *At*Ipk2β results in the constitutive or increased transcription of stress responsive genes such as lipid transfer protein, fructose-bisphosphate aldolase and raffinose synthase family protein/ seed inhibition protein. The induction of stress-response genes is considered as an important step in stress adaptation in plants (Thomashow, 1999). Transgenic plants expressing some of the stress responsive genes result in enhanced tolerance in stress (Smart et al., 2000; Yamada et al., 2000). Taken together, the results suggest a nuclear role of *At*Ipk2β in transducing abiotic stress-induced signals by transcriptional regulation of stress responsive genes. Whether *At*Ipk2β impacts on transcriptional regulation of stress-inducible genes in plant, by acting as a component of a transcriptional complex, or as modulator of chromatin structure just like the roles of yeast Ipk2 in arginine responsive and phosphate arginine gene expression (El Alami et al., 2003; Odom et al., 2000; Shen et al., 2003; Steger et al., 2003), or by an entirely novel mechanism, is currently unclear.

Surprisingly, over-expression of *At*Ipk2β does not confer stress tolerance in *Arabidopsis* (Yang et al., 2008), suggesting a different role *At*Ipk2β play in this organism. In fact, the Xia group observed that over-expression of *At*Ipk2β in Arabidopsis results in increase in branching of axillary shoots and hence increased axillary branches in mature plants (Zhang et al., 2007). Axillary shoot branching requires the formation of axillary meristems and the outgrowth of axillary buds, and in the *At*Ipk2β over-expressing lines both developmental processes are speeded up. Auxin is an important plant hormone that modulates growth in response to a plethora of developmental and environmental cues. Also, auxin has been shown to be important regulators of axillary shoot branching (Teale et al., 2006; Woodward and Bartel, 2005). The major natural occurring auxin, indole-3-acetic acid (IAA), has been shown to inhibit axillary bud growth and hence axillary shoot branching (Chatfield et al., 2000; Napoli et al., 1999). Indeed, Xia group found that *At*Ipk2β regulates axillary shoot branching via auxin signaling. The expression patterns of *At*Ipk2β and auxin transcriptional reporters are similar. Moreover, expression of *At*Ipk2β can be induced with addition of exogenous IAA in a dose-dependent manner, indicating *AtIPK2*β is an IAA responsive gene. IAA does not affect expression of AtIpk2α. Over-expression of *At*Ipk2β can alleviate the inhibition of elongation of primary roots by IAA, demonstrating *At*Ipk2β can negatively regulate IAA signaling. This regulation appears to be at least partly transcriptional, as over-expression of *At*Ipk2β results in decreased expression of one of the auxin biosynthetic gene *CYP83B1*, increase in expression of an auxin-transport gene PIN4 and, more importantly, decrease in transcription of the auxin inducible gene MAX4, which are required for auxin-mediated bud inhibition, and a cytochrome P450 homolog SPS which is required for suppression of axillary meristem initiation (Bainbridge et al., 2005; Tantikanjana et al., 2001). This study demonstrated another nuclear role for *At*Ipk2β in negative regulation of auxin hormone signaling by transcriptional control of some of the auxin responsive genes.

A recent structural study of the *Arabidopsis* ubiquitin ligase complex TIR1-ASK1 (Tan et al., 2007) provides a hint of the mechanism by which IPs may regulate auxin signaling transcriptionally. Transduction of auxin signaling is regulated by ubiquitin dependent proteolytic system. TIR1, which stands for transport inhibitor response protein 1, is a F-box protein and a subunit of the Skp1-Cullin-F-box protein (SCF^{TIR1}) ubiquitin ligase complex. ASK1 (Arabidopsis SKP1) is the adaptor subunit of the SCF^{TIR1} complex and links TIR1 to the E3 ubiquitin ligase complex. Components of the SCF^{TIR1} complex, including TIR1, have been shown to localize in the nucleus in Arabidopsis tonoplast culture (Tao et al., 2005). TIR1 has been shown to be a bona fide auxin receptor (Dharmasiri et al., 2005; Kepinski and Leyser, 2004; Kepinski and Leyser, 2005). Upon binding to the SCF^{TIR1} complex, auxin promotes the interaction between the TIR1 subunit and the transcription repressor Aux/IAA proteins. Subsequently Aux/IAA proteins are poly-ubiquitinated by SCF^{TIR1} and then degraded via the 26S proteasome pathway. Proteolysis of Aux/IAA proteins relieves the inhibition of the auxin response factor (ARF) family of transcription factor by Aux/IAA proteins. The activated ARFs then turn on the transcription of the auxin responsive genes (Hagen and Guilfoyle, 2002; Liscum and Reed, 2002; Reed, 2001; Tiwari et al., 2001; Zenser et al., 2001). A surprising finding in Tan et al. is that an IP_6 molecule was found to bind to the leucine-rich repeat domain of TIR1, adjacent to the auxin-binding site. IP_6 appears to be a structural co-factor for TIR1 and its role in TIR1 function remain to be elucidated. However, one attractive hypothesis is that IP_6 (or presumably other IPs), by binding to TIR1, regulates either auxin binding to the TIR1 or the ubiquitin ligase activity of the complex, and modulates the subsequent binding and degradation of Aux/IAA proteins, hence regulating the strength of the auxin signaling output.

*At*Ipk1 is the *Arabidopsis* Ipk1 homolog, identified by homology search using several fungal Ipk1 protein sequences as queries (Stevenson-Paulik et al., 2005). Recombinant *At*Ipk1 can phosphorylate I(1,3,4,5,6)P_5 to IP_6. It also functions as a 2-kinase towards I(1,3,4,6)P_4 and I(1,4,5,6)P_4 enabling the production of I(1,2,3,4,6)P_5 and I(1,2,4,5,6)P_5. Expression of *At*Ipk1 in the yeast *ipk1* null restores IP_6 synthesis and rescues the temperature sensitivity of the mutant, indicating *At*Ipk1 is able to make IP_6 in vivo (Sweetman et al., 2006). An *AtIPK1* mutant, named *atipk1-1* was identified in the Salk T-DNA collection. *atipk1-1* contains a T-DNA insertion 77 nucleotides upstream of the stop codon in the last exon of the ORF. *atipk1-1* mutant exhibits more then 70% drops in the *AtIPK1* transcript as judged by Northern blot, and the seed phytate (IP_6) levels in the *atipk1-1* mutant are reduced by 83%, demonstrating *At*Ipk1 plays a critical role in synthesis of IP_6 in plant. *atipk1-1* is hypersensitive to inorganic phosphate levels in the growth medium, which are optimal for the wild type plant. The *atipk1-1* mutant leaves, but not the wild type leaves, become abaxially curled (epinastic) when 1mM Pi is present in the medium. In addition, the *atipk1-1* mutant exhibits a higher intracellular Pi levels, indicating *atipk1-1*is unable to maintain a normal phosphate homeostasis. Taken together, it seems that *At*Ipk1 and its IP products are required for phosphate sensing and homeostasis in plants.

Surprisingly, *atipk1-1* mutant plants do not appear to have defects in auxin signaling pathways (Stevenson-Paulik et al., 2005). This is puzzling in light of the binding of IP_6 to the auxin receptor, TIR1 as described above. It is possible that the 5-10% of IP_6 produced in the *atipk1-1* hypomorphic mutants is sufficient to generate enough functional TIR1, thus a complete null in IP_6 production may indeed exhibit an auxin phenotype. Alternatively, loss of Ipk1 results in an accumulation of IP_5 to levels nearly equivalent to IP_6 in wild-type plants, thus it is plausible that IP_5 is capable of compensating for the loss of IP_6. To this end it is not known whether or not IP_5 binds TIR1 with equal affinity. If IP_5 serves a compensatory role, then it may be that loss of both *At*Ipk2α and *At*Ipk2β would result in a loss of auxin signaling.

IP_6 is also implicated in ABA signaling in guard cells (Lemtiri-Chlieh et al., 2000; Lemtiri-Chlieh et al., 2003). Studies by Brearley group showed that IP_6 level is rapidly induced by the stress hormone abscisic acid (ABA) in intact guard cells of *Solanum tuberosum*. Addition of submicromolar amount of IP_6 into guard cell protoplasts through patch clamp phenocopies the inhibitory effect of ABA or Ca^{2+} on the inward rectifying K^+ current. Co-administration of a Ca^{2+} chelator EGTA can alleviate this inhibitory effect by IP_6, suggesting it is Ca^{2+} dependent. Indeed, Brearley group showed that IP_6 does induce an increase in intracellular Ca^{2+}, not by Ca^{2+} influx, but by triggering Ca^{2+} release from endomembrane store particularly the guard cell vacuole. These data strongly indicate that IP_6 mediate ABA signaling in guard cells by mobilizing intracellular Ca^{2+} store. Similarly, IP_4 and IP_6 have been shown to regulate Ca^{2+} channel activity and store-operated Ca^{2+} influx by modulation of activities of IP_3 5-phosphatase, protein phosphatase and adenyl cyclase (Hermosura et al., 2000; Larsson et al., 1997; Yang et al., 2001).

In Arabidopsis, there are four I(1,3,4)P_3 5/6-kinase homologs identified to-date, namely *AtITPK-1, AtITPK-2, AtITPK-3,* and *AtITPK-4* (Qin et al., 2005; Shi et al., 2003; Sweetman et al., 2007; Wilson and Majerus, 1997). Only the in vivo functions of *At*Itpk-1 have been explored (Qin et al., 2005). *At*Itpk-1 can phosphorylate I(1,3,4)P_3 to either I(1,3,4,5)P_4 or I(1,3,4,6,)P_4 in vitro. In plants, a *At*Itpk1-GFP fusion protein is localized in the nucleus, where *At*Itpk1 binds to the COP9 signalosome (CSN), similar to what was observed for the human 5/6- kinase (Sun et al., 2002). The transcription and protein levels of *At*Itpk-1 are induced by red light (RL). Two T-DNA insertion mutants of AtITPK1, *atitpk-1-1* and *atitpk-1-2*, have been isolated. *AtITPK-1* transcript levels are drastically reduced in these mutants as judged by RT-PCR. When grown under pure RL, *atitpk-1-1* and *atitpk-1-2* exhibit shortened hypocotyls compared to WT, while transgenic plants over-expressing *At*Itpk-1 show increases in hypocotyls length. This suggests *At*Itpk-1 modulates photomorphogeneis under red light, possibly through association with the CSN. On the other hand, over-expression of a rice I(1,3,4)P_3 5/6-kinase, *Os*ITL1, in tobacco decreases tolerance to high salt during germination and seedling development, indicating *Os*Itl1 may function as a negative regulator of osmotic stress signaling (Niu et al., 2008).

ROLES OF IP AND PP-IP MOLECULES IN EMBRYONIC DEVELOPMENT, FERTILITY AND INSULIN SIGNALING

Mouse *Ipk2*, alternatively known as inositol phosphate multikinase, has been identified on Chromosome 10 (Frederick et al., 2005). During embryogenesis, the mouse *Ipk2* was found to express in the head fold, neural tube, bronchial arches, somites and hind limb bud. The mouse *Ipk2* gene was disrupted by homologous recombination, which removed the exon 4 of the gene resulting in a complete loss of function. By metabolic labeling, the homozygous *Ipk2* mutant embryo shows no detectable IP_6 synthesis, while the levels of inositol lipids phosphatidylinositol, phosphatidylinositol phosphate and phosphatidylinositol 4,5-bisphosphate remain unchanged. Moreover, ES lines from the homozygous Ipk2 mutant exhibits drastic loss in both IP_5 and IP_6 levels, while the levels of IP_3 [I(1,3,4)P_3 and I(1,4,5)P_3] and IP_4 are similar to the WT ES lines. This confirms that the mouse Ipk2 is required for IPs synthesis in vivo. On the other hand, agonist-induced changes in IPs and Ca^{2+} levels are comparable in the *ipk2* mutant ES cells and WT controls. Although Ipk2 is not required for the viability of ES cells, the homozygous *Ipk2* mutant is embryonic lethal. Gastrulation seems to be unaffected in the absence of Ipk2. However, starting from embryonic day E8.5, the mutant embryos are developmentally delayed, and become smaller and shorter along the anterior-posterior axis compared to the WT littermate, suggesting a proliferation defect. Addition defects include separation of the allantois and the chorion, lack of somite formation and massive accumulation and folding of neurectoderm in the mid-

hind region of the mutant embryos. This study highlights the important roles of Ipk2, and presumably production of IP_5 and IP_6, in the proper embryonic development in mice.

The mouse *Ipk1* homolog, also known as I(1,3,4,5,6)P_5 2-kinase, was studied by the Majerus group (Verbsky et al., 2005a). In these studies, Ipk1 was disrupted by a gene trap insertion where exon 1 of Ipk1 is fused to the β-galactosidase gene. While no cell lines have been derived from homozygous null embryos, mouse embryonic fibroblasts (MEF) lines derived from embryos heterozygous for the Ipk1 gene trap exhibit an accumulation IP_5 and PP-IP_4, indicating a decrease in conversion from IP_5 to IP_6 when one copy of *Ipk1* is disrupted. Homozygous *Ipk1* mutant is early embryonic lethal: the mutant embryos died and were reabsorbed before E8.5, demonstrating Ipk1 is essential for early embryonic development. Ipk1 is expressed in neural tube, notochord, somites, yolk sac, heart, cardiac vein, aortic, digestive tract and pharyngeal arches. Although the exact mechanism by which Ipk1 regulates embryonic development is unclear at present, the Majerus group suggested that strong expression of Ipk1 in the yolk sac are consistent with its role in nutrient absorption and delivery to the embryo and production of factors important for developmental patterning. Also, since increased levels of IP_6 has been shown to protect HEK293 cells from TNFα- and Fas-induced apoptosis (Verbsky and Majerus, 2005), it may be possible that the lack of IP_6 in the *Ipk1* mutant leads to uncontrolled apoptosis and hence the embryonic phenotype.

In mammalian cells, inositol hexakisphosphate kinases (IP6Ks, also known as IHPKs) are enzymes that convert IP_6 to PP-IPs. In mice, there are three IP6K homologs, IP6K1, 2 and 3. The Snyder group has generated an *ip6k1* knockout mice by targeted deletion of exon 6, which encodes the sub-domain required for catalytic activity (Bhandari et al., 2008). IP_7 and IP_8 productions from IP_6 are virtually undetectable in whole cell extract and cytosolic fraction from MEFs derived from homozygous *ipk6k1* mutant. Also, there is a drastic reduction in IP_7 levels in the mutant MEFs, indicating IP6K1 is the major IP6K1 activity in mice. Homozygous *ip6k1* mutant go through embryonic development and reach adulthood. However, males of homozygous mutant are sterile; there is a reduction in numbers of advanced spermatids in the seminiferous tubules and no sperm in the epididymis, demonstrating IP6K1 plays an important role in spermatogenesis. Male mutant mice are smaller than WT and there are reductions in weight in both males and females. Plasma levels of growth factor in the *ip6k1* mutant are similar to those of the wild type. On the other hand, there is a 65-70% reduction in plasma insulin levels in the mutant mice. Since it has been shown that IP_7 is required for efficient exocytosis of insulin-containing secretory granules in pancreatic β cells (Illies et al., 2007), the drop in insulin level is presumably due to a decrease in insulin secretion. This study demonstrates IP6K1 and IP_7 are required for spermatogeneis and regulation of body size and weight through regulating insulin secretion. A study by the Berggren group demonstrated that in pancreatic β cells glucose can stimulate a transient increase in IP_6 levels which induce Ca2+ influx by inhibition of protein phosphatase activity (Larsson et al., 1997). In light of data from Illes et al., the increase of IP_6 may also lead to an increase of IP_7 production and hence an increase in insulin secretion. So IP6K1 may also play a role in glucose sensing and stimuli-secretion coupling in pancreatic β cells. Of note, mutations in *IHPK1*, the human homolog of *IP6K1*, were identified in families having type II diabetes (Kamimura et al., 2004), thus implicating a role for IP6K1 in diabetes pathogenesis. Recently, the mouse knockout of IP6K2, referred to as IHPK2, was reported and found to develop normally (Morrison et al., 2009). Interestingly, chronic treatment of IP6K2 mutant mice with a UV-mimetic 4-nitroquinoline 1-oxide (4-NQO) results in a significant increase in the incidence of invasive squamous cell carcinoma (SCC), while also exhibiting resistance to ionizing radiation (Morrison et al., 2009). Thus the roles of IP6Ks remain an active and intriguing area of study.

ZEBRAFISH IPK1 REGULATES LEFT-RIGHT ASYMMETRY

The zebrafish Ipk1 is 57% identical to the human Ipk1, and can restore the IP_6 synthesis in the yeast *ipk2* null and complemented the synthetic lethality of the yeast *gle1-2 ipk1-4* double mutant, indicating it is a functional IP_5 2-kinase (Sarmah et al., 2005). Wente group then carefully examined the phenotype in zebrafish embryos in which Ipk1 is effectively knockdown by antisense morpholinos, and found that Ipk1 is involved in left-right (LR) asymmetry in zebrafish. In vertebrate embryos, internal organs show a conserved LR asymmetry, which is critical for proper development (McGrath et al., 2003; Webb and Miller, 2003). In zebrafish, a structure called Kupffer's vesicle (KV) has been shown to play a role in generating LR asymmetry by rotational movement of its motile cilia (Essner et al., 2005; Essner et al., 2002). Among other factors, Ca^{2+} has also been implicated in LR asymmetry generation in mice and chicken (McGrath et al., 2003; Raya and Izpisua Belmonte, 2004). In control embryos, >95% of heart tubes are asymmetrically positioned in the left side, while in Ipk1-morpholino treated embryos, around half of the heart tubes are on the right side and the other half on the left, indicating loss of Ipk1 results in randomization of heart asymmetry in zebrafish embryos. Furthermore, the asymmetrical positioning of other visceral organs (gut, pancreas, liver) and brain is also compromised by Ipk1 knockdown. Using a genetically encoded Ca^{2+} sensor Flash-pericam, Wente group then showed that there is a transient left oriented intracellular Ca2+ flux near KV in normal zebrafish embryo development at the stage when LR asymmetry is initiated, and this flux requires an intact KV. Interesting, Ipk1 knockdown leads to the disappearance of this asymmetrical Ca2+ flux, suggesting Ipk1 may regulate LR positioning through generation of asymmetrical Ca^{2+} flux.

GFP-Ipk1 is enriched in centrosomes and basal bodies, and the Ipk1 knockdown also results in reduction of KC ciliary beating and length (Sarmah et al., 2007). These defects can be rescued by co-injection of wild type Ipk1 mRNA but not a kinase-dead version, demonstrating the Ipk1 kinase activity is critical for proper KV cilia functions. Ipk1 knockdown also leads to decrease of cilia length in the pronephric duct and spinal canal cilia, indicating Ipk1 is important for cilia length maintenance in multiple organs. These data suggest a new pathway by which IPs induce local change in Ca^{2+} concentrations by regulating biased cilia movement.

IP_4 AND IP_7 REGULATES CHEMOTAXIS IN *DICTYOSTELIUM* AND NEUTROPHILS BY ANTAGONIZING $PI(3,4,5)P_3$ SIGNALING

Under starvation, the slime mold *D. discoideum*, release cAMP which acts as chemoattractant to induce chemotaxis and hence cell aggregation (Chung et al., 2001; Devreotes and Janetopoulos, 2003; Iijima et al., 2002). Upon binding to its surface receptor, cAMP elicits a localized, G-protein dependent activation of a phosphatidylinositol 3-kinase (PI3K) and inhibition of a phosphatidylinositol 3-phosphatase (PTEN), resulting in an increase in levels of phosphatidylinositol 3,4,5,-trisphosphate [$PI(3,4,5)P_3$]. The local increase in PI(3,4,5)P3 then recruits a subset of PH domain-containing proteins to the lead edge of the chemotaxing cells. Snyder group cloned the *Dictyostelium IP6K* and discovered that IP6K and its products IP_7 regulate chemotaxis in *Dictyostelium* (Luo et al., 2003). Disruption of *IP6K* results in drastic reductions in the IP_7 and IP_8 levels, while the concentrations of IP_3, IP_5 and IP_6 remains unchanged, indicating IP6K is required for IP_7 and IP_8 synthesis in *Dictyostelium*. The chemoattractant cAMP can induce increase in IP_7 and IP_8 levels in WT cells, while the *ip6k*- cells have increased sensitivity to cAMP, suggesting IP_7/IP_8 negatively regulates cAMP-induced chemotaxis. Indeed, in vitro, IP_7 can compete with $PI(3,4,5)P_3$ for binding to PH domain containing proteins, and deletion of *IP6K* enhances the translocation of a GFP-PH marker to the leading edge of the

chemotaxing cells. Moreover, GFP-PH protein isolated from amoeba cells was found associated with IP_6, IP_7 and IP_8, indicating IPs and PP-IPs can bind to PH domain in vivo. This study shows that IP_7 can negatively regulate $PI(3,4,5)P_3$ signaling through competition with this inositol lipid for PH domain binding. In another study by Luo group, chemotaxis of neutrophils through activation of $PI(3,4,5)P_3$ signaling is also negatively regulated by an IP, namely $I(1,3,4,5)P_4$ (Jia et al., 2007). $I(1,3,4,5)P_4$ also inhibits $PI(3,4,5)P_3$ by competition for binding to PH domain proteins. These two studies highlights a novel role of IPs and PP-IPs in regulating $PI(3,4,5)P_3$ signaling by competition for binding to downstream protein partners.

IP_6 IS A CO-FACTOR OF ADAR2 AND IS REQUIRED FOR RNA EDITING

An IP_6 molecule was found to be buried in the interior of the structure of hADAR2 by Bass group (Macbeth et al., 2005). ADAR2 encodes adenosine deaminases that act on RNA (Bass, 2002) and catalyze RNA editing by deaminating adenosine to inosine in double stranded RNA. IP_6 binds in the core of the catalytic domain, and is required for protein stability and enzyme activity. IP_6 is also required for activity of another class of RNA editing enzymes, ADAT1, which works on tRNA. These data uncovered an unexpected role for IP_6 as a structural co-factor of RNA editing enzymes.

DROSOPHILA PLC HOMOLOGS REGULATE PHOTOTRANSDUCTION, AND EYE AND WING DEVELOPMENT

There are three PLC homologs in fruit fly: small wing (*sl*), no receptor potential A (*norpA*) and PLC21C. sl belongs to the PLC-γ sub-type. Genetically null mutant of *sl* exhibit reduction of adult wing size and extra R7 photoreceptors in the compound eye (Thackeray et al., 1998). Each ommatidium of a compound eye consists of a precise assembly of eight photoreceptors, R1-R8. In many fly mutants that have altered MAPK signaling, there is an increase in R7 cells (Basler and Hafen, 1989; Brunner et al., 1994; Buckles et al., 1992). In fact, attenuation of MAPK signaling in the *sl* mutant by reduction of the gene dosage of EGFR by half, can almost completely rescue the extra R7 cell phenotype. This suggests that *sl* is a negative regulator of MAPK signaling in Drosophila eye development.

norpA is a PLCβ isoform, and is required for phototransduction in Drosophila eye (Bloomquist et al., 1988). Upon light activation, rhodopsin activates heteromeric Gq protein, which subsequently turns on norpA. norpA hydrolyze PIP_2 into IP_3 and DAG (Hardie and Raghu, 2001; Minke, 2001; Montell, 1999). Evidence suggests that DAG and its downstream metabolite, rather than IP_3 is responsible for opening of the light activated TRP channel to produce quantum pump (Hardie et al., 2002). On the other hand, norpA can inactivate its upstream G protein by acting as GTPase-activating protein (GAP) when associated with the PDZ scaffold protein INAD (Cook et al., 2000). The negative feedback mechanism was proposed to maintain high signal resolution of the response to light.

In addition to Plc, Ipk2 and Ipk1 homologs have been identified in Drosophila and the molecular basis of IP synthesis has been elucidated (Seeds et al., 2004). However, the developmental roles of fly IPKs remain elusive and are currently under active research in our lab.

SUMMARY

Inositol phosphates and inositol pyrophosphates are small molecule metabolites that play important roles in nuclear processes such as transcription control, mRNA export and DNA repair. On this wonderful occasion of the fiftieth anniversary of the Advances in Enzyme

Regulation conference, it is a privilege to participate through presenting recent developments in the area of inositol phosphate and pyrophosphate regulatory biology. This article summarizes recent advances in understanding IPs and PP-IPs biology in development and nuclear cell signaling. Data obtained from various model organisms hint at the emerging modes of mechanisms of these versatile molecules.

Studies in model organisms revealed that IPs and PP-IPs are critical for development and signaling in plants, mice, zebrafish and slime mold. In plants, IP molecules are required for signaling in response to stress, hormone, and nutrient, by transcriptional regulation of the stimuli-responsive genes. In some cases, IPs act as regulatory molecules as the levels of IPKs/IPs are induced by those stimuli and a constitutively induction of downstream events can be accomplished by over-expressing the IPKs. Nutrient sensing is a recurring theme in IP biology as IPs and PP-IPs are also involved in amino acid and phosphate signaling in yeast and possible glucose sensing in pancreatic β cells, indicating it maybe acquired early during evolution. There are some newly discovered nuclear roles of IPs: 1) binding to and possibly regulation of the SCF^{TIR1} ubiquitin ligase complex, and 2) RNA editing by acting as structural co-factor of ADAR2 and ADAT1. On the other hand, IPs and PP-IPs are also implicated in some novel non-nuclear processes: 1) insulin secretion, 2) negative regulation of PIP_3 signaling and 3) modulation of intracellular Ca^{2+} concentration. Following the discovery of new biological roles of IPs and PP-IPs, a few new receptors for IPs and PP-IPs were identified in the process. Three modes of receptor binding by IPs and PP-IPs can be summarized: 1) Direct binding to the receptor (e.g. TIR1), 2) displacement of a ligand (e.g. PIP_3) already bound to the receptor (e.g. PH domain containing proteins, and 3) acting as a structural co-factor and possibly incorporated inside the receptor during protein folding (e.g. ADAR2). Hopefully, more experimentation will uncover more receptors for and biological roles of these versatile molecules.

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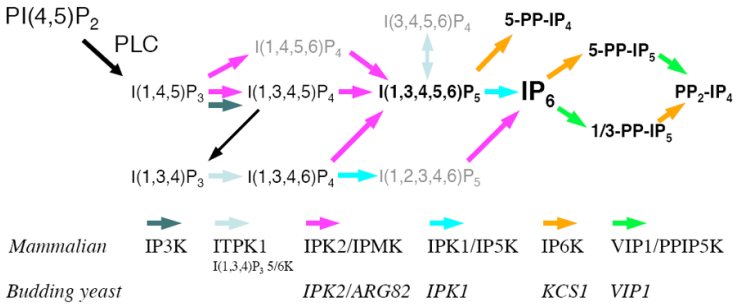

FIGURE 1. INOSITOL PHOSPHATE AND PYROPHOSPHATE PATHWAYS

Activation of phosphoinositide-specific phospholipase C (PLC) triggers the conversion of phosphatidylinositol 4,5-bisphosphate, $PI(4,5)P_2$, to the second messengers $I(1,4,5)P_3$ and 1,2-diacylglycerol (not shown). Metabolism of $I(1,4,5)P_3$ occurs to generate numerous inositol phosphate and inositol pyrophosphate chemical codes. There are several evolutionarily conserved inositol phosphate kinases that contribute to the production of these regulatory molecules: in mammals there are 6 distinct kinase activities, whereas in the budding yeast there are 4 gene products. The commonly used gene name abbreviations are listed. Inositol phosphatases are omitted for clarity except for the black arrow linking $I(1,3,4,5)P_4$ and $I(1,3,4)P_3$, which is encoded by a 5-phosphatase INPP5.