Published in final edited form as:
Cell. 2010 December 10; 143(6): 1030–1030.e1. doi:10.1016/j.cell.2010.11.045.

SnapShot: Inositol Phosphates

Ace J. Hatch and **John D. York**
HHMI, Pharmacology and Cancer Biology, Biochemistry, Duke University, Durham, NC 27710, USA

PLC-Dependent IP Code

Inositol phosphates (IPs) are signaling molecules found in all eukaryotes. Inositol is a six-carbon cyclic alcohol with an axial 2-hydroxyl (depicted with heavy tapered lines) and five equatorial hydroxyls. Mono- and diphosphorylation of the inositol scaffold generate a wide array of stereochemically distinct signaling molecules. Soluble IP_3 is formed by hydrolysis of the inositol lipid PIP_2 via phospholipase C (PLC) isozymes. PLC is stimulated by a host of extracellular signals acting through G protein-coupled receptors (GPCRs) and receptor tyrosine kinases (RTKs). An array of lipid-derived IP species arise through the actions of four evolutionarily conserved kinases (the common names are shown in the figure and table, and aliases are shown in parentheses). Inositol phosphate multi-kinase, IPMK (IPK2 or ARG82), produces I(1,3,4,5,6)P_5 from IP_3 by sequential phosphorylation of the 6- and 3-positions. It also possesses 5-kinase activity toward I(1,3,4,6)P_4 (in total eight substrates have been proposed including the lipid PIP_2—hence the name “multikinase”). IPK1 (IP5K) generates IP_6 from IP_5 by phosphorylation at the 2-position. IP6K (KCS1, IHPK) phosphorylates the 5-position of IP_5, IP_6, and IP_7 to generate diphosphoinositol phosphates (PP-IPs) 5-PP-IP_4, 5-IP_7, and 1,5-IP_8, respectively. VIP isoforms (PPIP5K, IP7K) generate diphospho-inositol products through a distinct 1-kinase, or possibly its enantiomeric 3-kinase, activity yielding 1-IP_7 and 1,5-IP_8. In multicellular organisms there are up to two additional IP kinases (see table in figure). Plants and mammals have an ITPK enzyme (5/6-kinase, IP56K) that phosphorylates I(1,3,4)P_3 at either the 5- or 6-position to generate I(1,3,4,5)P_4 or I(1,3,4,6)P_4, respectively. ITPK1 is also a reversible 1-kinase/phosphatase that controls the levels of I(3,4,5,6)P_4. Flies and mammals have IP_3 3-kinases (IP3K) that selectively phosphorylate I(1,4,5)P_3 to I(1,3,4,5)P_4. Additionally, several phosphatases that add to the diversity of IP species have been omitted for clarity; however we do show INPP5, a 5-phosphatase for which ten genes exist in mammals, in the context of its role in generating the I(1,3,4)P_3 substrate utilized by ITPK. In total, close to forty of the theoretical 728 inositol mono- and diphosphorylated species have been identified in eukaryotic cells representing the building blocks of what we depict as a PLC-dependent IP code.

Functional Roles of IPs

Ion Channels

Soluble IP_3 generated by the hydrolysis of PIP_2 through receptor-activated PLC isoforms (either PLCβ or PLCγ) directly binds endoplasmic reticulum-resident calcium channels and regulates their permeability. The flux of intracellular calcium has many biological effects, and the role of IP_3 in regulating calcium channels has been studied in great detail thereby serving as a canonical second messenger paradigm. Additionally, $I(3,4,5,6)P_4$ generated by the 1-phosphatase activity of ITPK1 regulates the permeability of the plasma membrane resident ClC3 chloride channel.

Phosphate Sensing

The Pho80-Pho85-Pho81 cyclin-CDK-CDKi complex acts to phosphorylate the Pho4 transcription factor, a modification that maintains its cytoplasmic localization when environmental phosphate is abundant. When environmental phosphate is scarce, Vip1-produced 1-IP_7 binds to the Pho80-Pho85-Pho81 complex inhibiting its kinase activity. Unphosphorylated Pho4 is then able to accumulate in the nucleus and initiate the transcription of genes required for phosphate scavenging.

Transcription

In yeast, Ipk2 is one of four components of the Mcm1-ArgR transcription complex responsible for regulating the transcriptional response to environmental arginine. Although Ipk2 does not bind DNA directly, it assembles with the complex in response to nutrient deprivation, providing both kinase-independent and -dependent functionalities that mediate changes in transcription.

Insulin Secretion and AKT

IPs are implicated in several different aspects of insulin secretion from pancreatic β cells. The regulation of intracellular Ca^{2+} is important for the control of secretory vesicle fusion and insulin release. IP_3 regulates Ca^{2+} release from intracellular stores and IP_6 regulates the flux through L-type Ca^{2+} channels. 5-IP_7 generated by IP6K1 in β cells has been shown to stimulate insulin secretion from the readily releasable pool (RRP) of vesicles. A paper published in this issue of *Cell* reports a role for IP6K-generated 5-IP_7 in regulating AKT signaling in response to insulin stimulation. Deleting IP6K in mice results in insulin hypersensitivity and increased fatty acid metabolism and protects against age-dependent insulin resistance analogous to human type 2 diabetes.

Embryonic Development

Mutations in individual kinases within the IP pathway cause multiple developmental defects. In mice loss of IPMK (Ipk2) or IPK1 is embryonic lethal. Zebrafish show randomization of left-right asymmetry when IPK1 is depleted. This defect is caused by shortened cilia that cannot beat properly. ITPK loss in mice results in profound neural tube defects. IP6K mutant organisms show sterility and signaling pathway defects. IP3K-deficient organisms show sterility and immunological and neural defects. The broad spectrum of defects across

species has necessitated the use of multiple model systems in the study of the IP metabolic pathway.

mRNA Export and Translation

IP_6 stimulates mRNA export from the nucleus by interacting with Gle1 on the cytoplasmic side of the nuclear pore complex. This interaction allows Gle1 to stimulate the ATPase activity of its binding partner, the RNA helicase Dbp5, and is essential for efficient mRNA export. The IP_6-Gle1-Dbp5 interaction has also been shown to be required for the recruitment of termination factors to polysomes and proper translation termination.

IP Structural Cofactors

Three independent structural studies have identified roles for IPs as structural cofactors. IP_6 is bound in the core of the RNA-modifying enzyme ADAR2 and the plant auxinsensing ubiquitin ligase complex Tir1-Ask1. Additionally, the plant Jasmonate receptor binds to IP_5 (not shown). In all cases, IP molecules appear to function as structural cofactors that have little to no “exchange” with bulk solvent.

Other Roles

This frame contains a list of additional biological roles in which IPs have been implicated. This list and the contents of the SnapShot are by no means exhaustive and are intended as a starting point for pursuing further reading.

REFERENCES

1. Alcazar-Roman AR, Wente SR. Inositol polyphosphates: a new frontier for regulating gene expression. Chromosoma. 2008; 117:1–13. [PubMed: 17943301]
2. Berridge MJ. Inositol trisphosphate and calcium signalling. Nature. 1993; 361:315–325. [PubMed: 8381210]
3. Burton A, Hu X, Saiardi A. Are inositol pyrophosphates signalling molecules? J. Cell. Physiol. 2009; 220:8–15. [PubMed: 19326391]
4. Irvine RF, Schell MJ. Back in the water: the return of the inositol phosphates. Nature Rev. 2001; 2:327–338.
5. Majerus PW. Inositol phosphate biochemistry. Annu. Rev. Biochem. 1992; 61:225–250. [PubMed: 1323235]
6. Michell RH. First came the link between phosphoinositides and Ca2+ signalling, and then a deluge of other phosphoinositide functions. Cell Calcium. 2009; 45:521–526. [PubMed: 19371949]
7. Mikoshiba K. IP3 receptor/Ca2+ channel: from discovery to new signaling concepts. J. Neurochem. 2007; 102:1426–1446. [PubMed: 17697045]
8. Monserrate JP, York JD. Inositol phosphate synthesis and the nuclear processes they affect. Curr. Opin. Cell Biol. 2010; 22:365–373. [PubMed: 20359876]
9. Sauer K, Cooke MP. Regulation of immune cell development through soluble inositol-1,3,4,5-tetrakisphosphate. Nat. Rev. Immunol. 2010; 10:257–271. [PubMed: 20336153]
10. Shears SB. Molecular basis for the integration of inositol phosphate signaling pathways via human ITPK1. Adv. Enzyme Regul. 2009; 49:87–96. [PubMed: 19200440]