Phosphoinositides I: Enzymes of Synthesis and Degradation

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Preface

When I was approached to shape a book about phosphoinositide signaling, I first felt honored and humbled. On second thought, this appeared to be an impossible task. Phosphoinositides have grown from being just a curious lipid fraction isolated from bovine brain, showing increased radioactive metabolic labeling during intense stimulation protocols, to become the focus of immense interest as key regulatory molecules that penetrate every aspect of eukaryotic biology. The expansion of this field in the last three decades has been enormous: it turned from a basic science exercise of a devoted few to highly translatable science relevant to a large number of human diseases (isn't this the nature of good basic science?). These include cancer, metabolic-, immuno- and neurodegenerative disorders, to name just a few. Reviewing the large number of enzymes that convert phosphoinositides would fill a book—let alone the diverse biological processes in which phosphoinositides play key regulatory roles. Given the interest, a collection of up-to-date reviews compiled in a book is clearly warranted, which was enough to sway me to accept this assignment. As one editor is unable to handle this enormous task, I was delighted when Matthias Wymann and John York were kind enough to join me in this ambitious effort.

When thinking about potential authors, the obvious choice would have been to approach the people whose contributions have been crucial to push and elevate this field to the level it is today. Bob Michell, prophetically placed phosphoinositides in the center of signal transduction in a 1975 Biochem. Biophys. Acta review (Michell 1975), Michael Berridge had a key role in linking phosphoinositides and Ca^{2+} signaling and whose fascinating reviews have inspired many of us (Berridge and Irvine 1984). Robin Irvine, whose group found that InsP_3 was a mixture of two isomers, the active Ins(1,4,5)P_3 and an inactive Ins(1,3,4)P_3, and who described the tetrakisphosphate pathway (Irvine et al. 1986), and who always challenges us with most provocative ideas. Philip Majerus, who has insisted on the importance of inositide phosphatases (Majerus et al. 1999) very early on. The group of Lewis Cantley, with the discovery of PI 3-kinase activities and the mapping of downstream effectors (Whitman et al. 1988; Franke et al. 1997), or the Waterfield lab where the first PI 3-kinase catalytic subunit was isolated and cloned (Otsu et al. 1991; Hiles et al. 1992). Peter Downes, who recognized the translational value of phosphoinositide research. Jeremy Thorner and Scott Emr, whose work in baker's yeast still forms the

foundation of our understanding of the role of inositol lipids in trafficking (Strahl and Thorner 2007) or Pietro De Camilli, whose group documented the central role of inositides in brain and synaptic biology (Cremona et al. 1999). There are many others who made valuable or even greater contributions to phosphoinositide research. The above list reflects my bias, as these researchers had the largest impact on my thinking and the directions of my work. Research is, however, a constantly evolving process and we (now Matthias and John being involved) wanted to involve contributions of scientists who represent a second or third wave of researchers infected with the interest in phosphoinositides. We made an effort to recruit authors who have been trainees of these founding laboratories. With this selection our goal was to sample the view of the current and future generation. By selecting their trainees, we feel that we pay tribute to the "Founding Fathers", and show that the research they put in motion is alive and continues with fresh ideas, new ambitions and a translational and therapeutic value.

Phosphoinositide research in the 1980s went hand in hand with research on Ca^{2+} signaling pursued in "non-excitable" cells and was also marked with the discovery of the family of protein kinase C enzymes, regulated by diacylglycerol, one of the products of phosphoinositide-specific phospholipase C enzymes. These areas of research developed and expanded to form their own fields, and could not be discussed here in detail—even though they are linked historically to the development of phosphoinositide signaling. The enormous work of the groups of Yasutomi Nishizuka on protein kinase C, and Katsuhiko Mikoshiba on cloning and characterizing the Ins(1,4,5)P_3 receptors are prime examples of these achievements. Although we could not cover all these areas, we included a chapter on Ca^{2+} signaling via the Ins(1,4,5)P_3 receptor by Colin Taylor, a trainee of the Michael Berridge's lab, where important links between Ca^{2+} release and Ins(1,4,5)P_3 receptor signaling were discovered. We also decided to allocate some space to inositol phosphates, the soluble counterparts of some of the phosphoinositides. These molecules for long had been viewed only as the metabolic products of the second messenger Ins(1,4,5)P_3 but recently gained significant prominence as regulators of important physiological processes. With the discovery of the highly phosphorylated and pyrophosphorylated inositols and the enzymes that produce them, it became clear that this system represents a whole new regulatory paradigm with exciting new developments.

Finally, it was a difficult dilemma whether to include a Chapter on the early history of phosphoinositides. We decided against it for a number of reasons. First, the really interesting history is traced back to studies that preceded the landmark 1975 Bob Michell review and included the work of the Hokins (1987), Bernard Agranoff (2009) and other pioneers of phosphoinositide research. Nobody could tell these early developments better than Bob Michell in his several recollections (Michell 1995) or Robin Irvine who commemorated the 20 years of Ins(1,4,5)P_3 and the period leading to its discovery (Irvine 2003). We encourage the young readers to go back and read these recollections, as they show several examples of how seemingly uninspiring observations formed the beginning of something that became huge as it unfolded. What came after these landmark discoveries is so overwhelming that each one of us has own views and subjective memories and stories to tell on some aspects of

it. As Editors we felt that our views should not be elevated above others on these historical aspects, and leave it to the authors of the individual Chapters to elucidate the diversity in this respect. The only exception is a Chapter on the history of PI 3-kinases by Alex Toker that we felt deserves special emphasis as it had the most transforming impact on the field since the late 1980s.

One needs to understand that selection of authors is a subjective process and does not always reflect on who contributed the most in a selected field. However, we are confident that proper credit is given in the individual Chapters to each groups and individuals whose work has moved this field forward. It should also be understood that a field that generates over 10,000 entries in PubMed with each keyword that relates to phosphoinositides cannot be covered without missing some aspects that could be important. However, we trust that this collection will be found useful for both the experts and the novices.

References

Agranoff BW (2009) Turtles all the way: Reflections on myo-Inositol. *J Biol Chem* 284(32):21121–21126

Berridge MJ, Irvine RF (1984) Inositol trisphosphate, a novel second messenger in cellular signal transduction. *Nature* 312:315–321

Cremona O, et al (1999) Essential role of phosphoinositide metabolism in synaptic vesicle recycling. *Cell* 99:179–188

Franke TF, Kaplan DR, Cantley LC, Toker A (1997) Direct regulation of the Akt protooncogene product by PI3,4P2. *Science* 275:665–668

Hiles ID et al (1992) Phosphatidylinositol 3-kinase: structure and expression of the 110 kDa catalytic subunit. *Cell* 70:419–429

Hokin LE (1987) The road to the phosphoinositide-generated second messengers. *Trends Pharmacol Sci* 8:53–56

Irvine RF (2003) 20 years of Ins(1,4,5)P3, and 40 years before. *Nat Rev Mol Cell Biol* 4(7):586–590

Irvine RF, Letcher AJ, Heslop JP, Berridge MJ (1986) The inositol tris/tetrakis phosphate pathway—demonstration of inositol (1,4,5)trisphosphate-3-kinase activity in mammalian tissues. *Nature* 320:631–634

Majerus PW, Kisseleva MV, Norris FA (1999) The role of phosphatases in inositol signaling reactions. *J. Biol Chem* 274:10669–10672

Michell B (1995) Early steps along the road to inositol-lipid-based signalling. *Trends Biochem Sci* 20(8):326–329

Michell RH (1975) Inositol phospholipids and cell surface receptor function. *Biochim Biophys Acta* 415:81–147

Otsu M et al (1991) Characterization of two 85 kDa proteins that associate with receptor tyrosine kinases, middle-T/pp60c-src complexes, and PI3-kinase. *Cell* 65:91–104

Strahl T, Thorner J (2007) Synthesis and function of membrane phosphoinositides in budding yeast, Saccharomyces cerevisiae. *Biochim Biophys Acta* 1771(3):353–404

Whitman M, Downes CP, Keeler M, Keller T, Cantley L (1988) Type-I phosphatidylinositol kinase makes a novel inositol phospholipid, phosphatidylinositol-3-phosphate. *Nature* 332:644–646

Contents

Abbreviations

AD	Alzheimer's disease
AMPK	5′-AMP-activated protein kinase
ALL	Acute lymphocytic leukemia
ALS	Amyotrophic lateral sclerosis
AML	Acute myeloblastic leukemia
ARNO	Arf nucleotide binding site opener
ASK1	Apoptosis signal-regulating kinase 1
ATM	Ataxia telangiectasia mutated
ATX	Arabidopsis trithorax 1
Bad	Bcl-XL/Bcl-2-associated death promoter
BAFF	B cell activation factor of the TNF family
BCR	B cell receptor
Bcr/Abl	Break point cluster region/Abelson kinase fusion protein
Btk	Bruton's tyrosine kinase
c-Kit	Stem cell growth factor receptor
CAD	Caspase activated DNase
CCR(L)	C-C chemokine receptor (ligand) type
CDK	Cyclin-dependent kinase
CDKN2A	Cyclin-dependent kinase inhibitor 2A
CERT	Ceramide transfer protein
CIN85	Cbl-interactin protein of 85kD (also Ruk (regulator of ubiquitous kinase), SETA (SH3 domain-containing gene expressed in tumorigenic astrocytes))
CML	Chronic myeloid leukemia
CMT	Charcot-Marie-Tooth
COPI/II	Coatomer protein complex I/II
CXCR(L)	C-X-C chemokine receptor (ligand) type
DAAX	Death domain-associated protein
DAG	Diacylglycerol
DGK	Diacylglycerol kinase
DH	Dbl-homology
DMSO	Dimethyl sulfoxide

DNA-PK_{cs}	DNA-dependent protein kinase, catalytic subunit
DOCK2	Dedicator of cytokinesis 2
Dpm1	Dolichol phosphate mannosyltransferase
EGF(R)	Epidermal growth factor (receptor)
eEF1A	Eukaryotic elongation factor 1A
eIF4E	Elongation initiation factor 4E
EMT	Epithelial-to-mesenchymal transition
EnaC	Epithelial sodium channel
ER	Estrogen receptor, or endoplasmic reticulum
ErbB1	Epidermal growth factor receptor
ERM	Ezrin/radexin/moesin
FAK	Focal adhesion kinase
FAPP1	Phosphoinositol 4-phosphate adaptor protein 1
FAPP2	Phosphoinositol 4-phosphate adaptor protein 2
FcεRI	High affinity receptor for Fc fragment of IgE
FOXO	Forkhead transcription factor, class O
FYVE	Fab1, YOTB, Vac1, EEA-1 homology
G6P	Glucose-6-phosphatase
Gab	Grb2-associated binder
GAP	GTPase-activating protein
GEF	Guanine nucleotide exchange factor
GFP	Green fluorescent protein
GIST	Gastrointestinal stromal tumors
GK	Glucokinase
GLUT4	Glucose transporter type 4
GM-CSF	Granulocyte and macrophage colony stimulating factor
GPCR	G protein-coupled receptors
GRK2	G protein-coupled receptor kinase 2 (also βARK1 (adrenergic receptor kinase 1)
Grp1	General receptor for phosphoinositides
GSK-3	Glycogen synthase kinase-3
GST-2xFYVE	Glutathione S-transferase-tagged to tandem FYVE domains
HAUSP	Herpesvirus-associated ubiquitin-specific protease
Hdac2	Histone deacetylase 2
HSCs	Hematopoietic stem cells
IκBK	IκB kinase
ING2	Inhibitor of growth protein 2
Inpp5e/INPP5E	72 kDa inositol polyphosphate 5-phosphatase
Ins	*Myo*-inositol
IGF1(R)	Insulin-like growth factor (receptor)
ILK	Integrin-linked kinase
Ins(1,4)P_2	Inositol 1,4-bisphosphate
Ins(1,4,5)P_3	Inositol 1,4,5-trisphosphate; also used $InsP_3$
IPMK	Inositol polyphosphate multikinase
IRS	Insulin receptor substrate

ITAM	Immunoreceptor tyrosine-based activation motif
ITIM	Immunoreceptor tyrosine-based inhibitory motif
JAK	Janus-activated kinase
JNK	Jun N-terminal Kinase
Kv1.3	Voltage-gated K^+ channel
LAT	Linker for activation of T cells
LOH	Loss of heterozygosity
LSCs	Leukemic stem cells
LTP	Long term potentiation
MAPK	Mitogen-activated protein kinase
MAPKAP-2	Mitogen-activated protein kinase-activated kinase 2
M-CSF	Macrophage colony-stimulating factor
MDM2	Murine double minute 2
MDS	Myelodysplastic syndrome
MEFs	Mouse embryonic fibroblasts
miRNA	Microrna
MPP(+)	1-methyl-4-phenylpyridinium iodide
MSN	Medium sized spiny projection neurons
MTM	Myotubularin
MTMR	Myotubularin related
mTOR	Mammalian target of rapamycin, see also TOR
MVB	Multivesicular body
MVP	Major vault protein
Nedd4	Neural-precursor-cell-expressed developmentally down-regulated 4
NFκB	Nuclear factor κB
NLS	Nuclear localization signal
NMDA(R)	N-methyl-D-aspartate (receptor)
NOS3/eNOS	NO-synthase 3
NTAL	Non-T cell activation linker, also named LAB (Linker of activation for B cells) or LAT2
OSBP	Oxysterol binding protein
OCRL	Oculocerebrorenal syndrome of Lowe
OGD	Oxygen–glucose deprivation
PAO	Phenyalrsine oxide
PCAF	p300/CBP-associated factor
PDE	Phosphodiesterase
PDGF(R)	Platelet-derived growth factor (receptor)
PDZ	Post synaptic density protein, Drosophila disc large tumor suppressor, zonula occludens-1 protein
PDK1	Phosphoinositide-dependent kinase 1
PEPCK	Phosphoenolpyruvate carboxy kinase
PEST	Proline, glutamic acid, serine, threonine
PH	Plecktrin-homology
PHD	Plant homeodomain
PH-GRAM	Pleckstrin homology glucosyltransferase Rab-like GTPase activator

PHTS	PTEN hamartoma tumor syndrome
PI3K	Phosphoinositide 3-kinase; catalytic subunits of class I PI3K are referred to as p110α, p110β, p110γ and p110δ
PI3Kc	PI3K catalytic domain
PI3Kr	PI3K regulatory subunit
PI4K	Phosphatidylinositol 4-kinase
PI4KII	Type II phosphatidylinositol 4-kinase
PI4KIII	Type III phosphatidylinositol 4-kinase
PICS	Pten-loss–induced cellular senescence
PID	Phosphoinositide interacting domain
PIKE	PI-3-kinase enhancer
PIKK	Phosphoinositide 3-kinase-related kinase
PIP4K	Phosphatidylinositol 5-phosphate 4-kinase (also called type II PIP kinase)
PIP5K	Phosphatidylinositol 4-phosphate 5-kinase (also called type I PIP kinase)
PIPP	Proline-rich inositol polyphosphate 5-phosphatase
PIX	PAK-associated guanine nucleotide exchange factor
PKA	Protein kinase A
PKB/Akt	Protein kinase B, also called Akt after the transforming kinase encoded by the AKT8 retrovirus
PKC	Protein kinase C
PLC	Phospholipase C
PLD	Phospholipase D
PM	Plasma membrane
PML	Promyelocytic leukemia protein
PPI	Polyphosphoinositide
pRB	Retinoblastoma protein
PRD	Proline-rich domain
P-Rex	PtdIns(3,4,5)P_3-dependent Rac exchanger
PSD95	Post synaptic density protein 95
PtdIns	Phosphatidylinositol
PtdIns4P	Phosphatidylinositol 4-phosphate; short PIP
PtdIns3P	Phosphatidylinositol 3-phosphate; PIP should not be used here
PtdIns5P	Phosphatidylinositol 5-phosphate; PIP should not be used here
PtdIns(4,5)P_2	Phosphatidylinositol 4,5-bisphosphate; short PIP_2
PtdIns(3,4)P_2	Phosphatidylinositol 3,4-bisphosphate; the abbreviation PIP_2 should not be used here.
PtdIns(3,5)P_2	Phosphatidylinositol 3,5-bisphosphate; the abbreviation PIP_2 should not be used here.
PtdIns(3,4,5)P_3	Phosphatidylinositol 3,4,5-trisphosphate; short PIP_3
PtdOH	Phosphatidic acid (also used PA)
PTEN	Phosphatase and Tensin homolog deleted on chromosome Ten, [also MMAC (mutated in multiple advanced cancers), TEP1 (TGF-β-regulated and epithelial cell enriched phosphatase 1)]

PX	Phox-homology
RAN	Ras-related nuclear protein
RID	Rac-induced recruitment domain
RNAi	Ribonucleic acid interference
ROS	Reactive oxygen species
RSK	Ribosomal S6 kinase
R-SMAD	Receptor regulated SMAD
RTK	Receptor tyrosine kinase
Rb2	Retinoblastoma-related gene $p130^{Rb2}$
RYR1	Type 1 ryanodine receptor
Sac	Suppressor of actin
SCIP	Sac domain-containing inositol phosphatases
SCV	*Salmonella*-containing vacuole
SGK	Serum- and glucocorticoid-induced protein kinase
SH2	Src homology 2
SHIP	SH2 domain-containing inositol 5'-phosphatase
SID	Set interacting domain
siRNA	Short-interfering RNA
SKICH	SKIP carboxy homology
SKIP	Skeletal muscle and kidney enriched inositol phosphatase
SNP	Single nucleotide polymorphism
SSC	Squamos cell carcinoma
Star-PAP	Poly(A) polymerase
Syk	Spleen tyrosine kinase, member of the Src tyrosine kinase family
TAC	Transverse aortic constriction
TDLU	Terminal ductal lobuloalveolar units
TGFβ	Transforming growth factor β
Tiam	T-lymphoma invasion and metastasis inducing protein
TNF	Tumour necrosis factor
TopoIIα	Topoisomerase IIα
TOR	Target of rapamycin (also called FRAP or mTOR)
TPIP	TPTE and PTEN homologous inositol lipid phosphatase
TPTE	Trans-membrane phosphatase with tensin homology
TRAPs	Transmembrane adapter proteins, link immune-receptors to downstream signaling cascades. Examples: LAT, NTAL/LAB
TSC	Tuberous sclerosis complex
UTR	Untranslated region
Vps34p	Vacuolar protein sorting mutant 34 protein
WASP	Wiskott Aldrich Syndrome protein
Wm	Wortmannin
WT	Wild type