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Abstract

Phosphoinositide signalling molecules interact with a plethora of effector proteins to regulate cell proliferation and survival, vesicular trafficking, metabolism, actin dynamics and many other cellular functions. The generation of specific phosphoinositide species is achieved by the activity of phosphoinositide kinases and phosphatases, which phosphorylate and dephosphorylate, respectively, the inositol headgroup of phosphoinositide molecules. The phosphoinositide phosphatases can be classified as 3-, 4- and 5-phosphatases based on their specificity for dephosphorylating phosphates from specific positions on the inositol head group. The SAC phosphatases show less specificity for the position of the phosphate on the inositol ring. The phosphoinositide phosphatases regulate PI3K/Akt signalling, insulin signalling, endocytosis, vesicle trafficking, cell migration, proliferation and apoptosis. Mouse knockout models of several of the phosphoinositide phosphatases have revealed significant physiological roles for these enzymes, including the regulation of embryonic development, fertility, neurological function, the immune system and insulin sensitivity. Importantly, several phosphoinositide phosphatases have been directly associated with a range of human diseases. Genetic mutations in the 5-phosphatase *INPP5E* are causative of the ciliopathy syndromes Joubert and MORM, and mutations in the 5-phosphatase *OCRL* result in Lowe's syndrome and Dent 2 disease. Additionally, polymorphisms in the 5-phosphatase SHIP2 confer diabetes susceptibility in specific populations, whereas reduced protein expression of SHIP1 is reported in several human leukaemias. The 4-phosphatase, INPP4B, has recently been identified as a tumour suppressor in human breast and prostate cancer. Mutations in one SAC phosphatase, *SAC3/FIG4,* results in the degenerative neuropathy, Charcot-Marie-Tooth disease. Indeed, an understanding of the precise functions of phosphoinositide phosphatases is not only important in the context of normal human physiology, but to reveal the mechanisms by which these enzyme families are implicated in an increasing repertoire of human diseases.

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Chapter 12
Inositol Polyphosphate Phosphatases in Human Disease

Sandra Hakim, Micka C. Bertucci, Sarah E. Conduit, David L. Vuong and Christina A. Mitchell

Abstract Phosphoinositide signalling molecules interact with a plethora of effector proteins to regulate cell proliferation and survival, vesicular trafficking, metabolism, actin dynamics and many other cellular functions. The generation of specific phosphoinositide species is achieved by the activity of phosphoinositide kinases and phosphatases, which phosphorylate and dephosphorylate, respectively, the inositol headgroup of phosphoinositide molecules. The phosphoinositide phosphatases can be classified as 3-, 4- and 5-phosphatases based on their specificity for dephosphorylating phosphates from specific positions on the inositol head group. The SAC phosphatases show less specificity for the position of the phosphate on the inositol ring. The phosphoinositide phosphatases regulate PI3K/Akt signalling, insulin signalling, endocytosis, vesicle trafficking, cell migration, proliferation and apoptosis. Mouse knockout models of several of the phosphoinositide phosphatases have revealed significant physiological roles for these enzymes, including the regulation of embryonic development, fertility, neurological function, the immune system and insulin sensitivity. Importantly, several phosphoinositide phosphatases have been directly associated with a range of human diseases. Genetic mutations in the 5-phosphatase *INPP5E* are causative of the ciliopathy syndromes Joubert and MORM, and mutations in the 5-phosphatase *OCRL* result in Lowe's syndrome and Dent 2 disease. Additionally, polymorphisms in the 5-phosphatase SHIP2 confer diabetes susceptibility in specific populations, whereas reduced protein expression of SHIP1 is reported in several human leukaemias. The 4-phosphatase, INPP4B, has recently been identified as a tumour suppressor in human breast and prostate cancer. Mutations in one SAC phosphatase, *SAC3/FIG4,* results in the degenerative neuropathy,

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Charcot-Marie-Tooth disease. Indeed, an understanding of the precise functions of phosphoinositide phosphatases is not only important in the context of normal human physiology, but to reveal the mechanisms by which these enzyme families are implicated in an increasing repertoire of human diseases.

Abbreviations

ADAM	A disintegrin and a metalloprotease
ALL	Acute lymphoblastic leukaemia
AML	Acute myeloid leukaemia
AP	Adaptor protein
APPL1	Adaptor protein containing Pleckstrin homology domain, PTB domain and Leucine Zipper motif 1
AR	Androgen receptor
ARF-GAP	ADP-ribosylation factor GTPase activating protein
ARF-GEF	ADP-ribosylation factor Guanine nucleotide-exchange factor
ASH	Abnormal spindle-like microcephaly-associated protein/spindle pole body/hydrin
ASPM	Abnormal spindle-like microcephaly-associated protein
ATLL	Adult T cell leukaemia/lymphoma
AVP	Arginine vasopressin
BAFF	B cell activating factor belonging to the TNF family
BCR	B cell receptor
BMM	Bone marrow macrophage
BMMC	Bone marrow mast cell
Btk	Bruton's tyrosine kinase
C. elegans	*Caenorhabditis elegans*
C/EBPβ	CCAAT enhancer-binding protein β
CAP	Cbl interacting protein
CD2AP	CD2-associated protein
Cdk5	Cyclin-dependent kinase 5
CD-MPR	Cation-dependent mannose-6-phosphate receptor
CI-MPR	Cation-independent mannose-6-phosphate receptor
CK5/6	Cytokeratin 5/6
CLL	Chronic lymphocytic leukaemia
CML	Chronic myeloid leukaemia
CMT	Charcot-Marie-Tooth
CRMP2	Collapsin response mediator protein 2
DAP12	DNAX-activating protein of 12 kD
DC	Dendritic cell
DS	Down's syndrome
EGFR	Epidermal growth factor receptor
Epo	Erythropoietin
ER	Endoplasmic reticulum
ER	Oestrogen receptor
ER^-	Oestrogen receptor negative
ER^+	Oestrogen receptor positive

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73	ERGIC	Endoplasmic reticulum-to-Golgi intermediate compartment
74	*F. tularensis*	*Francisella tularensis*
75	F-MuLV	Friend murine leukaemia virus
76	FYVE	Fab1, YOTB, Vac1, EEA1
77	G6Pase	Glucose-6-phosphatase
78	GAP	GTPase activating protein
79	G-CSF	Granulocyte colony-stimulating factor
80	GIPC	GAIP-interacting protein C terminus
81	GK	Goto Kakizaki
82	GSK3β	Glycogen synthase kinase-3 β
83	HDAC2	Histone deacetylase 2
84	HER-2	v-erb-b2 erythroblastic leukaemia viral oncogene homologue 2
85	IGF-1	Insulin-like growth factor
86	INPP4A	Inositol polyphosphate 4-phosphatase type I
87	INPP4B	Inositol polyphosphate 4-phosphatase type II
88	INPP5A	Inositol polyphosphate 5-phosphatase type I
89	INPP5B	Inositol polyphosphate 5-phosphatase type II
90	INPP5E	Inositol polyphosphate 5-phosphatase type IV
91	Ins(1,2,3,4,5)P_5	Inositol 1,2,3,4,5-pentakisphosphate
92	Ins(1,3,4)P_3	Inositol 1,3,4-trisphosphate
93	Ins(1,3,4,5)P_4	Inositol 1,3,4,5-tetrakisphosphate
94	Ins(1,4)P_2	Inositol 1,4-bisphosphate
95	Ins(1,4,5)P_3	Inositol 1,4,5-trisphosphate
96	Ins(1,4,5,6)P_4	Inositol 1,4,5,6-tetrakisphosphate
97	Ins(3,4)P_2	Inositol 3,4-bisphosphate
98	IRS	Insulin receptor substrate
99	ITIM	Immunoreceptor tyrosine-based inhibitory motif
100	LAT	Linker for activation of T cells
101	M-CSF	Monocyte colony-stimulating factor
102	MDS	Miller–Dieker syndrome
103	MEFs	Mouse embryonic fibroblasts
104	miR-155	MicroRNA-155
105	MNB/DYRK1A	Dual-specific tyrosine phosphorylation-regulated kinase 1A
106	NCA	Na^+/Ca^{2+} antiporter
107	NCoR	Nuclear corepressor
108	NF-κB	Nuclear factor-κB
109	NPF	Asparagine-proline-phenylalanine
110	NTAL	Non-T cell activation linker
111	OCRL	Oculocerebrorenal syndrome of Lowe
112	PAS	(PIKfyve–ArPIKfyve–Sac3)
113	PBMs	Peripheral blood monocytes
114	PDGF	Platelet-derived growth factor
115	PDK1	Phosphoinositide-dependent kinase-1
116	PEPCK	Phosphoenolpyruvate carboxykinase

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117	PGN	Peptidoglycan
118	PH	Pleckstrin homology
119	PI	Phosphoinositide
120	PI(3)P	Phosphatidylinositol 3-phosphate
121	PI(3,4)P_2	Phosphatidylinositol 3,4-bisphosphate
122	PI(3,4,5)P_3	Phosphatidylinositol 3,4,5-trisphosphate
123	PI(3,5)P_2	Phosphatidylinositol 3,5-bisphosphate
124	PI(4)P	Phosphatidylinositol 4-phosphate
125	PI(4,5)P_2	Phosphatidylinositol 4,5-bisphosphate
126	PI(5)P	Phosphatidylinositol 5-phosphate
127	PI3K	Phosphatidylinositol 3-kinase
128	PIPP	Proline-rich inositol polyphosphate 5-phosphatase
129	PLCγ	Phospholipase C γ
130	PLD	Phospholipase D
131	PR	Progesterone receptor
132	PTB	Phosphotyrosine binding
133	PTEN	Phosphatase and tensin homolog
134	RANKL	Receptor activator of nuclear factor-κB ligand
135	Rho-GEFs	Rho-Guanine nucleotide exchange factors
136	*S. flexneri*	*Shigella flexneri*
137	SAC	Supressor of actin
138	SCC	Squamous cell carcinoma
139	SCF	Stem cell factor
140	SCIPs	SAC domain-containing inositol phosphatases
141	SCVs	*Salmonella* containing vacuoles
142	SF	Steel-factor
143	SHIP	SH2-containing inositol phosphatase
144	SKIP	Skeletal muscle and kidney inositol phosphatase
145	SNP	Single nucleotide polymorphism
146	SODD/BAG4	Silencer of death domain
147	SPD2	Spindle pole body 2
148	SYNJ1	Synaptojanin 1
149	SYNJ2	Synaptojanin 2
150	T-ALL	T cell acute lymphoblastic leukaemia
151	TGFβ	Transforming growth factor β
152	TGN	Trans-Golgi network
153	Tir	Translocated intimin receptor
154	TIRFM	Total internal reflection fluorescent microscopy
155	TLR-2	Toll-like receptor-2
156	TMEM55A	Transmembrane protein 55A
157	TMEM55B	Transmembrane protein 55A
158	TREM2	Triggering receptor expressed on myeloid cells-2
159	UTR	Untranslated region

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Introduction

Phosphoinositides (PIs) are ubiquitous membrane associated signalling molecules, composed of an inositol headgroup which can be phosphorylated, a glycerol moiety and two fatty acid chains that enable insertion into lipid membranes. There are 7 different signalling species derived from phosphatidylinositol, which differ based on the number and position of phosphates on the inositol ring at the D-3, D-4 and/or D-5 positions. Specific phosphoinositides are restricted to and thus specify various subcellular compartments, recruit downstream effector proteins and initiate intracellular signalling networks to mediate a diverse range of cellular functions (Liu and Bankaitis 2010; Sasaki et al. 2009). The spatio-temporal production of phosphorylated phosphoinositides is critical for context-dependent cellular functions, and is achieved by an exquisitely orchestrated activity of phosphoinositide kinases and phosphatases (see Fig. 12.1). AQ1

Phosphoinositide phosphatases are highly conserved and comprise diverse classes of enzymes which hydrolyse phosphorylated phosphoinositide species. There are 35 mammalian phosphatases identified, which can be classified based on substrate specificity, into D-3, D-4 or D-5 position phosphate hydrolysing enzymes designated 3-, 4- and 5-phosphatases, respectively. The 3-phosphatases include PTEN and the myotubularins. The SAC phosphatases do not display phosphate positional phosphatase specificity, and along with the 4-phosphatases, share a Mg^{2+}-independent catalytic mechanism mediated by a conserved CX_5R motif (Guo et al. 1999; Norris et al. 1997a; Ungewickell et al. 2005). In contrast the 5-phosphatases contain a unique conserved catalytic domain and display Mg^{2+}-dependent phosphatase activity with a mechanism shared by base excision repair endonucleases (Tsujishita et al. 2001; Whisstock et al. 2000).

Phosphoinositide phosphatases are implicated in a large and diverse array of human diseases, which include cancer, diabetes and neurological diseases. Additionally, many knockout mouse models of specific phosphoinositide phosphatases have revealed the physiological role these enzymes play (see Table 12.1). The 3-phosphatases PTEN and the myotubularins will not be discussed here, rather, this chapter will focus on 4-, 5- and SAC phosphatases. Specifically, the cellular function of each enzyme will be illustrated, and the biological functions both in animal models, and particularly in the context of human disease will be discussed.

Inositol Polyphosphate 4-Phosphatases

The phosphoinositide 4-phosphatases comprise 4 mammalian enzymes. In addition, several bacterial homologues possessing 4-phosphatase catalytic activity exist that contribute to human diseases. The 4-phosphatases contain a conserved CX_5R catalytic motif, with Mg^{2+}-independent activity to hydrolyse the D-4 position phosphate from phosphoinositide species (Norris et al. 1997a, 1998; Ungewickell

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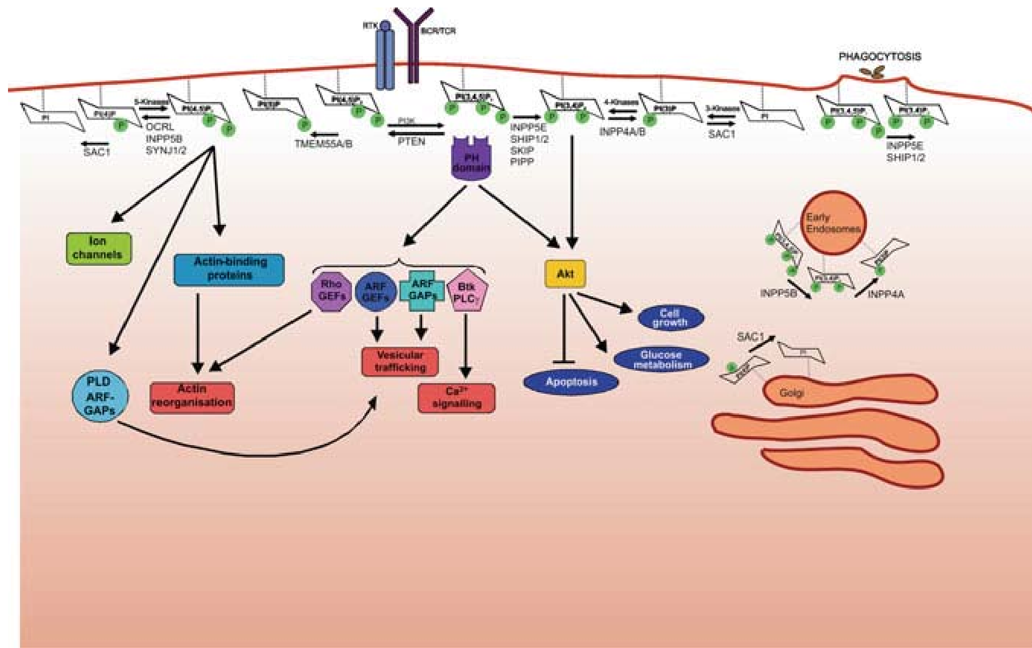

Fig. 12.1 *Phosphoinositide signalling is coordinated by phosphoinositide kinases and phosphatases*. The major PI phosphatases and kinases are depicted above, and highlight only the major substrates and functions of some PI phosphatase family members. Activation of cell surface receptors initiates PI3K activity, transiently phosphorylating PI(4,5)P_2 to the second messenger PI(3,4,5)P_3 on the inner leaflet of the plasma membrane. PI(3,4,5)P_3 recruits various signalling proteins via their PH domain, including Rho-Guanine nucleotide exchange factors (Rho-GEFs), ADP ribosylation factor-Guanine nucleotide exchange factors (ARF-GEFs), ARF-GTPase activating proteins (ARF-GAPs), as well as Bruton's tyrosine kinase (Btk), Phospholipase C γ (PLCγ) and Akt resulting in their allosteric activation and initiation of downstream signalling pathways to promote various cellular effects such as actin polymerisation, cell proliferation and cell growth. PI(3,4,5)P_3 signals are hydrolysed by 3-phosphatases such as PTEN to form PI(4,5)P_2, as well as 5-phosphatases (INPP5E, SHIP1/2, SKIP and PIPP) forming PI(3,4)P_2. PI(3,4)P_2 can be further hydrolysed to PI(3)P through the actions of 4-phosphatases (INPP4A/B). The 5-phosphatases OCRL, INPP5B and SYNJ1/2 dephosphorylate PI(4,5)P_2 to form PI(4)P, and therefore modulate cellular activities which are orchestrated by PI(4,5)P_2 signals, including vesicular trafficking via Phospholipase D (PLD) and ARF-GAPs, actin reorganisation via actin-binding proteins and ion channels. INPP5B and INPP4A hydrolyse PI(3,4,5)P_3 and PI(3,4)P_2, respectively, at forming/early endosomes, and the SAC phosphatases hydrolyse monophosphorylated PI species to form PI. PI(4,5)P_2 is also hydrolysed by the PI(4,5)P_2 4-phosphatases TMEM55A/B to form PI(5)P

201 et al. 2005). The 4-phosphatases are broadly classified based on their ability to
202 hydrolyse PI(3,4)P_2 or PI(4,5)P_2.

203 *PI(3,4)P_2 4-Phosphatases*

204 The two mammalian PI(3,4)P_2 metabolising 4-phosphatase enzymes designated
205 inositol polyphosphate 4-phosphatase I and II have been identified, encoded by the
206 *INPP4A* and *INPP4B* genes, respectively. Although INPP4A and INPP4B are only

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Table 12.1 Substrate specificity, human disease associations and animal model phenotypes of phosphoinositide 4-, 5- and SAC phosphatases

Protein name	Alias(es)	Gene name(s)	Substrate(s)	Human disease	Animal model
4-Phosphatases					
Inositol polyphosphate 4-phosphatase type I (INPP4A)		*INPP4A*	Ins(1,3,4)P_3, Ins(3,4)P_2, PI(3,4)P_2		*Inpp4a^{wbl}* mutant mouse—Purkinje cell loss, early onset ataxia, postnatal lethality 2–3 weeks of age (Nystuen et al. 2001). *Inpp4a$^{-/-}$* mouse—neuronal death in striatum, involuntary movements, postnatal lethality by 2–3 weeks of age (Sasaki et al. 2010)
Inositol polyphosphate 4-phosphatase type II (INPP4B)		*INPP4B*	Ins(1,3,4)P_3, Ins(3,4)P_2, PI(3,4)P_2	Tumour suppressor in breast cancer (Fedele et al. 2010; Gewinner et al. 2009) and loss of expression in prostate cancer (Hodgson et al. 2011)	*Inpp4b$^{-/-}$* mouse—reduced bone density and volume at 8 weeks of age, as well as decreased osteoclast number and size (Ferron et al. 2011)
IpgD (Bacteria)		*IpgD*	PI(4,5)P_2	Shigellosis (Bacillary dysentery) due to *Shigella flexineri* infection (Allaoui et al. 1993; Niebuhr et al. 2000)	Not applicable
SigD (Bacteria)		*SigD*	PI(4,5)P_2	Gastroeneteritis due to *Salmonella Typhimurium* infection (Marcus et al. 2001)	Not applicable
SopB (Bacteria)		*SopB*	PI(4,5)P_2	Gastroeneteritis due to *Salmonella Dublin* infection (Norris et al. 1998)	Not applicable
PI(4,5)P_2 4-phosphatase type I (TMEM55B)		*TMEM55B*	PI(4,5)P_2		Not reported
PI(4,5)P_2 4-phosphatase type II (TMEM55A)		*TMEM55A*	PI(4,5)P_2		Not reported
5-Phosphatases					
Inositol polyphosphate 5-phosphatase	43 kDa inositol polyphosphate 5-phosphatase	*INPP5A*	Ins(1,3,4,5)P_4, Ins(1,4,5)P_3		Not reported

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type I (INPP5A)					
Occulocerebrorenal of Lowe protein (OCRL)	Lowe's protein	*OCRL* *INPP5F*	Ins(1,3,4,5)P_4, Ins(1,4,5)P_3, PI(3,5)P_2, PI(3,4,5)P_3, PI(4,5)P_2	Mutations in *OCRL* occur in Lowe's syndrome and Dent 2 disease (Attree et al. 1992; Hoopes et al. 2005)	*Ocrl*$^{-/-}$ mouse—viable and does not display the characteristics of Lowe's syndrome (Jänne et al. 1998). *Ocrl*:*Inpp5b* double knockout mouse—embryonically lethal (Jänne et al. 1998)
Inositol polyphosphate 5-phosphatase type II (INPP5B)	75 kDa inositol polyphosphate 5-phosphatase, 5-phosphatase-II	*INPP5B*	cIns(1:2,4,5)P_3, Ins(1,3,4,5)P_4, Ins(1,4,5)P_3, PI(3,4,5)P_3, PI(4,5)P_2		*Inpp5b*$^{-/-}$ mouse—males testicular degeneration leading to infertility (Hellsten et al. 2001; Jänne et al. 1998)
Inositol polyphosphate 5-phosphatase type IV (INPP5E)	Pharbin (rat), 72 kDa inositol polyphosphate 5-phosphatase	*INPP5E*	PI(3,5)P_2, PI(3,4,5)P_3, PI(4,5)P_2	Mutations in *INPP5E* occur in ciliopathy syndromes Joubert and MORM (Bielas et al. 2009; Jacoby et al. 2009; Poretti et al. 2009)	*Inpp5e*$^{-/-}$ mouse—embryonic to early post natal lethality. Features recapitulate ciliopathy syndrome including anencephaly, exencephaly, ossification defects, kidney cysts, polydactyly, and bilateral anophthalmos (Jacoby et al. 2009).
SH2-containing inositol phosphatase-1 (SHIP1)	SHIP, SHIP-1	*INPP5D* *SHIP1*	Ins(1,3,4,5)P_4, PI(3,4,5)P_3	Mutations in *SHIP1* are detected in human acute myeloid leukaemia (AML), T cell acute lymphoblastic leukaemia (T-ALL) and acute lymphoblastic leukaemia (ALL) (Lo et al. 2009; Luo et al. 2004), and chronic myeloid leukaemia (CML) (Jiang et al. 2003; Satre et al. 1999)	*Ship1*$^{-/-}$ mouse—myeloid cell infiltration of the lung, ~~haemopoietic~~ perturbations and shortened life span (Helgason et al. 1998). bPten/Ship1$^{-/-}$ (B cell-specific double knockout) mouse—Spontaneous B cell lymphoma (Miletic et al. 2010). T cell-specific *Ship1*$^{-/-}$ mouse—CD4$^+$ skewing towardss a Th1 phenotype and altered cytokine production, and increased cytotoxic activity of CD8$^+$ T cells (Tarasenko et al. 2007)
SH2-containing inositol phosphatase-1 (SHIP2)	SHIP-2, 51C protein	*INPPL1* *SHIP2*	Ins(1,2,3,4,5)P_5, Ins(1,3,4,5)P_4, Ins(1,4,5,6)P_4, PI(3,5)P_2, PI(3,4,5)P_3, PI(4,5)P_2	Mutations in *SHIP2* which confer susceptibility to diabetes and the metabolic syndrome have been identified in population studies (Ishida et al. 2006; Kagawa et al. 2005; Kaisaki et al. 2004; Marion et al. 2002)	*Ship2*$^{-/-}$ mouse—obesity resistance and enhanced insulin sensitivity on a high fat diet (Sleeman et al. 2005). *Ship2*-AS rat (antisense oligonucleotide knockdown)—enhanced glucose tolerance on high fat diet (Buettner et al. 2007). Ship2-Tg (transgenic overexpression) mouse—mild body weight gain and elevated serum glucose (Kagawa et al. 2008)

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Table 12.1 (continued)

Protein name	Alias(es)	Gene name(s)	Substrate(s)	Human disease	Animal model
Skeletal muscle and kidney enriched inositol phosphatase (SKIP)		*SKIP* *INPP5K*	$Ins(1,3,4,5)P_4$, $Ins(1,4,5)P_3$, $PI(3,4,5)P_3$, $PI(4,5)P_2$		*Skip*$^{-/-}$ mouse—embryonically lethal at E10.5 (Ijuin et al. 2008). *Skip*$^{+/-}$ mouse—viable, insulin sensitivity and increased glucose tolerance (Ijuin et al. 2008). *Skip*-Tg (transgenic overexpression) mouse—reduced plasma osmolality and impaired water excretion in the kidney (Pernot et al. 2011)
Proline-rich inositol polyphosphate 5-phosphatase (PIPP)	Phosphatidylinositol (4,5) bisphosphate 5-phosphatase A	*PIB5PA* *INPP5* *INPP*	$Ins(1,3,4,5)P_4$, $Ins(1,4,5)P_3$, $PI(3,4,5)P_3$, $PI(4,5)P_2$		Not reported
Synaptojanin 1	SJ1, SYNJ1	*SYNJ1* *INPP5G*	$Ins(1,3,4,5)P_4$, $Ins(1,4,5)P_3$, PI(3)P, $PI(3,5)P_2$, $PI(3,4,5)P_3$, PI(4)P		*Synj1*$^{-/-}$ mouse—85 % die within 24 h of birth, with the remaining surviving up to 15 days after birth. Neurons exhibit an accumulation of clathrin-coated vesicles in nerve endings (Cremona et al. 1999)
Synaptojanin 2	SYNJ2	*SYNJ2* *INPP5H*	$Ins(1,3,4,5)P_4$, $Ins(1,4,5)P_3$, PI(3)P, $PI(3,5)P_2$, $PI(3,4,5)P_3$, PI(4)P		*Mozart* mouse (ENU-generated mutation)—hearing loss and severe deafness at 12 weeks of age (Manji et al. 2011)
SAC phosphatases					
SAC1		*SAC1*	PI(3)P, PI(4)P, $PI(3,5)P_2$		Sac1–/– mouse—preimplantation lethality (Liu et al. 2008)
SAC2	INPP5F	*INPP5F*	$PI(4,5)P_2$, $PI(3,4,5)P_3$		*Inpp5f*$^{-/-}$ mouse—increased stress-induced cardiac hypertrophy *Inpp5f*-Tg (transgenic overexpression) mouse—resistant to stress-induced cardiac hypertrophy (Zhu et al. 2009)
SAC3	FIG4	*FIG4*	$PI(3,5)P_2$, $PI(4,5)P_2$, $PI(3,4,5)P_3$	Mutations in *SAC3* are linked to Charcot-Marie-tooth (CMT) disease type 4J (Chow et al. 2007)	*Fig4*$^{-/-}$ "pale tremor" mouse—abnormal gait, severe tremor, neurodegeneration, juvenile lethality (Chow et al. 2007; Ferguson et al. 2009; Zhang et al. 2008)

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207 37 % identical at the amino acid level, they share a highly conserved CX_5R
208 catalytic phosphatase motif and catalytic domain (Norris et al. 1997a), with a
209 similar substrate repertoire, hydrolysing the soluble inositol species Ins(1,3,4)P_3
210 and Ins(3,4)P_2, but preferentially hydrolysing membrane-bound PI(3,4)P_2 to form
211 PI(3)P (Bansal et al. 1987, 1990; Norris et al. 1997b; Norris and Majerus 1994).
212 Both enzymes contain N-terminal C2 domains which mediate interactions with
213 lipid membranes and phosphoinositides (Ferron and Vacher 2006; Shearn and
214 Norris 2007). Alternative splicing at the C-terminus generates α and β isoforms,
215 with β forms lacking enzyme activity resulting from an additional C-terminal
216 hydrophobic region (Norris et al. 1997a). Despite these similarities, INPP4A and
217 INPP4B exhibit distinct cellular functions, tissue distributions and disease
218 associations.

219 INPP4A

220 The human *INPP4A* gene is located on chromosome 2q11.2 (Joseph et al. 1999)
221 and encodes inositol polyphosphate 4-phosphatase I, which was initially purified
222 from rat brain extract (Norris et al. 1995). INPP4A undergoes alternative splicing
223 of the 107 kDa α isoform to generate a 110 kDa isoform that contains an addi-
224 tional internal 40 amino acids encoding a PEST sequence. The α isoforms have
225 different tissue distributions, with the 107 kDa form expressed almost exclusively
226 in human brain, and the 110 kDa isoform predominantly expressed in human
227 platelets. Expression of both α isoforms is evident in mouse heart, lung, uterus and
228 spleen (Shearn et al. 2001).
229 INPP4A localises to the plasma membrane and early endosomes mediated by
230 its C2 domain. INPP4A forms a complex with the 5-phosphatase, INPP5B and
231 Rab5, to contribute to the production of PI(3)P from PI(3,4)P_2 on forming early
232 endosomes (Ivetac et al. 2005; Shin et al. 2005). INPP4A generated PI(3)P pro-
233 motes transferrin endocytosis (Shin et al. 2005). INPP4A negatively regulates cell
234 proliferation in mouse primary megakaryocytes downstream of GATA-1 expres-
235 sion (Vyas et al. 2000), and in HeLa cells increases cell survival (MacKeigan et al.
236 2005). Loss of INPP4A expression leads to PI(3,4)P_2 accumulation in fibroblasts,
237 enhanced Akt activation and cellular transformation. In addition, SV40
238 transformed *Inpp4a*$^{-/-}$ mouse embryonic fibroblasts (MEFs) form tumours in
239 xenografted mouse models (Ivetac et al. 2009). INPP4A is a common site of viral
240 insertion for murine leukaemia virus (Erkeland et al. 2004), and *INPP4A* gene
241 expression is increased in cell culture models of B cell chronic lymphocytic leu-
242 kaemia (CLL) (Edelmann et al. 2008). Furthermore *INPP4A* is upregulated in
243 metastatic human prostate cancer (LaTulippe et al. 2002) and undergoes chro-
244 mosomal translocations which result in production of a chimeric protein, INPP4A-
245 HJURP, in metastatic cancer cell lines (Maher et al. 2009). However, whether
246 INPP4A is functionally implicated in human cancers remains to be shown.

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247 The in vivo function of INPP4A has been revealed by *Inpp4a*$^{-/-}$ mice, and the
248 characterisation of a spontaneously occurring INPP4A mouse mutant designated
249 'Weeble' (*Inpp4a*^{wbl}). *Inpp4a*^{wbl} arises due to a single nucleotide deletion in exon
250 10 of *Inpp4a* which is predicted to be nonsense (Nystuen et al. 2001). *Inpp4a*^{wbl}
251 mice exhibit a recessive but severe neurological phenotype resulting in death
252 2–3 weeks after birth. *Inpp4a*^{wbl} mice display severe locomotor instability (ataxia)
253 and neuronal loss in the hippocampus and cerebellum as a consequence of
254 degeneration of hippocampal pyramidal cells and cerebellar Purkinje cells
255 (Nystuen et al. 2001). Targeted deletion of *Inpp4a* in mice results in a similar
256 phenotype. *Inpp4a*$^{-/-}$ mice die by 4 weeks of age, are unable to walk and exhibit
257 an involuntary movement disorder resembling Huntington's disease. Additionally,
258 in contrast to the *Inpp4a*^{wbl} mouse, neurodegeneration in *Inpp4a*$^{-/-}$ mice is
259 observed specifically in the striatum, with increased apoptosis of medium-sized
260 spiny projection neurons (Sasaki et al. 2010).
261 The neurodegeneration in both *Inpp4a*$^{-/-}$ and *Inpp4a*^{wbl} mice may be a con-
262 sequence of glutamate excitotoxicity. *Inpp4a*^{wbl} mice display neurodegeneration in
263 specific Purkinje cell subsets dependent on the expression of specific glutamate
264 receptor types (Sachs et al. 2009). In addition, *Inpp4a*$^{-/-}$ medium-sized spiny
265 projection neurons display degeneration, characteristic of excitoxicity due to glu-
266 tamate receptor hyperactivity. Furthermore, *Inpp4a*$^{-/-}$ mice exhibit PI(3,4)P_2 and
267 glutamate receptor accumulation in the post synaptic density of neuronal cells
268 (Sasaki et al. 2010). INPP4A loss is proposed to disrupt glutamate receptor
269 internalisation leading to excitotoxicity in neuronal cells. Indeed, INPP4A regulates
270 transferrin endocytosis in cell based systems (Shin et al. 2005). However, whether
271 this mechanism is applicable to neuronal glutamate receptor internalisation remains
272 to be explicitly demonstrated. Interestingly, the chromosomal locus 2q11.2 where
273 *INPP4A* is located is frequently deleted in human neurological disorders such as
274 schizophrenia and DiGeorge/velofacialcardio syndrome (Karayiorgou et al. 2010;
275 Ou et al. 2008), and undergoes chromosomal translocation in FOXG1 syndrome, a
276 congenital disorder related to Rett syndrome arising from mutations and chromo-
277 somal translocations involving the *FOXG1* gene (Kortüm et al. 2011). However,
278 INPP4A is yet to be directly implicated in human neurological diseases.
279 *INPP4A* has been identified as a candidate gene in asthma pathogenesis.
280 Microarray studies using platelet samples from human atopic asthmatic patients
281 have identified *INPP4A* polymorphisms, which are likely to decrease INPP4A
282 protein function (Sharma et al. 2008). Mouse models in which airway allergic
283 inflammation is induced display a downregulation of *Inpp4a* expression (Agrawal
284 et al. 2009). INPP4A associates with the p85 subunit of phosphoinositide-3 kinase
285 (PI3K) in platelets (Munday et al. 1999). INPP4A is rapidly cleaved by calpain
286 upon thrombin-mediated activation of human platelets and this may lead to
287 PI(3,4)P_2 accumulation, which is required for platelet aggregation (Norris et al.
288 1997b). Emerging evidence suggests that platelets derived from *Inpp4a*^{wbl} mice
289 may have an increased propensity to aggregate (Marjanovic et al. 2011) although
290 this confers aberrant allergic responses in asthma remains to be shown.

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INPP4B

The human *INPP4B* gene is located on chromosome 4q31.21 and encodes inositol polyphosphate 4-phosphatase II. INPP4B is more highly conserved across species than INPP4A, and is widely expressed in many human tissues, with highest expression in skeletal muscle and heart, and relatively low expression in the brain (Norris et al. 1997a). INPP4B also undergoes additional splicing of the α isoform to generate a shorter protein designated αs (Ferron and Vacher 2006).

Amplified PI3K signalling is a feature of many human cancers. Increased PI3K signalling leads to elevated $PI(3,4,5)_3$ signals, which initiates downstream signalling, including the phosphorylation and activation of Akt, to promote cancer cell proliferation and survival (Vara et al. 2004). Many recent studies support the contention that INPP4B is a tumour suppressor. The transgenic mouse spi-1/PU.1 develops erythroleukaemia characterised by erythropoietin (Epo) independent growth of proerythroblasts. *Inpp4b* expression is lost in the transformation of benign to malignant proerythroblast cells, and reintroduction of *Inpp4b* expression decreases Akt activation and cell transformation (Barnache et al. 2006). shRNA-mediated knockdown of INPP4B in human mammary epithelial cells enhances insulin-mediated Akt phosphorylation (Gewinner et al. 2009), and increases basal Akt phosphorylation, associated with increased cell proliferation and anchorage-independent growth of breast cancer cell lines (Fedele et al. 2010). Significantly, reconstitution of INPP4B expression in breast cancer cell lines which lack INPP4B expression, reduces Akt phosphorylation and anchorage-independent growth (Fedele et al. 2010). Furthermore, siRNA-mediated silencing of INPP4B induces cellular transformation in human mammary epithelial cells (Westbrook et al. 2005), and increases tumour formation in xenograft mouse models (Fedele et al. 2010). Significantly, overexpression of INPP4B in breast cancer cell lines reduces tumour formation in xenografted mouse models (Gewinner et al. 2009).

Loss of INPP4B expression has been recently defined in several human cancers. Loss of heterozygosity (LOH) at 4q27-31, which includes the *INPP4B* gene, is frequently observed in sporadic human primary breast tumours (Naylor et al. 2005). INPP4B is normally expressed in human mammary ductal luminal epithelial cells and a subset of lobular cells. Specifically, INPP4B is expressed in non-proliferative oestrogen receptor positive (ER^+) cells but not oestrogen receptor negative (ER^-) cells in normal breast tissue, and may function to inhibit proliferation in these cells (Fedele et al. 2010). INPP4B expression positively correlates with ER expression in human breast cancer cell lines and human primary breast tumours (Fedele et al. 2010; West et al. 2001), and INPP4B expression is frequently lost in ER^- cell lines and tumours.

The basal-like subtype of breast tumours is associated with increased metastatic potential and poor prognosis (Sørlie et al. 2003). Basal-like human breast cancers typically display loss of ER, progesterone receptor (PR) and v-erb-b2 erythroblastic leukaemia viral oncogene homologue 2 (HER-2), but express the epidermal growth factor receptor (EGFR) and/or cytokeratin 5/6 (CK5/6), and can be classified based on these molecular markers (Cheang et al. 2008). Reduced INPP4B

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335 protein expression occurs frequently in basal-like tumours, and rarely in the less
336 aggressive hormone receptor positive luminal A and B subtypes (Fedele et al.
337 2010). INPP4B protein expression is lost in cancers with expression of basal
338 marker CK5/6, and ER^- and PR^- status in both primary tumours and invasive
339 ductal carcinoma (Fedele et al. 2010). *INPP4B* LOH occurs frequently in sporadic
340 basal-like breast cancers which are triple negative (ER^-, PR^- and HER-2^-) and in
341 *BRCA1* germline mutation tumours (Gewinner et al. 2009). *INPP4B* LOH corre-
342 lates with reduced breast cancer patient survival (Gewinner et al. 2009).
343 The basis of the relationship between hormone receptor status and INPP4B
344 expression levels still remains to be elucidated. Oestradiol and progesterone
345 stimulation of MCF-7 cells does not modulate INPP4B protein expression (Fedele
346 et al. 2010) and INPP4B gene expression is not induced in response to hormone
347 treatment in breast cancer cell lines (Agoulnik et al. 2011). However, given the
348 strong correlation between aggressive hormone receptor negative cancers and
349 decreased INPP4B expression, INPP4B expression may be a useful prognostic
350 marker to predict patient outcomes. Additionally, INPP4B loss correlates with
351 high tumour grade, increased tumour size and proliferative potential (Fedele et al.
352 2010).
353 *INPP4B* LOH occurs frequently in ovarian cancer and melanoma, and *INPP4B*
354 LOH in ovarian cancer correlates with increased lymph node metastases and
355 decreased patient survival (Gewinner et al. 2009). Additionally, the tumour
356 suppressor phosphatase and tensin homolog (PTEN) is frequently lost in many
357 sporadic human cancers. Germline mutations in PTEN predispose individuals to
358 developing a range of cancers (Chalhoub and Baker 2009; Hollander et al. 2011).
359 INPP4B loss occurs in 49 % of human breast cancer samples with PTEN loss
360 (Fedele et al. 2010). It is not understood how combined loss of PTEN and INPP4B
361 cooperate in tumorigenesis, although p53 loss may be an additional event which
362 promotes tumorigenesis in these cancers, since p53 is frequently lost in ovarian
363 cancers with loss of PTEN and INPP4B (Gewinner et al. 2009).
364 INPP4B is also implicated in human prostate cancer. INPP4B is normally
365 expressed in prostate epithelium, but is frequently lost in human primary prostate
366 cancer (Hodgson et al. 2011), and metastatic prostate cancer (Taylor et al. 2010).
367 Significantly, INPP4B loss correlates with reduced recurrence-free survival for
368 prostate cancer patients (Hodgson et al. 2011). Interestingly, INPP4B expression is
369 induced downstream of the transcriptional coactivator, nuclear corepressor
370 (NCoR), in response to androgen receptor (AR) signalling in prostate cell lines
371 (Hodgson et al. 2011), and may act to negatively modulate AR signalling
372 (Agoulnik et al. 2011). However, it is not yet established if INPP4B expression is
373 lost in aggressive AR independent tumours and how INPP4B loss contributes to
374 AR independent cancer growth (Hodgson et al. 2011).
375 Additionally, a recent report has implicated INPP4B in osteoporosis. INPP4Bα
376 is specifically expressed in osteoclasts (bone resorbing cells), and is upregulated
377 during osteoclast differentiation (Ferron et al. 2011). Overexpression of INPP4B in
378 the monocytic cell line RAW 264.7 decreases osteoclast differentiation, reduces
379 bone resorption and increases apoptosis in vitro. INPP4B predominantly

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380 hydrolyses Ins(1,3,4)P_3 in osteoclasts, and overexpression of INPP4B in RAW
381 264.7 cells decreases intracellular calcium oscillations, correlating with decreased
382 NFATc1 nuclear translocation and gene transcription. INPP4B expression is
383 reduced in the bone tissue and osteoclasts of the osteoporotic mouse *gl/gl*.
384 *Inpp4b*$^{-/-}$ mice display reduced bone density and volume at 8 weeks of age, along
385 with decreased osteoclast number and size. Primary osteoclasts from *Inpp4b*$^{-/-}$
386 mice show increased intracellular calcium oscillations, as well as increased
387 NFATc1 nuclear translocation and gene transcription. Interestingly, several single
388 nucleotide polymorphisms (SNPs) occurring in the human *INPP4B* gene have
389 been identified in healthy pre-menopausal subjects, which are associated with bone
390 mineral density variability (Ferron et al. 2011). However, the role of INPP4B in
391 human osteoclast function and osteoporosis remains to be fully characterised.

392 *PI(4,5)P_2 4-Phosphatases*

393 Bacterial PI(4,5)P_2 4-Phosphatases

394 *Shigella flexneri (S. flexneri)* is a bacterial pathogen which invades the colonic
395 epithelium in humans to cause bacillary dysentery (Labrec et al. 1964), a severe
396 form of diarrhoea also referred to as shigellosis. *Shigella* species reside and
397 propagate in the cytoplasm of intestinal epithelial cells where following inter-
398 nalisation, bacterial cells escape from endosomes via lysis (Clerc et al. 1987).
399 *Shigella* virulence is mediated by a plasmid which encodes the machinery for
400 bacterial entry and pathogenesis in mammalian host cells (Sansonetti et al. 1982).
401 *Shigella* virulence induces morphological changes in host cells to facilitate bac-
402 terial entry and invasion of neighbouring cells, and induces cell survival pathways
403 to allow sustained propagation of bacteria (Ibarra and Steele-Mortimer 2009).
404 *IpgD* is one of several genes in the *Shigella* virulence plasmid and encodes a
405 60 kDa IpgD protein, secreted by the type III secretion system (Allaoui et al. 1993;
406 Niebuhr et al. 2000). IpgD contains the highly conserved CX_5R catalytic motif
407 (Norris et al. 1998), and acts as a potent PI(4,5)P_2 4-phosphatase, with lesser
408 activity towards other phosphoinositide and soluble inositol species (Niebuhr et al.
409 2002). IpgD hydrolysis of PI(4,5)P_2 leads to increased PI(5)P. Accumulation of
410 PI(5)P is instrumental in *Shigella* pathogenesis. IpgD-mediated accumulation of
411 PI(5)P induces Rac and Cdc42 dependent remodelling of the actin cytoskeleton to
412 produce membrane blebbing, and reduced membrane adhesion of actin fibres
413 (Niebuhr et al. 2002). Akt is recruited and activated at sites of PI(5)P production,
414 which accumulates at *S. flexneri* entry points (Pendaries et al. 2006). Interestingly,
415 *Shigella* infects T lymphocytes, and IpgD impairs T cell polarisation and che-
416 motaxis via depletion of PI(4,5)P_2 (Konradt et al. 2011). IpgD also inhibits T cell
417 receptor (TCR) activation and signalling via accumulation of PI(5)P (Guittard
418 et al. 2010). However, the significance of *Shigella* infection of T cells in vivo is
419 only emerging.

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420 In addition to IpgD, other bacterial homologues have been identified that 421 exhibit phosphoinositide phosphatase activity. SopB and SigD are highly homol-422 ogous bacterial phosphatases required for virulence of *Salmonella Dublin* (Norris 423 et al. 1998) and *Salmonella typhimurium* (Marcus et al. 2001), respectively. These 424 *Salmonella* strains are also pathogenic in humans and cause gastroenteritis and 425 severe diarrhoea. However, unlike *Shigella*, *Salmonella* species reside and prop-426 agate in intracellular vacuolar structures termed *Salmonella* containing vacuoles 427 (SCVs), reviewed in (Knodler and Steele-Mortimer 2003).

428 SopB and SigD are encoded on virulence plasmids and are delivered into host 429 cells via type III secretion systems. SopB and SigD both contain a region of 430 homology with the synaptojanin 1 (SYNJ1) 5-phosphatase domain (Marcus et al. 431 2001) and share the highly conserved CX_5R catalytic motif (Norris et al. 1998). 432 SopB and SigD exhibit broad substrate specificity towards soluble inositol species 433 and phosphoinositides in vitro (Marcus et al. 2001; Norris et al. 1998) although 434 $PI(4,5)P_2$ is the preferred substrate in cellular assays (Terebiznik et al. 2002).

435 SigD hydrolyses $PI(4,5)P_2$ at bacterial entry sites upon bacterial invasion to 436 promote membrane fission in the formation of SCVs (Terebiznik et al. 2002). An 437 interaction in the N-terminus of SopB with Cdc42 promotes the localisation of 438 SopB to SCVs, and is required for efficient bacterial replication (Rodríguez-439 Escudero et al. 2011). SopB maintains PI(3)P pools on the outside of SCVs via 440 depletion of $PI(4,5)P_2$, leading to Rab5 and Vps32 recruitment to SCVs to produce 441 PI(3)P (Hernandez et al. 2004; Mallo et al. 2008). In addition, SopB is implicated 442 in actin reorganisation of host cells, via IP_5 hydrolysis to induce Cdc42 and Rac-443 mediated reorganisation of the actin cytoskeleton (Zhou et al. 2001). SigD also 444 promotes membrane translocation and activation of Akt (Marcus et al. 2001; 445 Steele-Mortimer et al. 2000) however, Akt translocation to membrane ruffles is not 446 dependent on SigD phosphatase activity (Steele-Mortimer et al. 2000). In addition, 447 SopB-mediated Akt membrane translocation and activation is insensitive to the 448 PI3K inhibitor, wortmannin, but requires the activity of Rictor and phosphoino-449 sitide-dependent kinase-1 (PDK1) (Cooper et al. 2011). However, the exact 450 mechanisms by which SopB/SigD promotes Akt membrane translocation and 451 activation remain to be fully elucidated.

452 TMEM55A and TMEM55B

453 The mammalian $PI(4,5)P_2$ 4-phosphatases were initially identified via screening 454 the human genome for mammalian homologues of bacterial $PI(4,5)P_2$ 4-phos-455 phatases. The mammalian $PI(4,5)P_2$ 4-phosphatase I and II are encoded by the 456 *TMEM55B* and *TMEM55A* genes positioned at 14q11.2 and 8q21.2, respectively. 457 TMEM55A and TMEM55B share 51 % amino acid identity, and contain the 458 conserved CX_5R catalytic motif, however, show no homology to the $PI(3,4)P_2$ 459 4-phosphatases INPP4A and INPP4B outside of this motif.

460 TMEM55A and TMEM55B are both widely expressed in human tissues, with 461 highest expression in the brain, heart and liver (Ungewickell et al. 2005).

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462 Recombinant TMEM55A and TMEM55B enzymes hydrolyse PI(4,5)P_2, produc-
463 ing PI(5)P in vitro, and when expressed in cells localise to late endosomes and
464 lysosomal membrane compartments (Ungewickell et al. 2005). The cellular
465 functions of TMEM55A and TMEM55B have not been extensively investigated.
466 TMEM55A/TMEM55B overexpression in EGF stimulated HeLa cells leads to the
467 accumulation of PI(5)P, correlating with EGFR degradation (Ungewickell et al.
468 2005). Additionally, genotoxic treatment of HeLa cells causes redistribution of
469 TMEM55B into the nucleus to generate nuclear pools of PI(5)P, which enhances
470 p53 stability and increases stress-induced p53-dependent apoptosis (Zou et al.
471 2007). As yet there are no reports of TMEM55A/TMEM55B animal knockouts, or
472 associations with human disease.

473 Inositol Polyphosphate 5-Phosphatases

474 There are 10 mammalian inositol polyphosphate 5-phosphatases. These enzymes
475 are Mg^{2+} dependent and catalyse the hydrolysis of the D-5 position phosphate
476 from both soluble inositol polyphosphates as well as membrane-bound phospho-
477 inositides PI(3,5)P_2, PI(4,5)P_2 and PI(3,4,5)P_3. The 5-phosphatases contain a
478 conserved 300 amino acid catalytic domain which folds similarly to the apurinic/
479 apyramidic endonuclease family of enzymes (Tsujishita et al. 2001; Whisstock
480 et al. 2000). The synaptojanins contain an additional catalytic suppressor of actin
481 (SAC) domain containing a CX_5R motif, conferring catalytic activity to hydrolyse
482 PI(3,4)P_2, PI(3)P and PI(4)P to PI (Guo et al. 1999). 5-phosphatases were initially
483 classified based on in vitro substrate specificity, however, extensive character-
484 isation of 5-phosphatases in vivo has revealed that the previous classifications do
485 not hold true for all enzymes.

486 Many of the 5-phosphatases contain additional domains which mediate
487 subcellular localisation and protein or substrate interactions. Although several
488 5-phosphatase enzymes have been subject to extensive analysis, others are far less
489 characterised. The in vivo function of most 5-phosphatases has been explored by
490 the generation of knockout mouse models, and furthermore, several human
491 diseases have been directly linked to 5-phosphatase dysfunction. Each of the 10
492 mammalian 5-phosphatase enzymes will be discussed in the following sections.

493 *INPP5A*

494 Inositol polyphosphate 5-phosphatase type I is a 43 kDa enzyme encoded by the
495 *INPP5A* gene located on human chromosome 10q26.3. INPP5A is the smallest
496 5-phosphatase and contains a central 5-phosphatase domain and a C-terminal
497 CAAX motif (Laxminarayan et al. 1994). INPP5A hydrolyses only the soluble
498 inositol species Ins(1,3,4,5)P_4 and Ins(1,4,5)P_3 forming Ins(1,3,4)P_3 and

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499 $Ins(1,4)P_2$, respectively (De Smedt et al. 1994; Laxminarayan et al. 1993; Speed
500 and Mitchell 2000). INPP5A association with 14-3-3ζ increases its hydrolysis of
501 $Ins(1,4,5)P_3$ (Campbell et al. 1997).
502 There are few studies which have identified the cellular functions of INPP5A, and
503 there are no reports of an INPP5A knockout mouse. Antisense-mediated depletion of
504 INPP5A increases $Ins(1,4,5)P_3$ and intracellular Ca^{2+} levels in stimulated and
505 unstimulated cells (Speed et al. 1999), although the functional role INPP5A plays in
506 calcium signalling in vivo remains to be determined. However, reduced INPP5A
507 expression in normal rat kidney cells leads to cellular transformation and tumour
508 formation in mouse xenograft models (Speed et al. 1996). Additionally, chromo-
509 somal deletions at 10q26.3 frequently occur in human brain cancers (Fults and Pedone
510 1993; Lee et al. 2001), and human cutaneous squamous cell carcinoma (SCC) tissue
511 shows reduced INPP5A expression (Sekulic et al. 2010). The role INPP5A plays in
512 human cancer is only emerging.

513 ## *OCRL/INPP5F*

514 *OCRL* (also known as *INPP5F*) is located on human chromosome Xq25, and
515 encodes the occulocerebrorenal syndrome of Lowe protein (OCRL), also known as
516 the Lowe's protein. OCRL is a 105 kDa 5-phosphatase with catalytic activity
517 towards $Ins(1,4,5)P_3$, $Ins(1,3,4,5)P_4$, $PI(3,4,5)P_3$, $PI(3,5)P_2$ and $PI(4,5)P_2$, how-
518 ever, $PI(4,5)P_2$ is the preferred substrate in vivo (Olivos-Glander et al. 1995;
519 Schmid et al. 2004; Zhang et al. 1995). OCRL shares 45 % amino acid identity and
520 a similar domain structure with INPP5B. OCRL contains the conserved 5-phos-
521 phatase domain, an abnormal spindle-like microcephaly-associated protein
522 (ASPM)/spindle pole body 2 (SPD2)/hydrin (ASH) domain, Rho-GTPase acti-
523 vating protein (Rho-GAP) domain and pleckstrin homology (PH) domain, all of
524 which mediate multiple interactions with trafficking effectors and adaptor proteins
525 (Hou et al. 2011; Mao et al. 2009). OCRL is widely expressed with high
526 expression in the kidney and brain (Jänne et al. 1998; Olivos-Glander et al. 1995).
527 *OCRL* was first identified as the gene mutated in Lowe's syndrome (also known
528 as oculocerebrorenal syndrome of Lowe) (Attree et al. 1992), an X-linked disorder
529 characterised by renal Fanconi syndrome, congenital cataracts, mental retardation,
530 maladaptive behaviour, rickets, hypotonia and areflexia (Kenworthy et al. 1993;
531 Lowe et al. 1952). Disease causing mutations have been reported throughout the
532 *OCRL* coding region (Addis et al. 2007; Peverall et al. 2000), and include non-
533 sense mutations clustered in the 3' region (Attree et al. 1992; Leahey et al. 1993),
534 and missense mutations which commonly occur in the 5-phosphatase, ASH, Rho-
535 GAP and Rab binding domains, which disrupt catalytic activity, protein–protein
536 interactions and/or protein stability (Addis et al. 2004; Erdmann et al. 2007; Hou
537 et al. 2011; Kawano et al. 1998; Kubota et al. 1998; Lin et al. 1998; Pirruccello
538 et al. 2011; Satre et al. 1999; Swan et al. 2010; Zhang et al. 1998). Recently,
539 mutations in *OCRL* have been reported in the related rare X-linked genetic

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disorder, Dent 2 Disease (Hoopes et al. 2005). Dent 2 disease patients exhibit renal Fanconi syndrome including low molecular weight proteinuria, hypercalciuria and nephrocalcinosis and extrarenal manifestations such as mild mental impairment and rickets (Hoopes et al. 2005). Missense mutations in Dent 2 disease cluster in the *OCRL* 5-phosphatase domain and impair catalytic activity (Shrimpton et al. 2009). Nonsense and frameshift mutations are also reported in the 5' region of *OCRL* (Hoopes et al. 2005; Shrimpton et al. 2009). It is not clear how mutations in *OCRL* result in either Lowe's or comparatively mild Dent 2 disease, although the nature and position of *OCRL* mutations in Lowe's compared to Dent 2 disease indicates that differences in the nature of mutations may be instrumental. Dent 2 mutations generally result in the expression of a truncated protein which retains some catalytic activity (Shrimpton et al. 2009), whereas Lowe's mutations are frequently characterised by loss of protein expression and/or catalytic activity. Furthermore, the contribution from additional modifier genes may also contribute to disease severity (Bökenkamp et al. 2009).

Regardless of the *OCRL* mutation, Lowe's syndrome patient fibroblasts exhibit elevated PI(4,5)P_2 (Suchy et al. 1995; Zhang et al. 1995, 1998), and it is proposed that Lowe's and Dent 2 disease features arise from disruption of cellular processes via a PI(4,5)P_2 imbalance (Zhang et al. 1995, 1998). Lowe's syndrome fibroblasts exhibit abnormal actin cysoskeletal organisation including enhanced sensitivity to depolymerising agents (Suchy and Nussbaum 2002). In addition, the OCRL Rho-GAP domain, although generally classified as an inactive GTPase activating protein (GAP) domain, binds Rac and exhibits low level RacGAP activity (Faucherre et al. 2003). OCRL regulates lamellipodia formation and PI(4,5)P_2 at lamellipodia, in a Rac-dependent manner (Faucherre et al. 2003, 2005).

Several recent studies have demonstrated OCRL regulates cytokinesis, which may contribute to Lowe's syndrome pathogenesis. Depletion of dOCRL in Drosophila cells leads to increased and mislocalised PI(4,5)P_2 resulting in abscission defects during cytokinesis (Ben El Kadhi et al. 2011) and this defect is also evident in Lowe's affected renal cells (Dambournet et al. 2011). The function of OCRL in abscission occurs via an interaction with Rab35 at the intracellular bridge in the late stages of cytokinesis (Dambournet et al. 2011), although specifically how this defect affects Lowe's pathophysiology is not yet established.

OCRL binds to multiple regulators of vesicular trafficking localising the phosphatase to the *trans*-Golgi network (TGN), early endosomes and endocytic clathrin-coated pits (Dressman et al. 2000; Erdmann et al. 2007; Olivos-Glander et al. 1995; Suchy et al. 1995; Ungewickell et al. 2004; Zhang et al. 1998). OCRL interacts with several Rab GTPases including Rab1, Rab5, Rab6, Rab8, Rab14, Rab31 and Rab35 (Dambournet et al. 2011; Hou et al. 2011; Rodriguez-Gabin et al. 2010). Rabs are restricted to and define particular endomembrane compartments, and specifically Rab1, Rab6 and Rab31 target OCRL to the TGN (Hyvola et al. 2006; Rodriguez-Gabin et al. 2010). Interestingly these interactions stimulate 5-phosphatase activity. Rab binding defective OCRL disease mutations abrogate OCRL recruitment to the TGN or endosomes (Hou et al. 2011). OCRL therefore may function on endomembrane domains to restrict PI(4,5)P_2

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585 accumulation, produce PI(4)P and thereby define membrane identity and regulate
586 the recruitment of specific trafficking adaptors (Hyvola et al. 2006).
587 OCRL interacts with clathrin via its Rho-GAP and PH domains (Choudhury
588 et al. 2005; Mao et al. 2009; Ungewickell et al. 2004) and assembles clathrin coats
589 in vitro (Choudhury et al. 2005). OCRL regulates a range of clathrin-mediated
590 trafficking processes. OCRL binds AP-2 and co-localises with transferrin and the
591 cation-independent mannose-6-phosphate receptor (CI-MPR) on clathrin-coated
592 vesicles (Ungewickell et al. 2004). Significantly, OCRL modulates transferrin
593 receptor endocytosis via interactions with clathrin (Choudhury et al. 2009).
594 Altered expression of OCRL blocks retrograde trafficking in vitro, resulting in
595 CI-MPR and AP-1 redistribution to endosomes (Choudhury et al. 2005;
596 Ungewickell et al. 2004). OCRL also regulates cation-dependent mannose-6-
597 phosphate receptor (CD-MPR) TGN to endosome trafficking in a complex with
598 Rab31 (Rodriguez-Gabin et al. 2010). The CI-MPR and CD-MPR deliver
599 hydrolyases to the lysosome, and notably, lysosomal enzymes are elevated in
600 Lowe's syndrome patient serum (Ungewickell and Majerus 1999). Hence, OCRL
601 mutations may disrupt MPR recycling or endocytosis, resulting in exocytosis of
602 lysosomal hydrolyase cargo via the default secretory pathway. Interestingly, dis-
603 ruption of the TGN to endosome pathway in Lowe's syndrome patient oligoden-
604 drocytes may perturb myelin synthesis and turnover, leading to the demyelination
605 observed in the central nervous system of some affected individuals (Rodriguez-
606 Gabin et al. 2010; Schneider et al. 2001).
607 Rab5 and its effector Adaptor protein containing PH domain, phosphotyrosine
608 binding (PTB) domain and Leucine Zipper motif 1 (APPL1) and Ses1 and 2
609 interact with OCRL on subsets of early endosomes (Erdmann et al. 2007; Noakes
610 et al. 2011; Swan et al. 2010). OCRL binding to APPL1 mediates an interaction
611 with GAIP-interacting protein C terminus (GIPC), which together interact with
612 and regulate the trafficking of multiple cell surface receptors, including megalin
613 and TrkA (Erdmann et al. 2007). TrkA plays a critical role in neuronal signalling,
614 and megalin is a scavenger receptor expressed on renal tubule epithelial cells that
615 mediates the cellular uptake of proteins and solutes from the urine (Leheste et al.
616 1999). Similar to Lowe's syndrome and Dent 2 disease, GIPC and megalin
617 knockout mice exhibit low molecular weight proteinuria (Leheste et al. 1999).
618 Decreased megalin shedding is detected in Lowe's patient urine (Norden et al.
619 2002) which may arise as a consequence of reduced plasma membrane megalin
620 levels on kidney tubule epithelial cells (Cui et al. 2010). Indeed, OCRL knock-
621 down and Lowe's syndrome renal epithelial cells exhibit ectopic localisation of
622 PI(4,5)P_2 on early endosomes, resulting in N-WASP-induced F-actin polymeri-
623 sation (Vicinanza et al. 2011). This is proposed to block trafficking of multiple cell
624 surface receptors, including megalin, at the early endodomes. However, the
625 molecular mechanisms by which altered F-actin dynamics inhibits early endo-
626 somal trafficking remain unclear. The characterisation of the role of wild type and
627 mutant OCRL play in megalin trafficking is still emerging and will provide useful
628 insight into Dent 2 Disease and Lowe's syndrome pathogenesis.

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Surprisingly, *Ocrl*$^{-/-}$ mice are viable, fertile and do not display the characteristic features of Lowe's syndrome (Jänne et al. 1998), possibly as a consequence of functional redundancy with other 5-phosphatase family members, such as INPP5B. Indeed, INPP5B and OCRL share many common binding partners, including various Rabs, APPL1, Ses1 and Ses2 (Erdmann et al. 2007; Noakes et al. 2011; Swan et al. 2010; Williams et al. 2007). Significantly, *Ocrl:Inpp5b* double knockout mice are embryonically lethal (Jänne et al. 1998). Blockade of both clathrin-dependent and independent trafficking pathways mediated by OCRL and INPP5B, respectively, may be the basis of lethality with loss of both enzymes (Erdmann et al. 2007; Williams et al. 2007), Interestingly, human *INPP5B* is unable to compensate for loss of mouse *Ocrl* and *Inpp5b*, as transgenic mice expressing human *INPP5B* which lack both mouse *Ocrl* and *Inpp5b* recapitulate the key features of Lowe's syndrome (Bothwell et al. 2011). Therefore, an intrinsic difference between human and mouse *INPP5B* in terms of 5-phosphatase expression, splicing and/or cellular function exists, resulting in the Lowe's syndrome phenotype in humans, but no phenotype in *Ocrl*$^{-/-}$ mice.

INPP5B

The *INPP5B* gene located on human chromosome 1p34 encodes INPP5B, also known as the inositol polyphosphate 5-phosphatase type II, 5-phosphatase-II or the 75 kDa 5-phosphatase. INPP5B hydrolyses the soluble inositol species Ins(1,4,5)P_3, Ins(1,3,4,5)P_4 and cIns(1:2,4,5)P_3, and membrane-bound PI(4,5)P_2 and PI(3,4,5)P_3 (Jackson et al. 1995; Jefferson and Majerus 1995; Matzaris et al. 1994, 1998; Mitchell et al. 1989; Ross et al. 1991). INPP5B contains a PH domain, 5-phosphatase catalytic domain, ASH domain, inactive Rho-GAP domain (Jefferson and Majerus 1995; Mao et al. 2009) and a C-terminal CAAX motif which contributes to its membrane localisation (Jefferson and Majerus 1995; Matzaris et al. 1994).

INPP5B is expressed during embryonic development, and is widely expressed in adults, with high levels in platelets (Hodgkin et al. 1994; Jänne et al. 1998; Speed et al. 1995; Takimoto et al. 1989). INPP5B binds to various Rabs, APPL1, Ses1 and Ses2 (Erdmann et al. 2007; Noakes et al. 2011; Swan et al. 2010; Williams et al. 2007). This indicates that similar to OCRL, INPP5B plays a role in the regulation of vesicular trafficking. However, INPP5B does not contain the clathrin or clathrin adaptor AP-2 binding sites present in OCRL (Williams et al. 2007). Significantly, INPP5B localises to components of the endomembrane network, particularly the *cis*-Golgi and the endoplasmic reticulum- (ER) to-Golgi intermediate compartment (ERGIC) (Shin et al. 2005; Williams et al. 2007). INPP5B overexpression leads to a block in Golgi-ER retrograde trafficking. However, there is evidence that INPP5B also regulates early endocytic events, where it is recruited to endosomes via ASH domain interactions with Rab5 (Shin et al. 2005; Williams et al. 2007), and cooperates in a cascade at the plasma membrane with Rab5 and INPP4A to produce PI(3)P and promote transferrin

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670 receptor endocytosis (Shin et al. 2005). In addition, INPP5B is recruited to
671 complement receptor 3 (CR3)-induced phagosomes, where it is then rapidly dis-
672 placed by the accumulation of PI(3)P, allowing PI(3,4,5)P_3 signals to increase and
673 phagosome internalisation to occur (Bohdanowicz et al. 2010).
674 The in vivo function of INPP5B has been investigated with the generation of
675 *Inpp5b*$^{-/-}$ mice. Male *Inpp5b*$^{-/-}$ mice display testicular degeneration and infer-
676 tility, characterised by spermatocyte and spermatid defects (Hellsten et al. 2001;
677 Jänne et al. 1998). *Inpp5b*$^{-/-}$ sperm exhibits reduced motility and oocyte adhesion
678 leading to decreased fertilisation ability. A Disintegrin and A Metalloprotease
679 (ADAM) 2 and ADAM3 processing during sperm maturation in the epididymis is
680 disrupted with INPP5B loss, impeding sperm-oocyte interactions (Hellsten et al.
681 2001; Marcello and Evans 2010). Additionally, *Inpp5b*$^{-/-}$ mice exhibit progres-
682 sive loss of spermatids and spermatocytes, resulting from sertoli cell dysfunction:
683 *Inpp5b*$^{-/-}$ sertoli cells show enlarged actin coated endosome-like vacuoles in the
684 cytosol which accumulate adherence junction components, resulting in disrupted
685 adherence junction function and sloughing of cells (Hellsten et al. 2002).
686 There is a high degree of functional redundancy between OCRL and INPP5B,
687 with similar domain structure, amino acid identity, common binding partners,
688 overlap in subcellular localisation and regulation of similar trafficking events and
689 *Inpp5b*$^{-/-}$ mice do not exhibit a Lowe's-like phenotype (Jänne et al. 1998).
690 Interestingly, the human *INPP5B* chromosomal region, 1q34, is linked to multiple
691 human diseases with characteristic features reminiscent of Lowe's syndrome
692 including mental retardation, optic abnormalities and congenital cataracts
693 (Bisgaard et al. 2007; Cormand et al. 1999; Shearman et al. 1996).

694 *INPP5E*

695 The *INPP5E* gene is located on human chromosome 9q34.3 and encodes INPP5E,
696 also known as the 72 kDa 5-phosphatase, inositol polyphosphate 5-phosphtase IV
697 or Pharbin. Unlike all other phosphoinositide 5-phosphatases, INPP5E has no
698 activity towardss soluble inositol phosphates, but hydrolyses PI(4,5)P_2, PI(3,5)P_2
699 and has the highest activity towardss PI(3,4,5)P_3 of all 5-phosphatase family
700 members (Kisseleva et al. 2000; Kong et al. 2000).
701 INPP5E is widely expressed, with high expression detected in the testis and brain
702 (Kong et al. 2000). INPP5E exhibits a cytosolic distribution with perinuclear/TGN
703 enrichment mediated via its N-terminal proline-rich domain (Kong et al. 2000). In
704 quiescent cells, the CAAX motif is suggested to localise INPP5E to the primary
705 cilium (Jacoby et al. 2009). In macrophages INPP5E is also recruited to the phag-
706 ocytic cup in response to Fcγ receptor activation, where its hydrolysis of PI(3,4,5)P_3
707 regulates pseudopod extension and phagosome closure (Horan et al. 2007).
708 INPP5E inhibits Akt phosphorylation in response to platelet-derived growth
709 factor (PDGF) and insulin-like growth factor (IGF-1) stimulation and sensitises
710 cells to Fas-induced apoptosis (Kisseleva et al. 2002; Wang et al. 2011). INPP5E
711 also regulates PI3K/Akt signalling downstream of insulin signalling in vivo:

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712 INPP5E is recruited to the p85-PI3K subunit and insulin receptor substrates (IRS)
713 in response to insulin stimulation degrading PI3K-generated PI(3,4,5)P_3 signals in
714 the rat hypothalamus. siRNA-mediated depletion of INPP5E leads to hypothalamic
715 accumulation of PI(3,4,5)P_3, associated with reduced food intake and body mass in
716 rats (Bertelli et al. 2006). In addition, expression of INPP5E in adipocytes induces
717 membrane translocation of the glucose transporter, GLUT4, via PI(3)P production
718 at the plasma membrane (Kong et al. 2006), although, whether INPP5E mediates
719 glucose homeostasis and insulin signalling in humans remains to be demonstrated.
720 An *Inpp5e*$^{-/-}$ mouse has recently been described that exhibits a lethal phe-
721 notype during late embryogenesis or early postnatal life (Jacoby et al. 2009).
722 *Inpp5e*$^{-/-}$ embryos display multiple abnormalities including exencephaly, poly-
723 dactyly, polycystic kidneys, bilateral anopthalmos and skeletal abnormalities.
724 Tamoxifen induced knockout of *Inpp5e* in 4-week-old mice results in multiple
725 defects including obesity, cystic kidneys and retinal degeneration (Jacoby et al.
726 2009). These features are characteristic of ciliopathy syndromes, developmental
727 disorders resulting from defects in primary cilium structure or function (D'Angelo
728 and Franco 2009). Primary cilia are microtubule-based organelles present on most
729 quiescent cells in the human body that are critical for embryonic development and
730 adult tissue homeostasis via regulation of diverse processes including signal
731 transduction, mechanosensation, olfaction and photoreception. *Inpp5e*$^{-/-}$ MEFs
732 display defects in cilia stability (Jacoby et al. 2009), although, how INPP5E
733 regulates cilia to produce this profound phenotype remains to be explicitly
734 demonstrated.
735 Significantly, mutations in *INPP5E* have been linked to the rare human cili-
736 opathy syndromes Joubert and MORM (Bielas et al. 2009; Jacoby et al. 2009;
737 Poretti et al. 2009). Joubert syndrome is characterised by midbrain–hindbrain
738 malformation (the molar tooth sign), cognitive impairment, polydactyly, liver
739 fibrosis, nephronophthisis and retinal dystrophy (Joubert et al. 1969). MORM
740 syndrome affected individuals exhibit mental retardation, truncal obesity, retinal
741 dystrophy and micropenis (Hampshire et al. 2006). All reported Joubert syndrome
742 mutations cluster in the *INPP5E* 5-phosphatase domain and disrupt the phos-
743 phoinositide binding site, reducing INPP5E catalytic activity (Bielas et al. 2009).
744 In contrast, MORM disease causing mutations arise from deletion of the C-ter-
745 minal region of INPP5E including the CAAX motif and abrogate INPP5E cilia
746 localisation, but do not impair catalytic activity (Jacoby et al. 2009). Both MORM
747 and Joubert *INPP5E* mutations result in cilia instability phenotypes, indicating that
748 INPP5E may regulate cilia phosphoinositide signalling, although, the phosphoin-
749 ositide content of this organelle is yet to be defined (Bae et al. 2009; Jin et al.
750 2010). Indeed, INPP5E may regulate a variety of processes to maintain cilia
751 function such as trafficking, signalling and/or cytoskeletal dynamics.
752 *INPP5E* is also implicated in human cancers, and is one of the top 5 genes
753 upregulated (57-fold) in human cervical cancer specimens relative to
754 non-cancerous tissue (Yoon et al. 2003). *INPP5E* is overexpressed 5.7-fold in
755 leiomyosarcoma compared to the normal myometrium (Quade et al. 2004).
756 *INPP5E* is also among the top 6 genes overexpressed in Non-Hodgkin's

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lymphoma following chemotherapy (Chow et al. 2006). In contrast, downregulation of *INPP5E* is detected in gastric cancer compared to normal stomach mucosa and in metastatic adenocarcinoma compared to primary tumours (Kim et al. 2003; Ramaswamy et al. 2003). Interestingly, primary cilia have recently been implicated in tumorigenesis via regulation of the cell cycle and signalling (Nigg and Raff 2009), however, the role INPP5E plays in tumorigenesis both dependent and independent of cilia regulation remains to be demonstrated.

SHIP1

The SH2-containing inositol phosphatase (SHIP) 5-phosphatases include two members, SHIP1 (also known as INPP5D) and SHIP2 (also called INPPL1) which have a similar domain structure comprising an N-terminal SH2 domain, central 5-phosphatase domain and divergent C-terminal proline-rich domains (Backers et al. 2003; Hejna et al. 1995; Liu and Dumont 1997). The SHIP1 C-terminus contains two NPXY motifs, which mediates the interaction following its phosphorylation with Shc, Dok 1, Dok 2 and four PxxP motifs that bind Grb2, Src, Lyn, Hck, Abl, PLCg1 and PIAS1, reviewed in (Hamilton et al. 2010; Rohrschneider et al. 2000). The human *SHIP1* gene is located on chromosome 2q37.1. Splicing of SHIP1 (SHIP1α) into three shorter isoforms generates SHIP1β, SHIP1δ and s-SHIP1 (Lucas and Rohrschneider 1999; Tu et al. 2001). SHIP1α and SHIP1δ are restricted to haematopoietic and spermatogenic cells (Liu et al. 1998b). s-SHIP is a stem cell-specific 104 kDa isoform, which lacks the SH2 domain that may be active in functioning mammary stem cells, the proposed precursor cells to basal-like human breast cancers (Bai and Rohrschneider 2010). s-SHIP1 may also contribute to the regulation of embryonic and haematopoietic stem cell growth and survival.

SHIP1 is a key negative regulator of PI3K/Akt signalling via hydrolysis of PI(3,4,5)P_3 in haematopoietic cells (Miletic et al. 2010) including B and T cells, dendritic cells, macrophages, mast cells, osteoclasts, platelets and neutrophils. In response to monocyte colony-stimulating factor (M-CSF), granulocyte colony-stimulating factor (G-CSF), interleukin-3 or stem cell factor (SCF) haematopoietic cells that lack SHIP1 exhibit enhanced proliferation and survival due to the activation of PI3K/Akt and mitogen activated kinase pathways, reviewed in (Hamilton et al. 2010). Many different groups have generated *Ship*$^{-/-}$ mice which exhibit a reproducible phenotype comprising splenomegaly and elevated white cell counts including macrophages and granulocytes, associated with myeloid cell infiltration of the lung, which leads to a shortened life span (Helgason et al. 1998; Liu et al. 1999). Interestingly, an ENU mutagenesis screen identified a mouse with concommittant loss of *Ship1* and *s-Ship* which leads to greater increases in myeloid cells, inflammatory markers and infiltration of the lungs by activated macrophages than that observed in *Ship1*$^{-/-}$ mice, suggesting that s-SHIP synergises with SHIP1 to suppress macrophage activation (Nguyen et al. 2011).

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SHIP1 Regulation of B Cell Function

SHIP1 associates with immunoreceptor tyrosine-based inhibitory motif (ITIM) containing proteins in B cells and regulates B cell numbers and function. SHIP1 also regulates signalling downstream of the autonomous B cell receptor (BCR) (Brauweiler et al. 2000), B cell activating factor belonging to the TNF family (BAFF) receptor, FcγRIIb and the chemokine receptor CXCR4 (Brauweiler et al. 2007; Crowley et al. 2009). SHIP1 controls the size of the peripheral B cell compartment by regulating B cell proliferation (Brauweiler et al. 2000; Helgason et al. 2000; Liu et al. 1998a). Aged *Ship1*$^{-/-}$ mice exhibit a reduction in circulating B cells as a consequence of elevated IL-6 secretion by macrophages (Maeda et al. 2010). SHIP1 may also regulate B cell maturation. Mice subjected to irradiation to destroy the endogenous bone marrow and reconstituted with *Ship*$^{-/-}$ haematopoietic cells, display a reduction in both immature and mature forms of B cells (Helgason et al. 2000; Liu et al. 1998a).

MicroRNA-155 (miR-155) regulates immune cell development and function (Baltimore et al. 2008). miR-155 targets and suppresses *SHIP1* gene expression via direct 3'UTR interactions (O'Connell et al. 2009). Interestingly, increased miR-155 expression correlates with reduced SHIP1 expression in diffuse large B cell lymphoma (Pedersen et al. 2009). In addition, miR-155 transgenic mice develop B lymphoma, and leukaemic B cells display progressively reduced SHIP1 expression (Costinean et al. 2009). Retroviral delivery of a miR-155-formatted siRNA against SHIP1 induces a myeloproliferative-like syndrome reminiscent of miR-155 transgenic mice and *Ship1*$^{-/-}$ mice (O'Connell et al. 2009). miR-155 is maximally expressed in pre-B cells, and miR-155 overexpression results in the reduced expression of SHIP1 as well as CCAAT enhancer-binding protein β (C/EBPβ) which act to inhibit B cell differentiation and promote proliferation of pre-B cells (Costinean et al. 2009).

B cell-specific deletion of *Ship1* in mice does not lead to the development of lymphoma (Miletic et al. 2010). Both SHIP1 and PTEN act to negatively regulate PI3K-generated signals. Concomitant deletion of *Pten* and *Ship1* in B cells (b*Pten/Ship1*$^{-/-}$) is sufficient to promote the development of spontaneous B cell lymphomas. Significantly, b*Pten/Ship1*$^{-/-}$ mouse B cells display increased Akt phosphorylation, cell survival and an enhanced proliferative response to BAFF, which is not observed with either *Pten* or *Ship1* deletion alone (Miletic et al. 2010). Therefore, SHIP1 may act in cooperation with PTEN to suppress the development of B cell lymphoma (Miletic et al. 2010).

SHIP1 Activity in T Cells

Multiple in vitro studies suggest SHIP1 regulates TCR signalling. SHIP1 is tyrosine phosphorylated in response to CD3 or CD28 activation of T cells (Edmunds et al. 1999; Freeburn et al. 2002). Phosphorylation of SHIP1 NPXY motifs, via the tyrosine kinase Lck, increases SHIP1 5-phosphatase activity and promotes the

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association with PTB domains of the adaptor protein, Shc (Edmunds et al. 1999; Lamkin et al. 1997). This induces SHIP1 recruitment to the plasma membrane, placing SHIP1 in an ideal spatial and temporal localisation to negatively regulate PI3K-generated PI(3,4,5)P_3. SHIP1 deficient Jurkat leukaemic T cell lines exhibit elevated basal and CD3-stimulated PI(3,4,5)P_3 signals, associated with increased Akt phosphorylation and activity (Freeburn et al. 2002; Horn et al. 2004). Additionally in response to TCR activation SHIP1 forms a multi-protein complex with the inhibitory adaptors Dok1 and Dok2, Grb2 and LAT which regulate Akt and kinase Zap-70 activity (Dong et al. 2006). The complex is suggested to act via a negative feedback loop to regulate TCR signalling and therefore T cell tolerance.

Ship1$^{-/-}$ mice exhibit a reduced number of T lymphocytes in the circulation (Helgason et al. 1998). However, *Ship1*$^{-/-}$ mice display increased numbers of T_{reg} cells which have an increased immunosuppressive activity (Collazo et al. 2009). $CD8^+$ T lymphocytes from T cell-specific *Ship1* knockout mice exhibit increased cytotoxic activity, associated with high granzyme B enzyme activity (Tarasenko et al. 2007). The ratio of $CD4^+$:$CD8^+$ T cells is normal in the thymus and periphery of *Ship1*$^{-/-}$ mice, however, $CD4^+$ T cell proportions are increased in the spleen (Kashiwada et al. 2006). Interestingly, within the $CD4^+$ T cell subset, *Ship1*$^{-/-}$ mice are skewed towardss Th2 phenotype (Kuroda et al. 2011). Hyperactivation of IL-3 and IgE signalling pathways in *Ship1*$^{-/-}$ basophils results in elevated IL-4 secretion, stimulating na Th cells to differentiate into Th2 cells. However, in contrast to global *Ship1*$^{-/-}$ mice, T cell-specific *Ship1* knockout mice exhibit skewing towardss a Th1 phenotype, with reduced production of Th2 cytokines (Tarasenko et al. 2007) and exhibit a reduced Th2 response in vivo (Roongapinun et al. 2010). Therefore, SHIP1 regulates the intrinsic differentiation of T lymphocytes to Th2, and the pro-inflammatory cytokine environment of *Ship1*$^{-/-}$ mice may overcome signals regulated by SHIP1.

Dendritic cells (DCs) present antigen to T cells to stimulate the generation of an immune response (Guermonprez et al. 2002). *Ship1*$^{-/-}$ mice demonstrate a tolerance to allografts, and do not exhibit graft rejection (Ghansah et al. al. 2004; Wang et al. 2002). *Ship1*$^{-/-}$ mice display increased DC populations which are poorly differentiated (Antignano et al. 2010). Additionally, the elevated IL-6 levels in global *Ship1*$^{-/-}$ mice may impair the ability of dendritic cells to stimulate T cell proliferation (Neill et al. 2007). Hence, defective DC function may promote allograft tolerance in *Ship1*$^{-/-}$ mice. However, recent reports suggest *Ship1*$^{-/-}$ DCs have increased antigen presentation capacity to stimulate T cell activation, and consistent with this, *Ship1*$^{-/-}$ T cells have an impaired DC signal response (Roongapinun et al. 2010).

The Role of SHIP1 in Macrophage Functions

Macrophages undergo classical activation (M1) in response to inflammatory signals to release pro-inflammatory cytokines and effector molecules, or alternative activation (M2) in response to events such as tissue remodelling to

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produce anti-inflammatory cytokines and molecules (Mantovani et al. 2007). *Ship1*$^{-/-}$ mice exhibit high levels of the pro-inflammatory cytokine IL-6, which is predominantly secreted by peritoneal macrophages. Loss of SHIP1 in peritoneal macrophages, in addition to increased FcγR signalling due to elevated IgG secretion by *Ship1*$^{-/-}$ B cells, drives IL-6 production (Maeda et al. 2010). Despite elevated serum pro-inflammatory cytokines, *Ship1*$^{-/-}$ mice display decreased M1 and increased M2 populations, corresponding to a reduced inflammatory response with *Salmonella enterica* infection, and impaired infection clearance (Bishop et al. 2008; Rauh et al. 2005). However, skewing of *Ship1*$^{-/-}$ macrophages to an M2 phenotype may occur as a consequence of SHIP1 activity to inhibit M2 skewing. IL-4 promotes M2 macrophage skewing. SHIP1 expression is decreased in macrophages following IL-4 stimulation, and *Ship1*$^{-/-}$ macrophages exhibit enhanced sensitivity to IL-4 induced M2 skewing in vitro (Weisser et al. 2011). In addition, inhibition of PI3K signalling in *Ship1*$^{-/-}$ bone marrow macrophages suppresses expression of the M2 marker arginase 1 (Rauh et al. 2005). AQ2

SHIP1 directly regulates M1-associated macrophage phagocytic activity. Many 5-phosphatase family members play a role in macrophage phagocytosis including SHIP1, SHIP2, INPP5B and INPP5E. SHIP1 regulates macrophage phagocytosis by hydrolysing PI(3,4,5)P_3 at the phagocytic cup during phagosome formation to promote the extension of pseudopodia and phagosome closure (Horan et al. 2007; Kamen et al. 2007; Swanson and Hoppe 2004). Altered distribution of PI(3,4,5)P_3 during phagocytosis interferes with phagosome formation, and in vitro studies have demonstrated that reduction in SHIP1 expression inhibits phagocytosis (Horan et al. 2007). SHIP1 preferentially regulates CR3-mediated phagocytosis although ~~the 5-phosphatase~~ displays activity in FcγR-mediated phagocytosis (Cox et al. 2001; Nakamura et al. 2002), whereas INPP5E regulates FcγR, and not CR3-mediated phagocytosis via regulation of PI(3,4,5)P_3 signals (Horan et al. 2007). The highly homologous SHIP2 also regulates FcγR-mediated phagocytosis independently of SHIP1, and is recruited to phagocytic cups, and inhibits Rac activity, thereby regulating actin dynamics during phagosome formation (Ai et al. 2006).

Francisella tularensis (*F. tularensis*) is a bacterial pathogen which causes the fatal disease tularemia in humans. Upon endocytosis, *F. tularensis* evades fusion with lysosomes and escapes into the cytosol of infected cells where it replicates and alters host cell signalling, reviewed in (Santic et al. 2010). In macrophages and monocytes, *Francisella* induces apoptosis which is associated with bacterial escape from endosomal compartments and failure to fuse with lysosomal compartments (Lai et al. 2001; Lai and Sjostedt 2003). Apoptosis induced by *Francisella* infection occurs via Fas signalling. Interestingly, Akt negatively regulates Fas expression and *Ship1*$^{-/-}$ macrophages display reduced Fas expression and increased phagosome-lysosomal fusion and bacterial clearance (Rajaram et al. 2009). Furthermore, SHIP1 is phosphorylated upon *Francisella novicida* infection and acts to negatively regulate PI3K/Akt signalling to inhibit nuclear factor-κB (NF-κB) gene transcription and pro-inflammatory cytokine production (Parsa et al. 2006). Human peripheral blood monocytes (PBMs) infected with the less virulent *F. tularensis* display increased miR-155 expression upon infection, leading to a reduction in SHIP1 expression.

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926 However, this induction is not observed with the more virulent *F. tularensis* strain.
927 The differential suppression of SHIP1 in host cells may therefore contribute to the
928 pathogenicity of different *Francisella* strains (Cremer et al. 2009).

929 The Role of SHIP1 in Osteoclast, Mast cell, Neutrophil 930 and Platelet Function

931 SHIP1 regulates the function of osteoclasts, bone marrow macrophage-derived cells
932 which promote bone resorption. The development of osteoclasts from bone marrow
933 macrophage (BMM) precursors requires M-CSF, which promotes their proliferation
934 and survival, and receptor activator of nuclear factor-κB ligand (RANKL), which is
935 required for osteoclast differentiation, reviewed in (Boyle et al. 2003; Pixley and
936 Stanley 2004). *Ship1*$^{-/-}$ mice exhibit a severe osteoporotic phenotype, associated
937 with a 2-fold increase in osteoclast numbers due to increased sensitivity to M-CSF,
938 and also as a consequence of the increased bone resorptive activity of *Ship1*$^{-/-}$
939 osteoclasts (Takeshita et al. 2002). SHIP1 localises to the podosomes of osteoclasts
940 to regulate bone resorption, and associates with Cas and c-Cbl (Yogo et al. 2006).
941 *Ship1*$^{-/-}$ osteoclasts exhibit increased proliferation in response to M-CSF stimu-
942 lation, without affecting differentiation or survival. SHIP1 inhibits M-CSF-mediated
943 Akt activation and suppresses the expression of D-type cyclins, which are increased
944 in *Ship1*$^{-/-}$ BMMs (Zhou et al. 2006). Although SHIP1 is not directly implicated in
945 bone disease in humans, it is reported to interact with the Triggering receptor
946 expressed on myeloid cells-2 (TREM2), and the associated adaptor protein DNAX-
947 activating protein of 12 kD (DAP12) in osteoclasts and macrophages. TREM2 and
948 DAP12 are mutated in Nasu-Hakola disease, a rare syndrome characterised by bone
949 cysts and dementia. Specifically, SHIP1 inhibits TREM2/DAP12 intracellular sig-
950 nalling by binding to DAP12 and preventing the recruitment of PI3K to the activated
951 receptor complex (Peng et al. 2010).

952 Mast cells express the high affinity IgE receptor (FcεRI), which aggregates
953 upon IgE-antigen crosslinking. FcεRI clustering generates intracellular signalling
954 leading to mast cell degranulation and the release of factors such as cytokines,
955 chemokines and histamine, which contribute to allergic inflammation and ana-
956 phylaxis, reviewed in (Galli and Tsai 2010). SHIP1 directly binds FcεRI via its
957 SH2 domain (Kimura et al. 1997; Osborne et al. 1996). The linker for activation of
958 T cells (LAT) and the non-T cell activation linker (NTAL) mediate the organi-
959 sation of FcεRI signalling complexes, with LAT promoting and NTAL inhibiting
960 mast cell degranulation. SHIP1 also binds to LAT and is recruited to FcεRI, where
961 it decreases Akt phosphorylation and inhibits mast cell survival (Roget et al.
962 2008). SHIP1 functions downstream of the FcεRI to regulate mast cell degranu-
963 lation and pro-inflammatory cytokine release. *Ship1*$^{-/-}$ mast cells display
964 degranulation in response to Steel-factor (SF, or mast cell growth factor) which is
965 not observed in wildtype mast cells, associated with increased PI(3,4,5)P_3 signals
966 and intracellular calcium (Huber et al. 1998b). In addition, *Ship1*$^{-/-}$ mast cells
967 also show enhanced degranulation in response to antigen-loaded IgE and IgE

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968 alone. SHIP1 acts to restrict calcium influx via regulation of PI3K-generated
969 signals, as PI3K inhibition inhibits calcium influx and subsequent degranulation in
970 *Ship1*$^{-/-}$ mast cells (Huber et al. 1998a). Moreover, *Ship1*$^{-/-}$ mast cells display
971 increased antigen-loaded IgE-induced IL-6 production downstream of NF-κB
972 activation (Kalesnikoff et al. 2002).
973 Altered mast cell activity contributes to the phenotype observed in *Ship1*$^{-/-}$
974 mice. *Ship1*$^{-/-}$ mice exhibit mast cell hyperplasia, as well as increased serum pro-
975 inflammatory cytokine release, and hypersensitivity to anaphylaxis (Haddon et al.
976 2009). *Ship1*$^{-/-}$ mice display infiltration of the lung with hyperactivated mast cells
977 (degranulating) (Oh et al. 2007). SHIP1 binds to Allergin 1, an immunoglobulin-
978 like receptor which opposes FcεRI signalling and suppresses mast cell degranu-
979 lation and anaphylaxis (Hitomi et al. 2010). In addition, *11βHSD1*$^{-/-}$ mice which
980 are susceptible to endotoxemia and cutaneous anaphylaxis display elevated SHIP1
981 expression (Zhang and Daynes 2007). LPS- and sMLA- stimulated BMMs and
982 bone marrow mast cells (BMMCs) display TLR4/MyD88 dependent transforming
983 growth factor β (TGFβ) production which has paracrine activity in inducing
984 SHIP1 expression to mediate hyporesponsiveness with subsequent challenge
985 (Cekic et al. 2011; Sly et al. 2003, 2009). Therefore, SHIP1 plays an important role
986 in negatively regulating mast cell degranulation and allergic inflammation. Sig-
987 nificantly, SHIP1 small molecule agonists reduce endotoxemia and cutaneous
988 anaphylaxis in endotoxemia mouse models, via inhibition of macrophage and mast
989 cell activation (Ong et al. 2007). Therefore, SHIP1 agonists may represent an
990 attractive tool for potential therapeutic use in human inflammatory disease.
991 SHIP1 is the major phosphoinositide phosphatase that regulates neutrophil
992 migration. *Ship1*$^{-/-}$ mice but not mice with granulocyte-specific deletion of *Pten*,
993 exhibit granulocytic infiltration of many organs including the lung (Nishio et al.
994 2007). SHIP1 also regulates neutrophil polarisation and motility. In neutrophils
995 SHIP1, but not PTEN, directs the spatial distribution of PI(3,4,5)P_3 which is
996 required for normal neutrophil chemotaxis (Nishio et al. 2007). Bacterial pepti-
997 doglycan (PGN)-stimulated *Ship1*$^{-/-}$ neutrophils display enhanced Akt activation
998 and pro-inflammatory cytokine release downstream of toll like receptor-2 (TLR-2)
999 activation, and *Ship1*$^{-/-}$ mice develop acute lung injury in response to PGN
1000 (Trotta et al. 2005).
1001 Platelet activation leading to aggregation is required for blood clot formation
1002 during normal haemostasis, reviewed in (Gratacap et al. 2008). PI(3,4,5)P_3 is
1003 rapidly produced upon platelet activation, followed by a more gradual and sus-
1004 tained increase of PI(3,4)P_2 correlating with platelet aggregation and integrin
1005 engagement, reviewed in (Gratacap et al. 2008). Both SHIP1 and SHIP2 are
1006 expressed in platelets, however, SHIP1 plays a more dominant role in regulating
1007 PI(3,4,5)P_3 signals in response to agonists (Giuriato et al. 2003). Upon thrombin-
1008 induced activation of platelet aggregation, SHIP1 is tyrosine phosphorylated in an
1009 integrin $\alpha_{IIb}\beta_3$-dependent mechanism, to increase PI(3,4)P_2 levels via PI(3,4,5)P_3
1010 hydrolysis (Giuriato et al. 1997). *Ship1*$^{-/-}$ mouse platelets display increased
1011 PI(3,4,5)P_3 and oscillatory calcium influx, corresponding to enhanced adhesion
1012 and spreading on fibronectin, and an increased adhesion on fibronectin under in

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1013 vitro blood flow conditions (Maxwell et al. 2004). However, platelets form
1014 *Ship1*$^{-/-}$ mice display decreased and disorganised aggregation in response to
1015 thrombin, collagen and thromboxane A_2 treatment, as well as decreased thrombus
1016 contraction. Functionally, *Ship1*$^{-/-}$ mice show an increased tail bleeding time in
1017 response to injury and exhibit smaller thrombus formation in vivo (Severin et al.
1018 2007). Collectively, these studies reveal that SHIP1 plays a critical role in the
1019 initial thrombus formation and in clot retraction and is therefore an important
1020 regulator of haemostasis. However, the precise ways in which SHIP1 facilitates
1021 these activities remains to be fully elucidated.

1022 **SHIP1 Expression and Activity is Altered in Human Leukaemias**

1023 Alterations in SHIP1 expression or activity in solid human tumours has not been
1024 widely reported, although *Ship1*$^{-/-}$ mice demonstrate enhanced tumour growth
1025 following tumour xenograft implantation (Rauh et al. 2005). However, SHIP1
1026 expression is lost in some human haematological cancers. SHIP1 is mutated and
1027 inactivated in T cell acute lymphoblastic leukaemia (T-ALL), as is the 3-phos-
1028 phatase PTEN (Lo et al. 2009). In addition, mutation of the *SHIP1* gene has been
1029 reported in human acute myeloid leukaemia (AML) and acute lymphoblastic
1030 leukaemia (ALL) (Luo et al. 2004). Further characterisation of one somatic
1031 mutation V684E in AML revealed that this mutation occurs in the SHIP1
1032 5-phosphatase domain, leading to reduced catalytic activity and increased Akt
1033 phosphorylation in leukaemic cells harbouring the mutation (Luo et al. 2003).
1034 Significantly, gene transfer of SHIP1 into AML patient leukaemic cells is sufficient
1035 to reduce proliferation following GM-CSF stimulation, and inhibit autonomous
1036 proliferation (Metzner et al. 2009).
1037 The BCR/ABL fusion protein arises from chromosomal translocation, and
1038 causes chronic myeloid leukaemia (CML) (Sattler and Griffin 2003). SHIP1 pro-
1039 tein expression is lost in human primary CML patient cells derived from the bone
1040 marrow, as well as CML cell lines expressing BCR/ABL (Sattler et al. 1999).
1041 Other studies indicate that SHIP1 expression is reduced in the chronic-blast stages
1042 of CML in some patients rather than in primitive leukaemic cells (Jiang et al.
1043 2003), and is therefore associated with disease progression rather than initiation.
1044 Recent studies have revealed that SHIP1 is phosphorylated by BCR/ABL, leading
1045 to its ubiquitination and proteasomal degradation (Ruschmann et al. 2010).
1046 HTLV-1 encodes the viral protein Tax, which causes human Adult T cell
1047 leukaemia/lymphoma (ATLL) (Yoshida 2001). Peripheral T cells from acute and
1048 chronic forms of ATLL also display reduced SHIP1 and PTEN expression asso-
1049 ciated with increased Akt phosphorylation (Fukuda et al. 2005). SHIP1 and PTEN
1050 expression is reduced as a result of Tax-mediated activation of NF-κB transcrip-
1051 tional suppression (Fukuda et al. 2009). Modulation of SHIP1 levels is also a
1052 feature of haematopoietic malignancies in some mouse models. The Friend murine
1053 leukaemia virus (F-MuLV) induces erythroleukaemia via activation of the Fli-1
1054 transcription factor which promotes erythroblast transformation. Fli-1 binds to the

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1055 SHIP1 promoter leading to transcriptional repression of SHIP1, which contributes
1056 to malignant transformation (Lakhanpal et al. 2010). Interestingly, *Ship1*$^{-/-}$ mice
1057 demonstrate accelerated F-MuLV-induced erythroleukaemia progression
1058 (Lakhanpal et al. 2010), consistent with a tumour suppressive role of SHIP1 in
1059 leukaemia development.

1060 ## *SHIP2*

1061 SH2-containing inositol phosphatase 2 (SHIP2), encoded by the gene *INPPL1* on
1062 human chromosome 11q23, is a 142 kDa enzyme that contains an N-terminal SH2
1063 domain, a central 5-phosphatase domain and a C-terminal proline-rich domain
1064 containing multiple WW, NPXY and SAM motifs, reviewed in (Backers et al.
1065 2003; Dyson et al. 2005). SHIP2 shares 51-% amino acid homology with SHIP1,
1066 although it is much more widely expressed, and is detected in the brain, heart and
1067 skeletal muscle, reviewed in (Muraille et al. 2001; Pesesse et al. 1997; Zhang et al.
1068 2009). SHIP2 hydrolyses soluble inositol phosphate species Ins(1,2,3,4,5)P_5,
1069 Ins(1,3,4,5)P_4 and Ins(1,4,5,6)P_4 and membrane-bound PI(3,5)P_2, PI(4,5)P_2 and
1070 PI(3,4,5)P_3 in vitro, although its main substrate in vivo has not been extensively
1071 characterised (Chi et al. 2004; Taylor et al. 2000). SHIP2 is phosphorylated at
1072 tyrosine residues which include sites in the NXPY motif (Prasad et al. 2009).
1073 SHIP2 phosphorylation occurs in response to growth factor and insulin stimulation
1074 of cells (Blero et al. 2001; Habib et al. 1998) and increases its catalytic activity.
1075 Inhibition of protein tyrosine phosphatase activity using vanadate analogues
1076 increases SHIP2 phosphorylation and results in a 5–10-fold increase in its phos-
1077 phatase activity in 1321N1 astrocytoma cells (Batty et al. 2007) and immuno-
1078 precipitated tyrosine phosphorylated SHIP2 displays 2.5-fold increased
1079 phosphatase activity (Prasad et al. 2009). Interestingly, it has recently been
1080 reported that SHIP2 is phosphorylated at additional sites including Ser132 which
1081 may alter SHIP2 stability and cellular localisation (Elong Edimo et al. 2011).

1082 In quiescent cells, SHIP2 is localised to the cytoplasm, however, upon stimu-
1083 lation, SHIP2 translocates to the plasma membrane and extracellular matrix
1084 (ECM) adhesion points where it interacts with a number of proteins involved in
1085 actin cytoskeleton dynamics. SHIP2 binds to filamin, and adaptor protein p130^{cas}
1086 to regulate submembranous actin filament formation, cell spreading and adhesion
1087 (Dyson et al. 2001; Prasad et al. 2001). Other proteins which bind SHIP2 include
1088 vinexin (Paternotte et al. 2005), LL5β (Takabayashi et al. 2010), c-met (Koch et al.
1089 2005) and Shc (Wisniewski et al. 1999). In addition, SHIP2 inhibits PI(3,4,5)P_3
1090 accumulation and Rac1/cdc42 activation in PC12 neuronal cells to regulate neurite
1091 number and length (Aoki et al. 2007). SHIP2 also associates with c-Cbl and binds
1092 c-Cbl interacting protein (CAP) via the SHIP2 proline-rich domain (Vandenbroere
1093 et al. 2003). The SAM domain of SHIP2 binds the GAP Arap3 (Raaijmakers et al.
1094 2007), and the Ephrin A2 receptor (Leone et al. 2008). SHIP2 also interacts with
1095 the bacterial translocated intimin receptor (Tir), a receptor which inserts into the

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membrane of epithelial cells and mediates epithelial cell adhesion via the induction of actin-rich pedestal formation. SHIP2 is recruited to Tir and interacts with Shc to induce PI(3,4)P_2-dependent actin remodelling (Smith et al. 2010). Recombinant SHIP2 has recently been shown to localise to endocytic clathrin-coated pits via interactions with intersectin, during early pit formation (Nakatsu et al. 2010).

PI3K/Akt signalling is critical in relaying insulin-stimulated signals to promote glucose uptake and glycogen synthesis (Taniguchi et al. 2006). There are several in vitro studies which have highlighted that SHIP2 negatively regulates PI3K-generated PI(3,4,5)P_3 in response to insulin signalling. SHIP2 translocates to the plasma membrane in response to insulin stimulation in 3T3-L1 adipocytes where it primarily regulates the phosphorylation of Akt2 (Sasaoka et al. 2004). Adenoviral-mediated gene transfer of SHIP2 in L6 myoblasts inhibits Akt and glycogen synthase kinase 3 β (GSK3β) phosphorylation, and decreases glycogen synthesis (Sasaoka et al. 2001), and in adipocytes depletes PI(3,4,5)P_3 levels associated with decreased Akt and GSK3β phosphorylation, as well as reduced glucose transporter GLUT4 translocation to the plasma membrane leading to decreased 2-deoxyglucose uptake (Wada et al. 2001). However, RNAi-mediated gene silencing of SHIP2 in adipoyctes does not significantly alter insulin signalling (Tang et al. 2005; Zhou et al. 2004), and although SHIP2 RNAi in C2C12 muscle cells enhances Akt phosphorylation, SHIP2 knockdown does not enhance glucose uptake (Gupta and Dey 2009).

Podocytes form the filtration barrier in the glomeruli of kidney nephrons, and podocyte damage occurs in diabetic nephropathy (Wolf and Ziyadeh 2007). SHIP2 is recruited to the plasma membrane in podocytes upon insulin stimulation, and binds to the actin-binding protein CD2-associated protein (CD2AP), although it is not yet established whether SHIP2 regulates the actin cytoskeleton in response to insulin. Overexpression of SHIP2 in podocytes reduces Akt activation and promotes apoptosis (Hyvonen et al. 2010). Interestingly, SHIP2 protein levels are increased in diabetic mouse and rat glomeruli (Hyvonen et al. 2010), however, the physiological relevance of SHIP2 in glomerular function and kidney disease remains to be defined.

SHIP2 Regulates Insulin Signalling in vivo: Studies Using Rodent Models

Two separate reports of SHIP2 knockout mice have emerged. Initially, *Ship2*$^{-/-}$ mice were reported to display enhanced insulin sensitivity as a consequence of increased membrane translocation of the glucose transporter GLUT4 in skeletal muscle, leading to hypoglycaemia and perinatal death (Clement et al. 2001). However, it was later revealed that the *Phox2a* gene was also inadvertently targeted in this mouse model. A more recent report of *Ship2*$^{-/-}$ mice has revealed that loss of SHIP2 results in viable mice. *Ship2*$^{-/-}$ mice exhibit normal insulin sensitivity, however, on a high fat diet, display obesity resistance and enhanced

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1138 insulin sensitivity, corresponding to reduced serum insulin, glucose and lipid
1139 levels, compared to wildtype littermates (Sleeman et al. 2005). Insulin-stimulated
1140 Akt phosphorylation in the liver and skeletal muscle is enhanced in *Ship2*$^{-/-}$ mice
1141 (Sleeman et al. 2005). In rat models, administration of SHIP2 antisense oligonu-
1142 cleotides (*Ship2*-AS) leads to decreased SHIP2 expression in the liver and skeletal
1143 muscle, associated with a sustained Akt phosphorylation in skeletal muscle. *Ship2*-
1144 AS also does not affect insulin sensitivity in rats on a normal chow diet, however,
1145 as is seen in *Ship2*$^{-/-}$ mice, *Ship2*-AS rats on a high fat diet display significantly
1146 increased glucose tolerance in response to insulin (Buettner et al. 2007). Therefore,
1147 SHIP2 may play a role in the development of diet-induced obesity and insulin
1148 resistance.

1149 Mutations in SHIP2 have been identified in the type 2 diabetic and hypertensive
1150 rat strain, Goto Kakizaki (GK). A mutation specifically in the SHIP2 proline-rich
1151 domain results in decreased insulin-stimulated Akt and MAP kinase activation in
1152 vitro (Marion et al. 2002). In addition, SHIP2 protein levels are increased in the
1153 insulin resistant and diabetic mouse strain *db/db*. SHIP2 expression is elevated in
1154 *db/db* mouse skeletal muscle and epididymal fat tissue, although not in the liver
1155 (Hori et al. 2002). Adenoviral-mediated and liver-specific overexpression of
1156 SHIP2 in heterozygote *db/+m* mice reduces Akt phosphorylation in the liver and
1157 decreases glucose tolerance in *db/+m* mice (Fukui et al. 2005). Additionally,
1158 overexpression of dominant negative ΔIP-*Ship2* in *db/db* mice restores the already
1159 diminished phospho-Akt levels in the liver, and rescues the decreased glucose
1160 tolerance (Fukui et al. 2005). Liver-overexpression of *Ship2* does not affect insulin
1161 signalling in other insulin responsive tissues such as skeletal muscle and adipose
1162 tissue (Fukui et al. 2005).

1163 Interestingly, mice with *Ship2* overexpression (*Ship2*-transgenic/*Ship2*-tg) dis-
1164 play only a mild phenotype, with 5 % body weight gain and slightly elevated
1165 blood glucose and serum insulin levels on a normal chow diet compared to
1166 wildtype littermates. In addition, these effects are not observed on a high fat chow
1167 diet (Kagawa et al. 2008). However, *Ship2*-tg mice demonstrate decreased Akt
1168 activation in skeletal muscle, fat and the liver, and have increased liver expression
1169 of gluconeogenic enzymes glucose-6-phosphatase (G6Pase) and phosphoenol-
1170 pyruvate carboxykinase (PEPCK), and decreased glycolytic enzyme glucokinase
1171 (Kagawa et al. 2008). Insulin signalling stimulates glycolytic and inhibits glu-
1172 coneogenic hepatic gene expression, and these actions are disrupted in insulin
1173 resistance as a consequence of type 2 diabetes (Saltiel and Kahn 2001). Overex-
1174 pression of ΔIP-*Ship2* in *db/db* mice decreases liver expression of G6Pase and
1175 PEPCK (Fukui et al. 2005). In addition, liver-specific inhibition of SHIP2 has been
1176 reported in a second type 2 diabetic mouse model, *KKA*^{Y} which is hyperglycaemic
1177 and insulin resistant. Adenoviral-mediated and liver-specific overexpression of
1178 ΔIP-*Ship2* in *KKA*^{Y} mice also increases Akt phosphorylation and decreases liver
1179 expression of G6Pase and PEPCK, in addition to increasing glucose tolerance
1180 (Grempler et al. 2007). Therefore, SHIP2 may negatively regulate insulin
1181 signalling to alter hepatic gene expression, and promote insulin resistance and
1182 systemic glucose homeostasis. Interestingly, administration of a small molecule

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1183 SHIP2 inhibitor, AS1949490, to *db/db* mice lowers plasma glucose and enhances
1184 glucose tolerance (Suwa et al. 2009) and may represent an attractive potential
1185 therapeutic tool for type 2 diabetes treatment in humans.

1186 SHIP2 is Implicated in Human Diabetes

1187 The metabolic syndrome is characterised by features such as type 2 diabetes,
1188 hypertension, abdominal obesity, dyslipidemia, impaired fibrolysis and insulin
1189 resistance, reviewed in (Palomo et al. 2006). A study which investigated type 2
1190 diabetic patients in UK and French cohorts has identified several *SHIP2* SNPs
1191 which are associated with metabolic syndrome features such as hypertension and
1192 obesity (Kaisaki et al. 2004).
1193 In addition, a deletion in the 3'UTR of the SHIP2 gene has been identified in
1194 human type 2 diabetic patients. The 3'UTR deletion disrupts a motif involved in
1195 protein synthesis, and the recombinant mutant SHIP2 displays increased mRNA
1196 and protein expression in vitro (Marion et al. 2002). Other reports of polymor-
1197 phisms in Japanese cohorts have revealed SNPs in the promoter and 5'UTR
1198 regions of the *SHIP2* gene, which are associated with an impaired fasting glyca-
1199 emia. In vitro studies using luciferase reporters have revealed increased promoter
1200 activity of mutant SHIP2 (Ishida et al. 2006). Interestingly, analysis of a Japanese
1201 cohort has revealed a number of polymorphisms associated with normal control
1202 rather than diabetic individuals, with one particular SNP (L632I) located in the
1203 SHIP2 5-phosphatase domain. In vitro studies using the recombinant L632I mutant
1204 SHIP2 results in enhanced insulin signalling, including reduced inhibition of
1205 PI(3,4,5)P_3 signals and Akt2 phosphorylation, suggesting that SNPs which sup-
1206 press SHIP2 catalytic activity may be protective in the development of type 2
1207 diabetes (Kagawa et al. 2005). Therefore, mutations which increase SHIP2
1208 expression and catalytic activity are associated with type 2 diabetic patients in ~~the~~
1209 populations, and those which decrease SHIP2 expression or activity appear in
1210 apparently normal individuals, and may confer protection. Again, these data
1211 highlight the potential value of SHIP2 as a therapeutic target for the treatment of
1212 type 2 diabetes.

1213 SHIP2 is Implicated in Human Cancer

1214 SHIP2 has been reported to have both pro- and anti-tumorigenic roles in human
1215 cancer and murine cancer models. For example SHIP2 mRNA and protein levels
1216 are increased in human primary breast cancer samples and a number of breast
1217 cancer cell lines. High SHIP2 protein expression is reported in human breast
1218 primary tumours, ductal carcinoma and invasive carcinoma. SHIP2 expression in
1219 invasive carcinoma is significantly and positively associated with reduced disease-
1220 free and overall survival of patients. In addition, SHIP2 expression positively
1221 correlates with EGFR expression (Prasad et al. 2008b). Significantly,

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siRNA-mediated SHIP2 depletion in the human breast cancer cell line MDA-MB-231 enhances EGFR degradation leading to suppression of downstream signalling, reducing cell proliferation and suppressing tumour growth and lung metastases in xenografted nude mice (Prasad et al. 2008a). SHIP2 RNAi-treated HeLa cells demonstrate redistribution of EGFR-containing endocytic vesicles, accompanied by enhanced c-Cbl-mediated ubiquitination and degradation of EGFR (Prasad and Decker 2005). In MDA-MB-231 breast cancer cells, siRNA-depletion of SHIP2 decreases EGF-stimulated Akt phosphorylation, and the CXCR4 receptor which is implicated in cancer cell metastasis is also downregulated, associated with decreased cell adhesion and migration (Prasad et al. 2009). Interestingly, SHIP2 regulates the internalisation of another cell surface receptor which is amplified in human cancers, EphA2. Overexpression of SHIP2 in COS-7 cells inhibits EphA2 internalisation, whereas siRNA-mediated silencing of SHIP2 in MDA-MB-231 breast cancer cells promotes PI3K-generated PI(3,4,5)P_3 accumulation and Rac1 activation, associated with enhanced EphA2 endocytosis and degradation (Zhuang et al. 2007). However, an association between EphA2 and SHIP2 expression in human cancer has not yet been reported. These studies demonstrate that SHIP2 may possess proto-oncogenic activity to regulate growth factor receptor stability, endocytosis and/or signalling leading to proliferation and metastasis. Given the multiple associations of SHIP2 with the actin cytoskeleton, it is also possible that SHIP2 may regulate actin dynamics to regulate cancer progression and metastasis, although this is yet to be specifically demonstrated.

Contrasting roles of SHIP2 have also been described in cancer models in vitro. miRNA-205 supresses SHIP2 expression in squamous cell epithelium. Squamous cell carcinoma (SCC) epithelial cell lines demonstrate increased miRNA-205 correlating with reduced SHIP2 expression and enhanced Akt phosphorylation. siRNA-mediated depletion of miRNA-205 decreases Akt phosphorylation and promotes apoptosis in SCC cell lines (Yu et al. 2008). Although miRNA-205 upregulation has been reported in a number of human cancers, reviewed in (Sotiropoulou et al. 2009), the role of SHIP2 in these contexts remains to be determined. In addition, overexpression of SHIP2 in glioblastoma cell lines reduces PI(3,4,5)P_2 and Akt phosphorylation leading to cell cycle arrest (Taylor et al. 2000).

SKIP/INPP5K

Skeletal muscle and kidney inositol phosphatase (SKIP) is encoded by the *SKIP/INPP5K* gene located on human chromosome 17p13.3. SKIP is a 51 kDa 5-phosphatase which is alternatively spliced to form a 43 kDa variant. SKIP hydrolyses the soluble inositol species Ins(1,4,5)P_3 and Ins(1,3,4,5)P_4, and membrane-bound PI species PI(4,5)P_2 and PI(3,4,5)P_3 (Ijuin et al. 2000), with highest in vitro phosphatase activity towards PI(4,5)P_2 (Schmid et al. 2004). SKIP is widely expressed in mammalian cells and tissues, with highest levels observed in skeletal muscle and kidney (Ijuin et al. 2000). The smaller isoform is expressed

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1263 highly in adipose tissue (Ijuin et al. 2008) and has a much lower 5-phosphatase
1264 activity to hydrolyse PI(3,4,5)P_3 and PI(4,5)P_2 compared to the full length enzyme
1265 (Ijuin et al. 2008). SKIP hydrolysis of PI(3,4,5)P_3 is inhibited by binding to the
1266 silencer of death domain (SODD/BAG4) (Rahman et al. 2011). SKIP localises to
1267 neurites in neuroblastoma cell lines, and has a perinuclear distribution in COS-7
1268 cells (Ijuin et al. 2000). SKIP plays a major role in insulin signalling both in vitro
1269 and in vivo.

1270 In response to insulin stimulation, a pool of SKIP redistributes from a
1271 perinuclear distribution to the plasma membrane, dependent on its C-terminal
1272 SKIP carboxyl homology (SKICH) domain, and acts to inhibit actin stress fibre
1273 formation and membrane ruffling (Gurung et al. 2003; Ijuin and Takenawa 2003).
1274 Interestingly, the SKICH domain of SKIP also interacts with the Hepatitis B virus
1275 core protein to inhibit HBV gene expression and viral replication (Hung et al.
1276 2009). SKIP overexpression depletes PI(3,4,5)P_3 signals and decreases
1277 Akt phosphorylation in response to insulin stimulation, and decreases translocation
1278 of the glucose transporter GLUT4 to the cell membrane, leading to decreased
1279 glucose uptake (Ijuin and Takenawa 2003). RNAi-mediated SKIP depletion in
1280 C2C12 myoblast muscle cells enhances Akt and GSK3β phosphorylation in
1281 response to insulin, correlating with enhanced glycogen synthase dephosphoryla-
1282 tion which promotes glycogen synthesis (Xiong et al. 2009). Therefore, in vitro,
1283 SKIP negatively regulates glucose uptake and glycogen synthesis in response to
1284 insulin.

1285 Targeted deletion of the *Skip* gene in mice is embryonically lethal at E10.5
1286 (Ijuin et al. 2008). *Skip*$^{+/-}$ mice are viable and physically indistinguishable from
1287 wildtype littermates, but display an insulin sensitivity phenotype, with enhanced
1288 serum glucose clearance following insulin administration, and enhanced glucose
1289 uptake in skeletal muscle. Skeletal muscle from *Skip*$^{+/-}$ mice exhibits increased
1290 insulin signalling, with enhanced Akt phosphorylation, leading to increased
1291 phosphorylation of downstream targets p70 S6 kinase and GSK3β. Although it has
1292 not been demonstrated in vivo, siRNA-mediated knockdown of SKIP in L6
1293 myoblast cells leads to increased GLUT4 translocation to the cell membrane (Ijuin
1294 et al. 2008) and may be the basis of the enhanced glucose uptake in skeletal muscle
1295 of *Skip*$^{+/-}$ mice.

1296 Significantly, *Skip*$^{+/-}$ mice display obesity resistance on a high fat diet, with
1297 lower serum leptin cholesterol and insulin levels compared to wildtype mice,
1298 correlating with enhanced Akt phosphorylation in skeletal muscle (Ijuin et al.
1299 2008). SKIP therefore plays an important role in regulating diet-induced insulin
1300 resistance and obesity via regulation of glucose homeostasis and insulin signalling
1301 in skeletal muscle. However, the role SKIP plays in insulin signalling in brain and
1302 adipose tissue, and whether these effects have a regulatory role in human diabetes
1303 and in obesity remains to be demonstrated. Interestingly, *Skip*$^{+/-}$ mice also display
1304 increased muscle mass (Ijuin et al. 2008), and SKIP is upregulated during C2C12
1305 myoblast differentiation dependent on MyoD regulation (Xiong et al. 2009).

1306 Transgenic mice which overexpress *Skip* in all tissues have recently been
1307 generated. *Skip* transgenic mice display reduced plasma osmolality, and an

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1308 impaired ability to excrete a water load. In addition, *Skip* transgenic mice have an
1309 increased response to arginine vasopressin (AVP) (Pernot et al. 2011). AVP
1310 induces an antidiuretic effect on the kidney and induces water retention. AVP
1311 precursor protein is released from the hypothalamus in response to dehydration
1312 and converted into active AVP in the bloodstream. *Skip* transgenic mice have an
1313 increased expression of the AVP receptor, AVPR2 and the water transporter AQP2
1314 in the kidney, although they display decreased AVP expression in the brain. The
1315 altered AVP/AQP2 axis may be the basis of the altered plasma osmolality and
1316 urine excretion capacity of the transgenic mice (Pernot et al. 2011). However, the
1317 way in which SKIP regulates the expression and function of AQP2 and AVPR2 in
1318 the kidney, and the expression of AVP in the brain remains to be described.
1319 The chromosomal locus in which the human *SKIP* gene is located is implicated
1320 in multiple human diseases. Miller–Dieker syndrome (MDS) arises from deletions
1321 in the 17p13.3 locus and is characterised by lissencephaly (lack of gyrations of the
1322 cerebellum) microcephaly, facial dysmorphism, cardiac malformation, mental
1323 retardation, seizures and a reduced lifespan (Dobyns et al. 1991). Critical regions
1324 which are commonly deleted include the *SKIP* gene (Bruno et al. 2010; Cardoso
1325 et al. 2003) although it has not been established what role SKIP may play in the
1326 development of MDS.
1327 The *SKIP* gene locus, 17p13.3, is frequently deleted or hypermethylated in a
1328 diverse range of human cancers. For example, deletions at 17p13.3 occur fre-
1329 quently in human breast cancers (Ellsworth et al. 2005; Parrella et al. 2005),
1330 advanced colorectal tumours (Risio, Casorzo et al. 2003), lung cancers (Konishi
1331 et al. 1998), ovarian cancer, cervical cancer (Guoling et al. 1997), bladder cancer
1332 (Zheng et al. 2002) and childhood medulloblastoma (Lamont et al. 2004).
1333 Significantly, SKIP expression has been reported to be altered in human cancers
1334 and is decreased in lung adenocarcinoma (Stearman et al. 2005), but increased in
1335 renal cell cancer (Jones et al. 2005). In addition, SKIP expression is associated
1336 with lymph node metastasis and poor outcome in bladder cancer (Sanchez-Car-
1337 bayo et al. 2006). Somatic mutation of the *SKIP* gene has been identified in human
1338 breast cancer samples (Sjöblom et al. 2006), although the frequency of this
1339 mutation in large data sets has not been evaluated. The precise roles that SKIP
1340 plays in human cancers are yet to be fully evaluated. AQ3

1341 *PIPP/INPP5J*

1342 The proline-rich inositol polyphosphate 5-phosphatase (PIPP) is encoded by the
1343 *PIPP/INPP5J* gene located on human chromosome 22q12.2. PIPP is a 107 kDa
1344 5-phosphatase that is highly expressed in brain, heart, kidney lung, intestine and
1345 stomach. PIPP contains proline-rich N and C termini, a putative N-terminal SH3
1346 domain, 6 putative RSXSXP protein binding domains, a SKICH domain and
1347 conserved 5-phosphatase catalytic domain (Mochizuki and Takenawa 1999). PIPP

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1348 hydrolyses both Ins(1,4,5)P_3, Ins(1,3,4,5)P_4, and membrane-bound PI(4,5)P_2 and
1349 PI(3,4,5)P_3 (Mochizuki and Takenawa 1999; Ooms et al. 2006).

1350 Ectopic expression of PIPP in COS-7 cells results in the accumulation of PIPP
1351 at ruffling membranes via its SKICH domain (Gurung et al. 2003; Mochizuki and
1352 Takenawa 1999), which also mediates PIPP localisation to the neurite growth cone
1353 and shaft of growth factor differentiated neuronal cell lines (PC12) (Ooms et al.
1354 2006). PIPP hydrolysis of PI(3,4,5)P_3 inhibits PC12 cell neurite elongation at the
1355 growth cone, but promotes polarised neurite formation in a complex with collapsin
1356 response mediator protein 2 (CRMP2) (Astle et al. 2011; Ooms et al. 2006). PIPP
1357 negatively regulates PI3K/Akt signalling via PI(3,4,5)P_3 hydrolysis, to inhibit
1358 PI3K/Akt induced cell transformation in fibroblasts (Denley et al. 2009), and
1359 mitotic and cleavage events in early embryogenesis (Deng et al. 2011). PIPP also
1360 promotes cell survival in HeLa cells (MacKeigan et al. 2005).

1361 There have been few studies to investigate the role PIPP plays in vivo, and no
1362 knockout mouse has been reported. However, several studies have identified
1363 associations between PIPP expression and human cancers. The chromosomal
1364 region in which *PIPP* is located is frequently mutated in human breast cancer
1365 (Hartikainen et al. 2006), and LOH of 22q12 occurs in both the stroma and
1366 epithelium of breast cancers (Kurose et al. 2001). 22q12 deletions occur frequently
1367 in invasive lobular carcinoma (Weber-Mangal et al. 2003), and in ER^+ tumours, as
1368 well as tumours which are well differentiated (Richard et al. 2000). Significantly,
1369 *PIPP* is one of the top 10 predictive genes identified for breast cancer outcomes.
1370 PIPP expression positively correlates with increased time to metastasis, and
1371 increased disease-free survival (Gevaert et al. 2006; Takahashi et al. 2004; van't
1372 Veer et al. 2002). PIPP is more highly expressed in ER^+ than ER^- primary breast
1373 tumours (Gruvberger et al. 2001), and separate studies indicate that PIPP
1374 expression positively correlates with ER expression in human breast cancer
1375 samples (van't Veer et al. 2002). Additionally, PIPP expression negatively cor-
1376 relates with *BRCA1* germline mutation (van't Veer et al. 2002).

1377 22q12.2. deletions are frequently observed in other human cancers including
1378 35 % of sporadic colorectal carcinomas (Zhou et al. 2002), primary hepatocellular
1379 carcinoma (Zhu et al. 2004) and in ovarian cancer (Benetkiewicz et al. 2005;
1380 Englefield et al. 1994). PIPP is upregulated in response to the novel drug Ellag-
1381 itannin, which inhibits cellular proliferation (Wen et al. 2009). However, the
1382 functional role PIPP plays in cancer remains unknown. Additionally, PIPP is
1383 implicated in rheumatoid arthritis where studies using microarray analysis to
1384 identify novel biomarkers for autoimmune diseases have revealed increased PIPP
1385 expression (Edwards et al. 2007; López-Pedrera et al. 2009).

1386 *SYNAPTOJANINS*

1387 There are two mammalian synaptojanin isoforms, designated synaptojanin 1 and
1388 synaptojanin 2, encoded by *SYNJ1/INPP5G* on human chromosome 21q22.11, and
1389 *SYNJ2/INPP5H* on chromosome 6q25.3, respectively. Both enzymes contain

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1390 N-terminal SAC domains, a central 5-phosphatase domain and a C-terminal pro-
1391 line-rich domain (McPherson et al. 1996), and share 53.8 and 57.2 % amino acid
1392 homology across their 5-phosphatase and SAC domains, respectively (Nemoto
1393 et al. 1997). The Sac domain hydrolyses PI(3)P, PI(4)P and PI(3,5)P_2 to PI, in
1394 addition to the 5-phosphatase domain which hydrolyses the 5-position phosphate
1395 from PI(4,5)P_2, PI(3,4,5)P_3, Ins(1,4,5)P_3 and Ins(1,3,4,5)P_4 (Guo et al. 1999;
1396 McPherson et al. 1996; Schmid et al. 2004).

1397 SYNJ1 and SYNJ2 are alternatively spliced in the C-terminal proline-rich
1398 domain. The most widely expressed splice variants for SYNJ1 are 145 and
1399 170 kDa isoforms (Nemoto et al. 1997, 2001; Ramjaun and McPherson 1996; Seet
1400 et al. 1998) which have broad expression in various tissues, with high levels in the
1401 brain for the 145 kDa isoform (Nemoto et al. 1997; Ramjaun and McPherson
1402 1996; Sakisaka et al. 1997). Six splice variants have been identified for SYNJ2,
1403 with 2A, 2B1 and 2B2 forms being most widely expressed. Isoform 2A displays
1404 ubiquitous expression, and 2B1 and 2B2 are highly expressed in the brain and
1405 testis (Nemoto et al. 1997, 2001; Seet et al. 1998).

1406 SYNJ1

1407 SYNJ1 regulates synaptic vesicle recycling and endocytosis, forming complexes
1408 with multiple proteins involved in these processes. The C-terminal proline-rich
1409 region of SYNJ1 binds to the SH3 domains of endocytic proteins including
1410 endophilin, amphiphysin, syndapin/pacsin and intersectin/Dap160 (De Heuvel et al.
1411 1997; McPherson et al. 1996; Qualmann et al. 1999; Ringstad et al. 1997; Roos and
1412 Kelly 1998). The 170 kDa isoform contains three asparagine-proline-phenylalanine
1413 (NPF) repeats which facilitate binding to the endocytic protein Eps15, the N-terminal
1414 domain of the clathrin heavy chain and to the ear domain of the α-adaptin component
1415 of the AP-2 complex (Haffner et al. 1997; Hughes et al. 2000). These interactions
1416 function to direct the subcellular localisation of SYNJ1 and/or increase hydrolysis of
1417 PI(4,5)P_2 (Lee et al. 2004; Ringstad et al. 1997). Total internal reflection fluorescent
1418 microscopy (TIRFM) studies have demonstrated differential temporal recruitment of
1419 the two SYNJ1 variants during clathrin-coated pit formation. The 170 kDa isoform is
1420 constitutively associated with forming endosomes during clathrin-coated pit for-
1421 mation, whilst the 145 kDa splice variant is rapidly recruited only at the late stages
1422 along with endophilin (Perera et al. 2006). Interestingly, the fatty acid composition of
1423 the lipid substrate PI(4,5)P_2 can influence the substrate specificity and subcellular
1424 targeting of SYNJ1, with preferential hydrolysis of long chain polyunsaturated fatty
1425 acids of PI(4,5)P_2 over short chain (Schmid et al. 2004). *Caenorhabditis elegans*
1426 *(C. elegans)* mutants which lack the preferred fatty acid groups on PI(4,5)P_2 display
1427 mislocalised SYNJ1 correlating with the accumulation of PI(4,5)P_2 at synapses and
1428 defective synaptic vesicle recycling (Marza et al. 2008).

1429 SYNJ1 undergoes constitutive phosphorylation in unstimulated synapses, and in
1430 response to depolarisation is dephosphorylated by the serine threonine phosphatase,
1431 calcineurin. Several lines of evidence indicate SYNJ1 catalytic activity and protein

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interactions are modulated via specific phosphorylation events. Cyclin-dependent kinase 5 (Cdk5)-mediated phosphorylation of SYNJ1 at S1144, which is adjacent to the endophilin binding site, inhibits interactions with SYNJ1 binding partners endophilin and amphiphysin, and suppresses catalytic activity (Lee et al. 2004). Similarly, EphB2 tyrosine phosphorylation of SYNJ1 proline-rich domain, reduces 5-phosphatase activity and interaction with endophilin A1 (Irie et al. 2005). Conversely, calcineurin mediates dephosphorylation of SYNJ1 at S1144, following Cdk5-mediated phosphorylation that enhances interactions with endophilin and stimulates its 5-phosphatase activity (Lee et al. 2004). Phosphorylation of SYNJ1 by the dual-specific tyrosine phosphorylation-regulated kinase 1A (MNB/DYRK1A) at multiple sites regulates amphiphysin1 and intersectin1 binding and modestly increases catalytic activity towardss PI(4,5)P_2 (Adayev et al. 2006).

In vivo, SYNJ1 regulates clathrin-mediated endocytosis and neuronal function. The majority of *Synj1*$^{-/-}$ mice (85 %) die within 24 h of birth and the remaining mice that live for up to 15 days exhibit severe neurological defects such as progressive ataxia, weakness and convulsions (Cremona et al. 1999). *Synj1*$^{-/-}$ neurons exhibit increased PI(4,5)P_2, correlating with an accumulation of clathrin-coated vesicles (Cremona et al. 1999). Similar phenotypes are observed in both the SYNJ1 null *C. elegans* (*unc-26*) and Synj1 null *Drosophila melanogaster (D. melanogaster)* (Harris et al. 2000). ENU mutagenesis screens in *Danio rerio* (*D. rerio*) larvae with vestibular defects identified mutant SYNJ1 induces abnormalities in hair cell basal blebbing via disrupted synaptic vesicle production and release at hair cell ribbon synapses (Trapani et al. 2009). The SAC and 5-phosphatase domains of SYNJ1 are required for normal vesicle endocytosis and uncoating of clathrin in vitro (Mani et al. 2007). PI(4,5)P_2 regulates the interaction of synaptic vesicles with the plasma membrane by recruiting proteins which mediate vesicle docking (Cremona et al. 1999; Harris et al. 2000; Mani et al. 2007), as well as restricting a readily releasable pool of synaptic vesicles at nerve synapses (Milosevic et al. 2005; Paolo et al. 2004). Therefore PI(4,5)P_2 may affect several steps in the synaptic vesicle cycle which rely on clathrin-dependent endocytosis, functioning to supply new synaptic vesicles during nerve stimulation (Haucke 2003; Kasprowicz et al. 2008). PI(4,5)P_2 is essential for clathrin-coated pit formation via the recruitment of various endocytic proteins and clathrin adaptors, including AP-2 and AP-180, to the plasma membrane (Haucke 2003). By degrading PI(4,5)P_2, SYNJ1 directs the uncoating of clathrin and thereby postendocytic vesicle reavailability. The endocytic defects that occur as a consequence of SYNJ1 loss can be attributed to the accumulation of PI(4,5)P_2 on endocytic vesicles (Cremona et al. 1999; Mani et al. 2007). Recent studies describe that SYNJ1, along with membrane curvature sensors such as the BAR protein endophilin, mediate hydrolysis of PI(4,5)P_2 orientation on curved membranes opposed to comparatively flat ones, suggesting that the PI(4,5)P_2 to PI(4)P conversion may be spatially restricted during membrane internalisation (Chang-Ileto et al. 2011). Studies in *C. elegans* demonstrate disruption of genes encoding the NCA (Na^+/Ca^{2+} antiporter) ion channel, or *unc-80*, which encodes a novel neuronal protein required for ion channel

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1477 subunit localisation, can partially suppress the defects observed in synaptojanin
1478 mutants (Jospin et al. 2007).
1479 *SYNJ1* maps to human chromosome 21q22.2. Trisomy of chromosome 21
1480 causes Down's syndrome (DS), which is characterised by intellectual disability,
1481 congenital heart disease and susceptibility to several cancers, reviewed in
1482 (Patterson 2009). Significantly, increased expression of SYNJ1 is reported in DS
1483 brain tissue (Arai et al. 2002; Cheon et al. 2003). Furthermore, the DS mouse
1484 model, Ts65Dn, displays elevated Synj1 expression associated with decreased
1485 PI(4,5)P_2 levels, leading to cognitive defects. Transgenic mice overexpressing the
1486 *Synj1* gene recapitulate these features (Voronov et al. 2008). Remarkably, crossing
1487 *Synj1* heterozygous mice with Ts65Dn mice restores Synj1 expression to wildtype
1488 levels, associated with a reversal of the DS phenotype and normalisation of
1489 PI(4,5)P_2 levels (Voronov et al. 2008). Screens in *D. melanogaster*, suggest that
1490 SYNJ1 is likely to function in conjunction with other proteins located on human
1491 chromosome 21 to regulate synaptic vesicle recycling. Overexpression of *synj*,
1492 *dap160* (intersectin) and *nla* (nebula) individually results in abnormal synaptic
1493 morphology in *D. melanogaster*, although impaired vesicle recycling, locomotor
1494 defects and defective endocytosis are only observed with combined overexpres-
1495 sion (Chang and Min 2009). Further details of how SYNJ1 mediates DS patho-
1496 physiology remain to be elucidated. Additionally, *C. elegans* with *unc-26*
1497 mutations display exacerbated polyglutamine toxicity implicating a possible pro-
1498 tective potential of SYNJ1, similar to its binding partner endophilin, in Hunting-
1499 ton's disease (Parker et al. 2007).

1500 SYNJ2

1501 SYNJ2 contains a similar domain structure to SYNJ1 however its carboxyl-ter-
1502 minal and proline-rich domains are unique (Nemoto et al. 1997). SYNJ2A contains
1503 a C-terminal PDZ domain which binds to the mitochondrial outer membrane
1504 protein OMP25, and may regulate the intracellular distribution of mitochondria
1505 (Nemoto and De Camilli 1999). In addition, SYNJ2B, SYNJ2B1 and SYNJ2B2,
1506 interact with SH3-containing endocytic proteins via their proline-rich
1507 domains (Nemoto et al. 2001), and are implicated in clathrin-mediated endocy-
1508 tosis. siRNA-mediated reduction of SYNJ2 expression in cell lines results in
1509 defective clathrin-mediated receptor internalisation as well as a reduction in
1510 clathrin-coated pits and vesicles (Rusk et al. 2003).
1511 SYNJ2 acts as a Rac1 effector, and interacts with Rac1 in a GTP-dependent
1512 manner. In vitro, expression of constitutively active Rac1 promotes SYNJ2
1513 translocation to the plasma membrane, and inhibits clathrin-mediated endocytosis
1514 (Malecz et al. 2000; Nemoto et al. 2001). Interestingly, SYNJ2 interactions with
1515 Rac1 are not restricted to endocytosis and have been implicated in Rac1-mediated
1516 malignant cell invasion and migration. siRNA-mediated depletion of either Rac1
1517 or SYNJ2 inhibits the formation of lamellipodia and invadopodia, associated with
1518 reduced cell migration and invasion in matrigel and rat brain slices (Chuang et al.

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1519 2004). Therefore, SYNJ2 may act as a downstream effector of Rac1 to regulate
1520 matrix degradation and cell migration.
1521 Although no SYNJ2 knockout mouse has been reported, SYNJ2 has recently
1522 been identified as a possible regulator of adult hearing. The ENU-generated mutant
1523 mouse, *Mozart*, is characterised by recessively inherited, non-syndromic
1524 progressive hearing loss and severe deafness at 12 weeks of age, attributed to the
1525 degeneration of cochlear hair cells and stereocilia (Manji et al. 2011). This mouse
1526 carries a single mutation in a critical catalytic residue in the 5-phosphatase domain
1527 of Synj2 which impairs its catalytic activity towardss PI(4,5)P_2 and PI(3,4,5)P_3
1528 (Manji et al. 2011). Cochlea expression of Synj2 is detected in both the inner and
1529 outer hair cells, but is absent from the spiral ganglion in wildtype mice. The
1530 mechanism by which SYNJ2 regulates hair cell maintenance and survival is yet to
1531 be established.

1532 SAC Phosphatases

1533 Members of the SAC phosphatase family contain a conserved SAC domain that
1534 was originally isolated in a genetic screen for modifiers of actin cytoskeleton
1535 defects in yeast (ySac1) (Novick et al. 1989). Several SAC domain-containing
1536 phosphoinositide phosphatases have since been identified which are evolutionarily
1537 conserved from yeast to mammals. The highly conserved SAC domain is com-
1538 prised of $\sim$400 amino acids arranged into 7 motifs, with the conserved CX_5R
1539 active site located within the sixth motif. The yeast Sac domain crystal structure
1540 comprises two closely packed sub-domains, an N-terminal (SacN) and a catalytic
1541 sub-domain (Manford et al. 2010), which confers unique interactions with regu-
1542 latory proteins and a differential dephosphorylation mechanism towardss phos-
1543 phoinositide substrates compared with other phosphatases (Manford et al. 2010).
1544 The SAC domain displays broad substrate specificity efficiently dephosphorylating
1545 PI(3)P, PI(4)P and PI(3,5)P_2 to PI (Guo et al. 1999).
1546 There are two classes of SAC family proteins, which are classified based on
1547 domain structure. Stand-alone SAC phosphatases contain a single N-terminal SAC
1548 domain and no other identifiable domains and include yeast ySac1 and yFig4, and
1549 human SAC1, SAC2/INPP5F and SAC3/FIG4. Enzymes containing a SAC
1550 domain in addition to a 5-phosphatase catalytic domain are termed SAC domain-
1551 containing inositol phosphatases (SCIPs) and include mammalian SYNJ1 and
1552 SYNJ2. SAC phosphatases exhibit varied cellular functions in mammalian cell
1553 systems and knockout mouse models, and are implicated in several human
1554 diseases including neurodegeneration and cardiac hypertrophy. The following
1555 section will outline the biological function of the mammalian stand-alone SAC
1556 phosphatases, highlighting their roles in human disease.

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SAC1

SAC1 is a 67 kDa type II transmembrane protein, and was the first mammalian SAC phosphatase identified (Nemoto et al. 2000). *SAC1* is located on human chromosome 3p21.3, and displays an identical substrate specificity to ySac1, hydrolysing PI(3)P, PI(4)P and PI(3,5)P_2 both in vitro and in vivo (Nemoto et al. 2000). SAC1 displays the greatest catalytic activity towardss monophosphorylated phosphoinositides, and in yeast cells mediates the majority of PI(4)P degradation (Foti et al. 2001; Nemoto et al. 2000). SAC1 contains two C-terminal domains that anchor it to intracellular membranes such that the hydrophilic region of the C-terminus faces the cytosol (Konrad et al. 2002). The ySac1 crystal structure has revealed the presence of a linker sequence between the catalytic and the carboxy-terminal transmembrane domain, which is predicted to enable access to its substrates on adjacent membranes, possibly allowing hydrolysis of multiple phosphoinositide pools (Manford et al. 2010).

SAC1 localises to the Golgi complex and ER membranes in both yeast and mammalian cells (Cleves et al. 1989; Nemoto et al. 2000; Rohde et al. 2003; Whitters et al. 1993). In yeast ySac1 regulates PI(3)P and PI(4)P hydrolysis at the ER, and PI(4)P levels at the Golgi (Foti et al. 2001; Konrad et al. 2002). In mammalian cells, SAC1 is shuttled to the Golgi via COP-II interactions where it degrades local PI(4)P pools upon serum deprivation (Blagoveshchenskaya et al. 2008; Cheong et al. 2010). Growth factor simulation of primary human fibroblasts promotes COP-I dependent localisation of SAC1 to the ER, leading to PI(4)P accumulation at the Golgi, which promotes the trafficking of signalling proteins to the cell periphery (Rohde et al. 2003; Schorr et al. 2001).

Cell culture studies and transgenic animal models have provided interesting insights to the functional role of SAC1. In yeast ySac1 depletion or mutation results in pleiotropic defects including disorganisation of the cytoskeleton (Cleves et al. 1989; Novick et al. 1989), inositol auxotrophy (Rivas et al. 1999), retardation of cell growth (Cheong et al. 2010; Liu et al. 2008), abnormal vacuole formation and trafficking (Foti et al. 2001; Tahirovic et al. 2005) and cell wall defects (Schorr et al. 2001). In mammalian cells, RNAi-mediated knockdown of SAC1 leads to disorganisation of the TGN and mitotic spindles, which is associated with inefficient cell cycle progression through G2/M (Liu et al. 2008). Additionally, SAC1 expression is required for the spatial regulation of Golgi PI(4)P and maintenance of normal Golgi organisation in mammalian cells (Cheong et al. 2010).

SAC1 is essential for embryonic development, with *Sac1*$^{-/-}$ mice displaying preimplantation lethality (Liu et al. 2008). In addition, *Drosophila Sac1* mutants display defective dorsal closure in embryogenesis (Wei et al. 2003). Mutant *Sac1 Drosophila* display elevated PI(4)P in addition to increased Hedgehog signalling (Jiang and Hui 2008; Yavari et al. 2010). Hedgehog signalling regulates many developmental processes, although whether phosphoinositide signalling directly influences hedgehog developmental programmes in *Drosophila* with loss of SAC1 remains to be elucidated.

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1600 ## *SAC2/INPP5F*

1601 Mammalian *SAC2*, also known as *INPP5F*, is located on human chromosome
1602 10q26.11. *SAC2* is ubiquitously expressed, with its highest expression detected in
1603 the heart, brain, kidney and skeletal muscle. Interestingly, mammalian SAC2 has
1604 no yeast homologue, and displays unique substrate specificity, dephosphorylating
1605 both PI(4,5)P_2 and PI(3,4,5)P_3 at the D-5 position (Minagawa et al. 2001). There
1606 has been little characterisation of SAC2, although a *Sac2*$^{-/-}$ mouse model has
1607 been reported which demonstrates increased sensitivity to stress-induced cardiac
1608 hypertrophy and hyperactivation of Akt and GSK3β by modulation of PI(3,4,5)P_3
1609 (Zhu et al. 2009). Interestingly, histone deacetylase 2 (HDAC2) transgenic mice
1610 display increased hypertrophy associated with decreased *Sac2* gene expression and
1611 elevated Akt/GSK3β signalling (Trivedi et al. 2007). Therefore, *Sac2* is implicated
1612 in cardiac hypertrophic signalling in mouse models, however, a role for SAC2 in
1613 human cardiac hypertrophy remains to be demonstrated. Recently, the spatio-
1614 temporal pattern of a transcriptional variant of *Sac2/Inpp5f, Inpp5f-v3,* during
1615 mouse development revealed expression specifically in mouse brain, suggesting
1616 that *Inpp5f-v3* may be involved in brain development (Yan et al. 2011).

1617 ## *SAC3/FIG4*

1618 Yeast yFig4 was discovered via genetic screens as a pheromone-induced gene
1619 required for yeast mating (Erdman et al. 1998). The mammalian homologue,
1620 SAC3 also known as FIG4, was initially isolated in the rat (rSac3) (Sbrissa et al.
1621 2007; Yuan et al. 2007). Human *SAC3/FIG4* is located on chromosome 6q21, and
1622 the SAC3 protein displays in vitro activity to hydrolyse PI(3,5)P_2, PI(4,5)P_2 and
1623 PI(3,4,5)P_3, with cell-based assays revealing a preference for PI(3,5)P_2 (Rudge
1624 et al. 2004; Sbrissa et al. 2007). SAC3 maintains PI(3,5)P_2 levels in a complex
1625 with the D5-kinase PIKfyve and PIKfyve regulator, ArPIKfyve termed the PAS
1626 (PIKfyve–ArPIKfyve–Sac3) complex (Ikonomov et al. 2009; Sbrissa et al. 2004,
1627 2008; Sbrissa and Shisheva 2005). SAC3 is stabilised and protected from degra-
1628 dation in the PAS complex (Ikonomov et al. 2010; Sbrissa et al. 2007), and this
1629 association promotes PI(3,5)P_2 synthesis via PIKfyve and ArPIKfyve; and
1630 PI(3,5)P_2 hydrolysis via SAC3 activity (Sbrissa et al. 2004; Sbrissa and Shisheva
1631 2005). SAC3 localises to the ER, Golgi, early and recycling endosomes (Sbrissa
1632 et al. 2007; Yuan et al. 2007).
1633 SAC3 is widely expressed in human and mouse tissues, with highest expression
1634 in the brain, lung and white adipose tissue (Sbrissa et al. 2007). Insulin-stimulated
1635 Sac3 depleted mouse adipocytes display increased cellular PI(3,5)P_2 levels,
1636 increased GLUT4 membrane translocation and glucose uptake (Ikonomov et al.
1637 2009) although whether SAC3 mediates insulin sensitivity in vivo and particularly
1638 in humans remains to be shown. In rats, *rSac3* is highly expressed in the central

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1639 nervous system (Chow et al. 2007), and in vitro studies have revealed that *rSac3*
1640 regulates neurite elongation in PC12 cells (Yuan et al. 2007).
1641 The 'pale tremor' mouse is a spontaneously occurring mouse mutant that
1642 exhibits an abnormal gait, peripheral neuropathy, selective neuronal degradation,
1643 severe tremor and juvenile lethality arising from a mutation due to a transposon
1644 insertion into intron 18 in *Sac3/Fig4* (*Fig4*$^{-/-}$) (Chow et al. 2007; Ferguson et al.
1645 2009). *Fig4*$^{-/-}$ pale tremor mice display pathological features which are charac-
1646 teristic of neurodegenerative diseases such as increased levels of autophagy
1647 markers, inclusion bodies and protein aggregates in the brain (Ferguson et al.
1648 2009). Pale tremor fibroblasts show significantly reduced levels of the Sac3 sub-
1649 strate, PI(3,5)P_2, due to disrupted PAS complex formation and decreased PIKfyve
1650 and ArPIKfyve activity (Duex et al. 2006a, b). In addition, *Fig4*$^{-/-}$ primary
1651 neuron and fibroblast cultures display extensive and enlarged LAMP-2 positive
1652 vacuoles (Chow et al. 2007; Ferguson et al. 2009; Zhang et al. 2008), although it is
1653 not yet clear how depleted PI(3,5)P_2 and loss of Sac3/Fig4 result in this phenotype.
1654 The clinical and pathological features observed in the *Fig4*$^{-/-}$ mouse are
1655 consistent with the human neuropathy Charcot-Marie-Tooth (CMT) disease.
1656 Significantly, SAC3 mutations have been indentified in CMT and include an Ile-
1657 to-Thr substitution at amino acid 41 (I41T) predicted to disturb the folding or
1658 stability of the protein, and this subtype is designated CMT4J (Manford et al.
1659 2010). In vitro studies have revealed that the CMT4J mutant SAC3 protein retains
1660 PI(3,5)P_2 hydrolysing capacity, but has disrupted ArPIKfyve-dependent stabili-
1661 sation resulting in its rapid degradation (Ikonomov et al. 2010). A recent study has
1662 further elucidated the consequences of the CMT-associated mutation within SAC3.
1663 The I41T mutation inhibits the interaction of SAC3 with its binding partner and
1664 scaffold protein, VAC14. The importance of this interaction is observed in
1665 *Vac14*$^{-/-}$ mice, which also display neurodegeneration accompanied by loss of
1666 Sac3 expression and perinatal death (Zhang et al. 2007). Interestingly, *Fig4*$^{-/-}$
1667 mice transgenically expressing moderate levels of the human FIG4-I41T mutated
1668 gene display low levels of FIG4-I41T protein, as is observed in human CMT4J
1669 patients, which is attributed to protein instability from impaired interactions of
1670 Vac14 with the mutant protein. Interestingly, when the FIG4-I41T mutant gene is
1671 highly overexpressed in the *Fig4*$^{-/-}$ mice, it rescues the *Fig4*$^{-/-}$ lethal phenotype.
1672 Therefore, it is possible that CMT4J patients could be treated by upregulating and/
1673 or stabilising the mutant phosphatase (Lenk et al. 2011).

1674 **Conclusion**

1675 Several new studies have revealed altered expression or function of the
1676 phosphoinositide phosphatases may contribute to human disease pathogenesis.
1677 However, despite two decades of investigation the functions of many phospho-
1678 inositide phosphatases remain to be fully elucidated. Animal studies, including
1679 emerging knockout mouse models, are proving to be a valuable tool for the

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1680 characterisation of phosphatase function in vivo. In addition, gene array studies
1681 continue to report altered expression of phosphoinositide phosphatases in various
1682 human diseases, highlighting potential roles for these enzymes in specific diseases.
1683 Future studies will be required to determine if these phosphatases can be targeted
1684 therapeutically.

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AQ3	Reference Risio, Casorzo et al. (2003) is cited in text but not provided in the reference list. Please provide reference in the list or delete this citation.	
AQ4	Please provide volume, page range for the references Astle et al. (2011), Hamilton et al. (2010), Rahman et al. (2011), Vicinanza et al. (2011).	
AQ5	Please provide volume for the reference Pernot et al. (2011).	

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