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Review

Inositol polyphosphate 5-phosphatases; new players in the regulation of cilia and ciliopathies

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ABSTRACT

Phosphoinositides regulate numerous cellular events via the recruitment and activation of multiple lipid-binding effector proteins. The precise temporal and spatial regulation of phosphoinositide signals by the co-ordinated activities of phosphoinositide kinases and phosphatases is essential for homeostasis and development. Mutations in two inositol polyphosphate 5-phosphatases, *INPP5E* and *OCRL*, cause the cerebrorenal syndromes of Joubert and Lowe's, respectively. INPP5E and OCRL exhibit overlapping phosphoinositide substrate specificity and subcellular localisation, including an association with the primary cilia. Here, we review recent studies that identify a new role for these enzymes in the regulation of primary cilia function. Joubert syndrome has been extensively linked to primary cilia defects, and Lowe's may represent a new class of 'ciliopathy associated' syndromes.

1. Introduction

Phosphoinositides are lipid signalling molecules which regulate numerous cellular processes including vesicular trafficking, cytoskeletal dynamics, protein synthesis, proliferation and survival. The spatial and temporal localisation of phosphoinositide signals is tightly regulated by phosphoinositide kinases and phosphatases including the inositol polyphosphate 5-phosphatases (5-phosphatases) INPP5E and OCRL. Mutations in *INPP5E* and *OCRL* are associated with the human cerebrorenal syndromes of Joubert and Lowe's respectively [1,2]. Here we will discuss recent studies reporting a role for these 5-phosphatases at the 'antenna-like' signalling centre, the primary cilia.

2. Primary cilia: structure, function and trafficking to cilia

Primary cilia are sensory organelles that project from the surface of most quiescent cells in vivo. The singular primary cilium senses the extracellular environment and plays a critical role in multiple signal transduction pathways. Primary cilia consist of a basal body, transition zone, ciliary axoneme and ciliary membrane (Fig. 1). The centrosome differentiates into the basal body during ciliogenesis and localises to the plasma membrane at the base of the primary cilia. The basal body is continuous with the cilia axoneme, which consists of 9 microtubule doublets providing structure to the cilia and docking sites for transport proteins [3]. The 9 + 0 microtubule axoneme arrangement defines the primary cilia as distinct from the 9 + 2 arrangement of the motile cilia. The ciliary membrane is continuous with the somatic plasma membrane, however, the membrane domains are separated by a putative diffusion barrier at the transition zone [4]. The protein, lipid and phosphoinositide composition of the ciliary membrane is largely undefined. Ciliogenesis, the formation of cilia, is widely accepted to occur when a cell exits the cell cycle, however, recent studies challenge this contention, as pro-proliferative signalling pathways depend on primary cilia for signal transduction [5,6].

Sorokin et al. (1962) [3] identified the key stages of primary cilia assembly (Fig. 1). Initially, a Golgi-derived primary ciliary vesicle attaches to the distal end of the mother centriole. The centriole extends distally via the acquisition of accessory structures, and differentiates into a basal body. The resulting structure consists of the ciliary bud (the site of microtubule assembly), or primitive axoneme, which is continuous with the mother centriole at one end and is surrounded by the primary ciliary vesicle (now termed the ciliary sheath) at the other. As the ciliary bud elongates by microtubule assembly, the ciliary sheath extends by fusion with secondary ciliary vesicles. Finally, the ciliary vesicle fuses with the plasma membrane and the axoneme continues to elongate by intraflagellar transport (IFT) and microtubule assembly.

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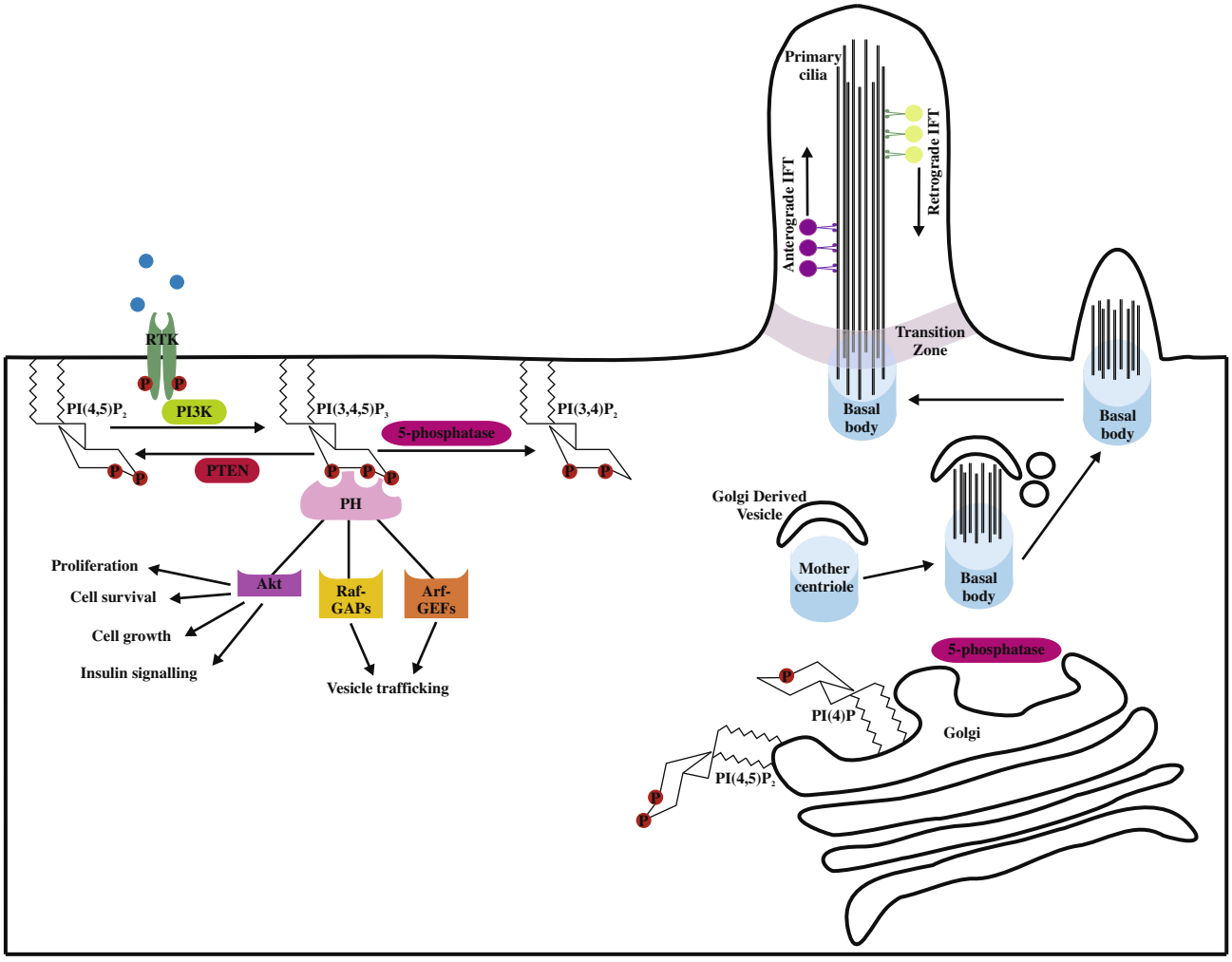

Fig. 1. Phosphoinositide signalling and cilia. Phosphoinositides localise to the plasma membrane and the endomembrane domains where they specify organelle identity and recruit specific lipid binding effector proteins. PtdIns(4)P is the major species present at the TGN, although low levels of PtdIns(4,5)P_2 are also detected. PtdIns(4,5)P_2 is the predominant phosphoinositide at the plasma membrane where it serves as a substrate for PI3-kinase, which once activated by receptor tyrosine kinases, transiently generates PtdIns(3,4,5)P_3. Multiple PH domain containing proteins are recruited to PtdIns(3,4,5)P_3 including Akt, Raf-GAPs and Arf-GAPs and regulate extensive downstream signalling pathways. PI3-kinase signalling is regulated by lipid phosphatases such as the 3-phosphatase PTEN and the 5-phosphatases, including INPP5E and OCRL, which generate PtdIns(3,4)P_2. The phosphoinositide content of the ciliary membrane, which is separated from the somatic plasma membrane via a putative diffusion barrier at the transition zone, remains to be explicitly defined. Primary ciliogenesis is initiated when the primary ciliary vesicle fuses with the mother centriole. Additional Golgi derived vesicles fuse with the primary ciliary vesicle, and the mother centriole differentiates into the basal body. The basal body then fuses with the plasma membrane and the axoneme elongates by IFT and microtubule assembly.

Primary cilia play critical roles in embryonic development and adult tissue homeostasis, in part via regulation of multiple cellular signalling pathways. Components of the platelet-derived growth factor (PDGF), hedgehog (Hh) and Wnt pathways, among others, localise to the primary cilia and in some cases the cilia may be essential for signal transduction [6–9]. Nodal cilia generate the leftward fluid flow responsible for establishing left–right body asymmetry. Furthermore, renal epithelial cilia sense fluid flow and are required for renal homeostasis.

Trafficking of membrane-associated and cytosolic proteins within the primary cilia is facilitated by IFT which requires IFT B-complex proteins and kinesin 2 to mediate anterograde transport, a process essential for ciliogenesis. The IFT A-complex and dynein in contrast facilitate retrograde IFT [10]. However, the molecular mechanisms and processes that regulate trafficking of proteins to the primary cilia from the cytosol/endocytic network remain poorly understood. Golgi-derived vesicles form the ciliary membrane during ciliogenesis and multiple integral cilia membrane proteins have been shown to traffic via the *trans*-Golgi network (TGN), suggesting a role for the Golgi in cilia trafficking, however, the process is only beginning to be defined [3].

3. Ciliopathy syndromes

Inherited mutations in essential cilia-associated genes result in a spectrum of cilia dysfunction diseases collectively termed ciliopathy syndromes (Table 1). The major organs affected by ciliopathy syndromes are the brain, kidney and eye. Although phenotypic variability exists between affected individuals, common characteristic features include cerebellar malformations, renal dysfunction (polycystic kidneys or Nephronophthisis (NPHP): in the latter cysts are observed in the corticomedullary border and tubular atrophy, basement membrane defects and diffuse interstitial fibrosis are evident), cognitive impairment, retinal degeneration, polydactyly, hypotonia and hyperpnoea/apnoea (reviewed in [11]). Significant allelism occurs within the ciliopathies whereby differing mutations in a single gene can result in multiple syndromes depending on the effect of the mutation on the protein product. For example

Table 1
Ciliopathy syndromes and associated genes.

Ciliopathy syndrome	Abbreviation	Genes
Joubert syndrome	JSRD	*INPP5E, ARL13B, KIF7, CEP290, NPHP1, RPGRIP1L, TMEM67, TMEM216, TMEM138, TMEM237, CC2D2A, AHI1, OFD1, TCTN1, TCTN2, CEP41, C5ORF42*
Meckel-Gruber syndrome	MKS	*NPHP3, CC2D2A, TMEM67, TMEM216, CEP290, TCTN2, RPGRIP1L, B9D1, B9D2, MKS1*
Cerebellar vermis hypo/aplasia, oligophrenia, congenital ataxia, ocular coloboma, and hepatic fibrosis	COACH	*CC2D2A, TMEM67, RPGRIP1L*
Nephronophthisis	NPHP	*NPHP1, NPHP4, NPHP3, INVS, WDR19, TMEM67, TTC21B, NEK8, GLIS2*
Mental retardation, truncal obesity, retinal dystrophy, and micropenis	MORM	*INPP5E*
Bardet-Biedl syndrome	BBS	*C2orf86, BBS5, ARL6, BBS7, BBS12, PTHB1, TRIM32, BBS1, BBS10, CEP290, CEP290, TTC8, BBS4, BBS2, MKS1, MKKS*
Orofacial digital syndrome		*OFD1*
Senior-Løken syndrome	SLSN	*NPHP1, NPHP4, IQCB1, CEP290, SDCCAG8*
Arima syndrome		
Cogan-type congenital oculomotor apraxia		*NPHP1*
Leber congenital amaurosis	LCA	*LCA9, RPE65, CRB1, RD3, KCNJ13, LRAT, TULP1, LCA5, IMPDH1, CEP290, RPGRIP1L, RDH12, SPATA7, AIPL1, GUCY2D, CRX*
Hydrolethalus syndrome	HLS	*KIF7, HYLS1*
Acrocallosal syndrome	ACLS	*KIF7*
Asphyxiating thoracic dystrophy	ATD	*TTC21B, IFT80, DYNC2H, ATD1*

TMEM216 (OMIM ID: 613277), *TMEM67* (OMIM ID: 609884), *CEP290* (OMIM ID: 610142), *RPGRIP1L* (OMIM ID: 610937) and *CC2D2A* (OMIM ID: 612013), are mutated in both Joubert syndrome and the more the severe Meckel-Gruber syndrome [12–19]. The two syndromes associated with mutations in *INPP5E* are described in more detail below.

3.1. Joubert syndrome

Joubert syndrome and related disorders (JSRD) are a genetically and phenotypically heterogeneous group of autosomal or X-linked recessive conditions united by the pathognomonic midbrain-hindbrain malformation defined as the molar tooth sign (MTS) on magnetic resonance imaging (MRI) [20,21]. Affected individuals also exhibit developmental delay, ataxia, hypotonia, irregular breathing and eye movements [20]. Joubert syndrome is variably associated with extra-neural manifestations including postaxial polydactyly, liver fibrosis, NPHP, cystic renal dysplasia, ocular colobomas and retinal dystrophy [20]. Mutations in 17 genes with established roles in cilia structure, function or trafficking have been linked to Joubert syndrome (Table 1) [2,12–16,22–32].

3.2. MORM syndrome

MORM is a rare autosomal recessive genetic disorder which has been described in a consanguineous Northern Pakistani family [33]. MORM-affected individuals exhibit static moderate mental retardation, truncal obesity, congenital retinal dystrophy and micro penis. The similar phenotypic features of MORM with Bardet-Biedl syndrome (BBS)-affected individuals indicate MORM is a ciliopathy syndrome. To date MORM has only been associated with mutations in *INPP5E* [34].

4. Molecular mechanisms of ciliopathy syndromes

The molecular mechanisms underlying ciliopathy syndromes remain poorly defined, although, all syndromes are united by a defect in the structure and/or function of the primary cilium. Ciliopathy-associated proteins often function co-operatively in multiprotein complexes and are implicated in the regulation of cilia assembly, Golgi dynamics, microtubule modifications and stability, function of the putative diffusion barrier and trafficking to the cilia. As many of these processes are intimately linked, for example defects in microtubule dynamics can influence Golgi trafficking and ciliogenesis, it is unclear what the precise causative defect is or whether it is a combination of these events. Aberrant trafficking of cilia localised transmembrane receptors is emerging as a favoured model particularly for the Joubert/Meckel-Gruber syndrome spectrum disorders.

Proteins are proposed to traffic to the primary cilia via three potential pathways; direct trafficking from the Golgi to the cilia, trafficking to the plasma membrane and recycling into the primary cilia, or alternatively lateral transport from the plasma membrane through the putative diffusion barrier into the cilia [35]. Recent studies have lead to an explosion in the identification of proteins that mediate trafficking to the primary cilia via these pathways, however, these studies have been in the context of multiple different ciliary cargo proteins. Therefore, it is difficult to draw a complete picture of how these proteins function co-ordinately to mediate trafficking to the cilia. Furthermore, the primary cilia plays an active role in multiple signalling pathways including Wnt, PDGF and Hh, in which receptors traffic into/out of the ciliary axoneme during signal transduction [7–9]. The molecular machinery mediating receptor trafficking to the cilia under these conditions remains to be defined but potentially a distinct subset of cilia-associated proteins may regulate trafficking in basal versus stimulated states.

Most Joubert syndrome-associated proteins form one of two functionally overlapping complexes, Tectronic and NPHP, at the cilia transition zone (between the basal body and the axoneme) (Fig. 1) [29,31,36]. These complexes regulate ciliogenesis and act as a diffusion barrier to specify protein composition of the ciliary membrane. Loss of a Tectronic or NPHP complex component abrogates cilia localisation of cilia-associated proteins such as ARL13B and Smoothened (Smo) [31]. The mammalian Tectronic complex consists of TCTN1, TCTN2, TCTN3, MKS1, TMEM216, TMEM67, CEP290, CC2D2A, B9D1 and studies in *Caenorhabditis elegans* (*C. elegans*) suggest TMEM237 is also a component [31,32]. Mutations in components of this complex cause Joubert syndrome, COACH or Meckle-Gruber syndrome or all three syndromes depending on the severity of the defect in complex function [31]. In contrast, the NPHP complex consists of NPHP1, NPHP4 and RPGRIP1L which when mutated result in NPHP or Senior-Løken syndrome [29]. Mutations in proteins that regulate the function of both complexes (*NPHP1* and *RPGRIP1L*) result in Meckle-Gruber syndrome and the rare cases of Joubert syndrome with NPHP [31].

Interestingly, the Joubert syndrome proteins INPP5E, ARL13B, KIF7, C5ORF42, TMEM138, ODF1, AHI1 and CEP41 have not been

identified as components of the Tectronic or NPHP complexes and affected individuals with mutations in these genes exhibit Joubert syndrome, but not Meckle-Gruber syndrome, NPHP or Senior-Løken syndrome [2,22–27,30]. The roles C5ORF42, OFD1, CEP41 and INPP5E (discussed below) play in cilia function are little characterised. However, notably ARL13B, KIF7, TMEM138 and AHI1 have been linked to trafficking to the primary cilia and may therefore represent a novel group of proteins distinct from the Tectronic or NPHP complexes that are involved in trafficking to the primary cilia. ARL13B is a member of the ARF family of GTPases which constitutively localises to the primary cilia membrane [37–39]. *Arl13b*^{hennin} mutant mice exhibit a classical ciliopathy syndrome phenotype and at the molecular level aberrant trafficking of Hh pathway components to the primary cilia is observed [37,39]. The phenotype of *Kif7*$^{-/-}$ mice is also consistent with a ciliopathy syndrome and *KIF7* knockdown retinal epithelial cells exhibit fragmentation of the Golgi and aberrant trafficking [24,40,41]. In vitro studies support a role for TMEM138 and AHI1 in regulating trafficking to the primary cilia [27,42]. Therefore as a collective, all of the Joubert syndrome proteins examined to date in this context have been shown to regulate trafficking to the cilia. Future studies on those proteins not yet characterised in this context, may reveal all Joubert syndrome proteins mediate trafficking to the cilia and defects in this process may underlie the syndrome. Significantly, many ciliopathy-associated proteins function in multiprotein complexes and notably many Joubert syndrome proteins complex with Rab8.

Rab8 is one of the most well characterised regulators of cilia trafficking, and modulation of its localisation and/or activity may be a common function shared by Joubert syndrome-associated proteins. Rab8 localises to the primary cilia and the base of the photoreceptor outer segment in its active GTP-bound conformation [43,44]. In retinal photoreceptors CC2D2A is proposed to recruit Rab8 to the cilia and is essential for Rab8 regulation of cilia function. *Cc2d2a* null zebrafish phenocopy dominant negative Rab8 overexpressing zebrafish, both exhibiting a characteristic ciliopathy phenotype including Kupffer's vesicle defects and delayed retrograde melanosome transport in response to adrenaline stimulation [43–45]. Rab8 regulates the trafficking of multiple cilia membrane receptors at the level of vesicle docking and fusion with the base of the primary cilia. Overexpression of constitutively active Rab8 in hTERT immortalized retinal pigmented epithelial (hTERT-RPE) cells increases the length of the cilia membrane and axoneme, suggesting increased docking of cilia-targeted vesicles with the ciliary membrane [44]. CEP290 binds Rab8 under ciliated and non-ciliated conditions, and its regulation of ciliogenesis is dependent on its interaction with Rab8 [46]. AHI1 also interacts with Rab8, recruiting it to the basal body and increasing cilia stability, therefore loss of AHI1 is proposed to result in ciliogenesis and trafficking defects due to Rab8 mislocalisation and degradation [42]. Furthermore, Rab8 binds to the 5-phosphatase OCRL, an interaction required for ciliogenesis and rhodopsin localisation to the primary cilia (discussed below) [47]. It is interesting to speculate that Joubert syndrome proteins may all bind to Rab8 and facilitate trafficking of essential components to the cilia that are required cilia stability, axoneme extension or transmembrane receptors for signal transduction.

Defects in the localisation of transmembrane receptors to the primary cilia due to aberrant trafficking (mutations in *ARL13B*, *KIF7*, *CC2D2A*, *CEP290*, *TMEM216*, *TMEM138* and *AHI1*) or function of the diffusion barrier at the transition zone (mutations in the NPHP and Tectronic complexes) may explain aspects of the Joubert syndrome phenotype. The molar tooth sign may result from altered Hh or Wnt signalling, due to defective Smo or Frizzled trafficking respectively. Retinal degeneration may be a consequence of rhodopsin mislocalisation [48,49].

Interestingly, extra-ciliary trafficking functions are being identified for traditionally defined cilia-associated proteins. For example, IFT complex B subunits IFT20, IFT57 and IFT88 form a complex in non-ciliated T lymphocytes which is required for T cell receptor (TCR) trafficking to the immune synapse [50]. These data suggest ciliopathy syndromes could result from more global defects in intracellular protein trafficking and the localisation of transmembrane receptors to the primary cilia, rather than as a consequence of specific defects in ciliogenesis or cilia structure.

5. Phosphoinositide metabolism

Phosphoinositides localise to the inner leaflet of the plasma membrane and endomembrane domains and consist of two fatty acids and a glycerol backbone linked to a soluble inositol ring. The inositol head group may be modified at the D3, D4 and D5 positions by phosphoinositide kinases and phosphatases to generate seven distinct signalling molecules. Although, phosphoinositides constitute only a minor proportion of total cellular phospholipids, they play key roles in regulation of cellular function via the recruitment and activation of phosphoinositide-binding proteins, leading to the formation of molecular scaffolds and activation of many signalling pathways on specific membrane compartments [51]. The localisation of phosphoinositides to endomembrane domains, which is tightly controlled by lipid kinases and phosphatases, defines organelle identity.

One of the most well studied phosphoinositide metabolic pathways is the generation and regulation of PtdIns(3,4,5)P_3 (and subsequently PtdIns(3,4)P_2) which is transiently produced by class IA phosphoinositide 3-kinase (PI3-kinase) phosphorylation of PtdIns(4,5)P_2 in response to growth factor activation of receptor tyrosine kinases (Fig. 1) [52]. Proteins containing pleckstrin homology (PH) domains bind PtdIns(3,4,5)P_3 and in some cases PtdIns(3,4)P_2 signals at the plasma membrane leading to their activation and downstream signal transduction [53]. PtdIns(3,4,5)P_3 is then dephosphorylated by 5-phosphatases (discussed below) to generate PtdIns(3,4)P_2, or is degraded by PTEN forming PtdIns(4,5)P_2 [54,55]. More than 250 PH domain-containing proteins have been identified with diverse roles in cellular function including regulation of proliferation, cell survival, cell growth, metabolism, vesicular trafficking and the actin cytoskeleton [56–58]. The serine/threonine kinase Akt binds both PtdIns(3,4,5)P_3 and PtdIns(3,4)P_2, enabling its activation by other PtdIns(3,4,5)P_3-dependent kinases including phosphoinositide dependent kinase 1 (PDK1) and mTORC2 [53,59,60]. Active Akt phosphorylates numerous signalling proteins to modulate their activity and thereby regulates extensive downstream pathways. Other PtdIns(3,4,5)P_3 effectors include Grp1, ADP-ribosylation factor guanine nucleotide-exchange factors (ARF-GEFs), ADP-ribosylation factor GTPase activating proteins (ARF-GAPs) and Rac-GEFs [59,61].

PtdIns(4)P is the predominant phosphoinositide at the TGN. Knockdown of the PtdIns 4-kinase that synthesises PtdIns(4)P, PI4IIα, abrogates TGN to plasma membrane trafficking [62]. Arf1 stimulates PtdIns 4-kinase and functions as a co-receptor with PtdIns(4)P to recruit trafficking adaptors [63,64]. This results in the recruitment of four-phosphate-adaptor protein (FPAP) 1 and 2 the clathrin adaptor proteins AP-1, and GGAs, thereby facilitating clathrin coat assembly at the TGN [62,64,65].

PtdIns(4,5)P_2 is the major phosphoinositide at the plasma membrane where it is a key regulator of actin cytoskeletal dynamics. PtdIns(4,5)P_2 activates multiple actin regulatory proteins including WASP family members, cofilin and gelsolin which mediate actin nucleation, severing and capping respectively and thereby promotes actin polymerisation [66–68]. PtdIns(4,5)P_2 is also present at low level on the TGN, and indeed phosphatidylinositol

4-phosphate 5-kinase, which generates PtdIns(4,5)P_2, and the 5-phosphatases INPP5E and OCRL localise to this organelle [64,69–73]. Multiple PtdIns(4,5)P_2 binding proteins such as dynamin and Golgi spectrin localise to the TGN, however, the role PtdIns(4,5)P_2 plays in Golgi trafficking remains poorly defined [74,75].

6. Phosphoinositides at the primary cilia

The phosphoinositide content of the primary cilia and the role these phospholipids play at the cilia remains largely unknown. Lobasso et al., (2010) [76] have shown no significant difference in the total phosphoinositide content of porcine olfactory ciliary membranes compared to epithelial membranes. However, this study did not examine the individual phosphorylated phosphoinositides species present in the ciliary membrane, therefore regional differences may exist. Several studies have indirectly detected phosphorylated phosphoinositides in the primary ciliary membrane. PtdIns(4,5)P_2 phosphodiesterase activity is present in channel catfish olfactory cilia and is stimulated in response to odorant receptor activation [77]. In *C. elegans*, 5-phosphatase *cil-1* truncation mutants exhibit ectopic PtdIns(3)P biosensor (2xFYVE domain) localisation to the cilia in male-specific sensory neurons [78]. The ciliary receptors PDK-2 and LOV-1 are mislocalised in *cil-1* mutants, suggesting PtdIns(3)P and/or PtdIns(3,5)P_2 may play a role in *C. elegans* cilia trafficking. Recently, two mammalian 5-phosphatases, INPP5E and OCRL, have been localised to the primary cilia and are the focus of this review [34,47,79].

The exocyst is a multiprotein complex which mediates vesicle tethering at the plasma membrane during exocytosis. Components of the complex (Sec6 and Sec8) localise to base of the forming primary cilia during ciliogenesis, while Sec10 knockdown in MDCK cells reduces cilia number and length [80,81]. Exo70, another component of the exocyst, binds to PtdIns(4,5)P_2 and PtdIns(3,4,5)P_3, and its ability to bind phosphoinositides is essential for recruitment of the exocyst to the plasma membrane and exocytosis [82]. The Tubby family member Tulp3 plays an important role in neuronal development and negatively regulates the Hh signalling pathway [83]. Tulp3 localises to the primary cilia and interacts with the IFT-A complex mediating localisation of a subset of G-protein coupled receptors (GPCR) including the somatostatin receptor 3 (SSTR3) and melanin-concentrating hormone receptor 1 (MCHR1) to the primary cilia [84]. Tulp3 contains a phosphoinositide binding domain that interacts with PtdIns(4,5)P_2, PtdIns(3,4)P_2 and PtdIns(3,4,5)P_3 and is required for MCHR1 trafficking to the primary cilia. Therefore PtdIns(4,5)P_2, PtdIns(3,4)P_2 and/or PtdIns(3,4,5)P_3 may localise to the primary cilia membrane to regulate cilia trafficking. The ciliopathy syndrome-associated multiprotein complex, the BBSome, functions as a planer coat complex that mediates lateral transport of transmembrane receptors to primary cilia [85]. The complex component, BBS5, contains two phosphoinositide binding PH-GRAM domains and interacts with PtdIns(3)P and to a lesser extent PtdIns(3,4)P_2 and PtdIns(3,5)P_2 as shown by phosphoinositide binding studies [44]. Furthermore, BBSome binding to liposomes and the formation of coated profiles on liposomes is enhanced in the presence of PtdIns(3,4)P_2, suggesting this phosphoinositide may mediate the recruitment of the BBSome and facilitate coat formation [85].

7. The inositol polyphosphate 5-phosphatases

The 5-phosphatases are a family of 10 mammalian and 4 yeast members which remove the D5 position phosphate from the inositol headgroup of phosphoinositides and inositol phosphates and regulate diverse processes including embryonic development, renal, neuronal and optic function, glucose homeostasis, the immune response and spermatogenesis. The conserved 300 amino acid, Mg^{2+} dependent 5-phosphatase domain exhibits a similar fold and catalytic mechanism to the apurinic/apyrimidinic endonucleases, [86,87]. INPP5B, OCRL, SHIP1, SHIP2, PIPP, SKIP, synaptojanin 1 and synaptojanin 2 exhibit overlapping substrate specificity, hydrolysing Ins(1,4,5)P_3 and Ins(1,3,4,5)P_4 and PtdIns(3,4,5)P_3, PtdIns(4,5)P_2 and in some cases PtdIns(3,5)P_2. INPP5A, in contrast, hydrolyses only Ins(1,4,5)P_3 and Ins(1,3,4,5)P_4 [88,89].

The 5-phosphatase family members contain multiple protein–protein interacting domains which provide specificity of function to these enzymes. Synaptojanin 1/2 and SHIP1/2 contain proline-rich domains (PRDs) mediating interactions with Src homology (SH) 3 domains. SH2 domains in SHIP1/2 bind phosphotyrosine residues in activated cell surface receptors. OCRL and INPP5B contain a microtubule binding [*A*bnormal spindle-like microcephaly-associated protein/spindle pole body/*h*ydrin] (ASH) domain and an inactive RhoGAP domain. These domains specify subcellular localisation and mediate the formation of multiprotein complexes to regulate 5-phosphatase activity.

Despite overlapping substrate specificity and broad tissue expression patterns, the 5-phosphatases generally exhibit non-redundant roles in cellular function. *Inpp5e, Skip*, *Ship1/2* and *Synj1* knockout mice exhibit significant and distinct phenotypes ranging from embryonic lethality to myeloproliferation and neurological dysfunction [34,90–93]. Furthermore, affected individuals with *INPP5E* or *OCRL* mutations exhibit the severe developmental disorders, Joubert syndrome and Lowe's syndrome respectively [1,2]. Specificity of function is also likely gained by distinct subcellular localisation and protein–protein interactions.

8. INPP5E and ciliopathy syndromes Joubert and MORM

INPP5E [also known as the 72 kDa 5-phosphatase (mouse), inositol polyphosphate 5-phosphtase IV (human) and Pharbin (rat)] is encoded by the *INPP5E* gene located on chromosome 9q34.3 [70,94,95]. INPP5E hydrolyses membrane-associated phosphoinositides PtdIns(4,5)P_2, and compared to SHIP1 and OCRL exhibits the highest in vitro activity towards PtdIns(3,4,5)P_3 [70,95]. Some in vitro evidence suggests INPP5E may also hydrolyse PtdIns(3,5)P_2 [70]. INPP5E is widely expressed, with enrichment in the brain and testis [70]. In dividing cells INPP5E exhibits a cytosolic distribution with perinuclear/TGN enrichment, potentially mediated by its N-terminal PRD [70]. In ciliated cells, the C-terminal CAAX motif is proposed to facilitate its localisation to the primary cilium [34]. INPP5E is also expressed in macrophages where it localises to the phagocytic cup during phagocytosis [96].

INPP5E negatively regulates PI3-kinase/Akt signalling in vitro and in vivo. Overexpression of INPP5E sensitises cells to Fas-induced apoptosis and reduces PI3-kinase mediated Akt phosphorylation following PDGF, or insulin like growth factor simulation [97,98]. In vivo INPP5E PtdIns(3,4,5)P_3 5-phosphatase activity is stimulated by its recruitment to the PI3-kinase p85 subunit and insulin receptor substrates in response to insulin stimulation. *Inpp5e* siRNA knockdown in rats induces hypothalamic PtdIns(3,4,5)P_3 accumulation and consequently reduced food intake and body mass [99].

9. INPP5E mutations and ciliopathy syndromes

All reported Joubert syndrome *INPP5E* mutations cluster in the 5-phosphatase domain and disrupt the charge of evolutionally conserved basic residues located on the surface of the protein (Fig. 2) [2,100]. Mutants exhibit variably reduced catalytic activity towards PtdIns(4,5)P_2 and more dramatically towards PtdIns(3,4,5)P_3 in vitro, but retain ciliary localisation [2]. Joubert syndrome muta-

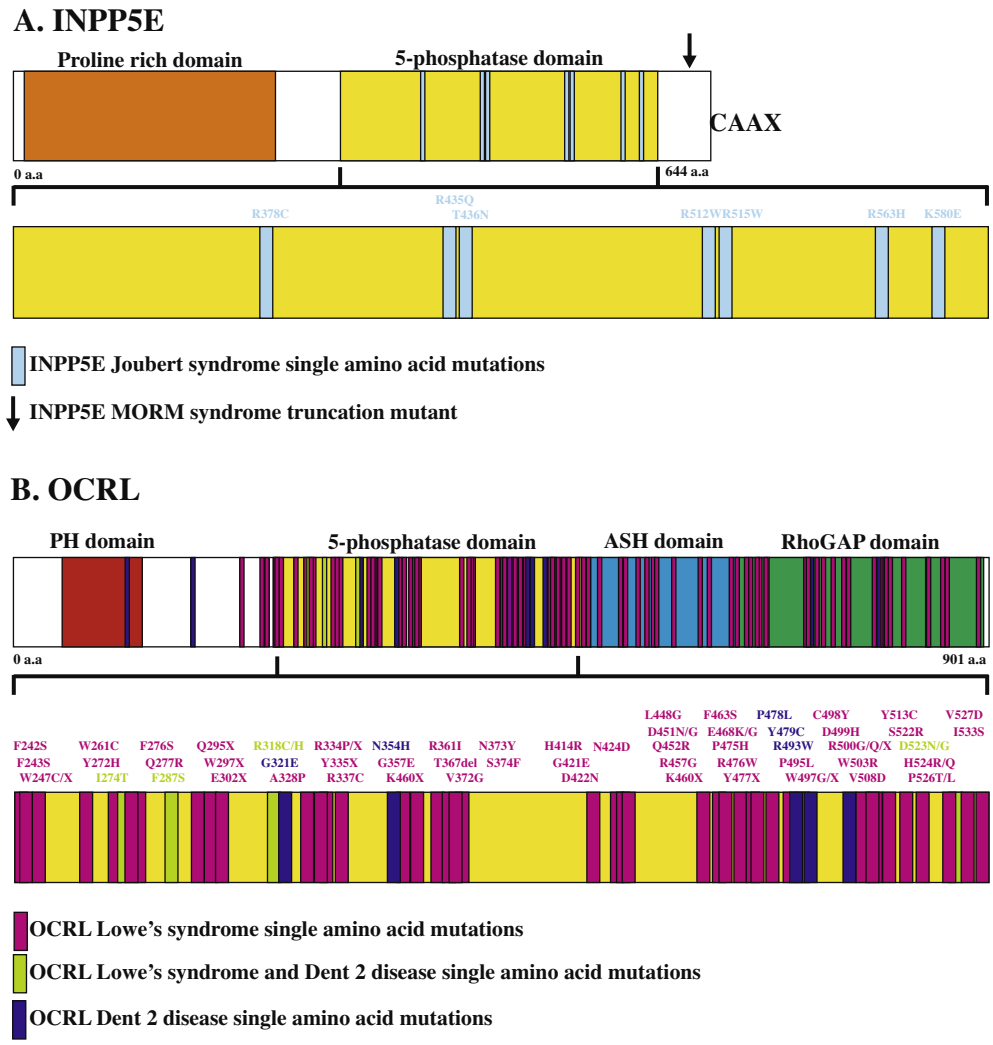

Fig. 2. INPP5E and OCRL domain structure and disease causing mutations. INPP5E Joubert syndrome mutations (blue) cluster in the 5-phosphatase domain [2,100]. INPP5E MORM mutations (arrow) result in deletion of the 18 C-terminal amino acids [34]. Lowe's syndrome missense, nonsense and in-frame deletion mutations in OCRL (pink) are distributed throughout the length of the protein [105,149,150]. OCRL Dent 2 disease missense and nonsense mutations (purple) generally cluster at the N-terminal region of the protein. Mutations (green) occur in both Lowe's syndrome and Dent 2 disease. (Frameshift and splicing mutations are not shown).

tions are located distinct from the phosphoinositide binding site on the surface of the 5-phosphatase domain. Therefore complex mechanism(s) of protein misfunction, such as defects in protein–protein interaction and/or subcellular localisation, as well as disrupted phosphoinositide metabolism, may be responsible for Joubert syndrome pathogenesis.

Mutations in *INPP5E* have also been identified in MORM syndrome [34]. The pathogenic *INPP5E* mutation in MORM syndrome results in deletion of the 18 C-terminal amino acids including the highly conserved CAAX motif (Fig. 2) [34]. This mutation restricts INPP5E to proximal regions of the primary cilia and reduces its association with 14-3-3, but does not impair in vitro 5-phosphatase catalytic activity.

10. Molecular mechanisms of INPP5E dysfunction in ciliopathy syndromes

Inpp5e$^{-/-}$ mice exhibit embryonic or early post natal lethality and recapitulate key features of the ciliopathy syndromes, thereby providing an ideal model to study the role INPP5E plays at the cilia and in ciliopathies [34]. *Inpp5e*$^{-/-}$ embryos exhibit exencephaly, polydactyly, bilateral anopthalmos, polycystic kidneys and skeletal malformations. Tamoxifen induced *Inpp5e* knockout in 4 week old mice induces obesity, retinal degeneration and cystic kidneys, but does not affect 6 month survival [34].

Inpp5e$^{-/-}$ mouse embryonic fibroblasts (MEFs) assemble cilia in response to serum starvation at a similar rate to wild type MEFs. However, the proportion of ciliated *Inpp5e*$^{-/-}$ MEFs is significantly reduced compared to wild type upon serum stimulation, a phenotype rescued by treatment of cells with the PI3-kinase inhibitor LY294002. This suggests cilia stability is reduced in *Inpp5e*$^{-/-}$ MEFs. Jacoby et al. (2009) [34] hypothesised that cilia stability is controlled by ciliary localised growth factor receptors (such as PDGFRα), which, once activated by serum, lead to ciliary PtdIns(3,4,5)P_3 production and cilia disassembly. Therefore, elevated PtdIns(3,4,5)P_3 signals in the *Inpp5e*$^{-/-}$ cilia are proposed to induce more rapid cilia disassembly, although neither the localisation or levels of PtdIns(3,4,5)P_3 were examined. Altered cilia stability also has not been shown in vivo and how reduced stability contributes to the phenotype of the *Inpp5e*$^{-/-}$ mouse is unknown.

INPP5E may play a role in trafficking under non-ciliated conditions. INPP5E localises to the primary cilia and the Golgi [34,70]. In adipocytes, INPP5E overexpression induces GLUT4 translocation and insertion into the plasma membrane [101]. In macrophages

INPP5E localises to the phagocytic cup following Fcγ receptor activation and regulates pseudopod extension and phagosome closure [96]. A growing body of evidence indicates deregulated trafficking to the primary cilia and/or mislocalisation of cilia-associated receptors may be common molecular mechanisms associated with ciliopathy syndromes.

The phenotype of *Inpp5e*$^{-/-}$ mice is significantly more severe (embryonic lethality and exencephaly) than the phenotype exhibited by Joubert-affected individuals with *INPP5E* mutations (cerebellar MTS) [2,34,102]. This is also the case for multiple other Joubert syndrome-associated genes including *ARL13B*, *KIF7*, *CC2D2A*, *TCTN1* and *TCTN2* [31,37,40]. The lethal phenotypes of *Cc2d2a* and *Tctn2* knockout mice more closely resemble Meckel-Gruber syndrome in which *CC2D2A* and *TCTN2* mutations have been identified [17,31,103]. Furthermore, *KIF7* mutations have recently been associated with foetal lethal hydrolethalus and acrocallosal, which share common features with *Kif7*$^{-/-}$ mice [40,104]. Nonsense and frameshift *KIF7* mutations cause hydrolethalus and acrocallosal, whereas Joubert syndrome-affected individuals exhibit in-frame *KIF7* deletions [24,40]. Therefore partial loss of function of ciliopathy-associated proteins may result in the relatively mild Joubert syndrome phenotype, whereas total loss of function may lead to severe developmental disorders and embryonic lethality. Interestingly, Joubert syndrome *INPP5E* mutations are located on the surface of the 5-phosphatase domain and reduce 5-phosphatase catalytic activity but do not influence subcellular localisation [34]. The effect of these mutations on protein expression is unknown, but reduced expression of Joubert syndrome INPP5E mutants may explain the reduced enzyme activity associated with all Joubert syndrome INPP5E mutants, irrespective of the position of the mutation relative to the catalytic domain. This is analogous to the location of Dent 2 disease mutations in OCRL (discussed below) which are predicted to result in the expression of a partially functional protein [105]. Lowe's syndrome mutations, in contrast, result in a complete loss of function of OCRL and a more severe phenotype than Dent 2 disease. Therefore, it is possible *INPP5E* mutations that prevent its expression or lead to a complete loss of function of INPP5E may cause a severe embryonically lethal phenotype, consistent with *Inpp5e*$^{-/-}$ mice.

11. OCRL, Lowe's syndrome and Dent 2 disease

The OCRL protein (also called Lowe's protein), which is mutated in the oculocerebrorenal syndrome of Lowe (OCRL), is encoded by the *OCRL* gene located on chromosome Xq25. OCRL exhibits a broader substrate profile than INPP5E and hydrolyses the 5-position phosphate from the inositol ring of Ins(1,4,5)P_3, Ins(1,3,4,5)P_4, PtdIns(3,4,5)P_3, PtdIns(3,5)P_2 and PtdIns(4,5)P_2, however, PtdIns(4,5)P_2 is its preferred in vivo substrate [106,107]. OCRL is widely expressed with enrichment in the brain and the kidneys [71,108]. The 105 kDa OCRL protein contains the conserved 5-phosphatase catalytic domain, an ASH domain, RhoGAP domain and PH domain mediating interactions with trafficking effectors and adaptors [109,110]. OCRL localises to multiple compartments in the endocytic network including the early endosomes, endocytic clathrin-coated pits, the Golgi and to the basal body and in a minority of cells to the ciliary axoneme [47,69,71,72,79,111–113].

12. Lowe's syndrome

Lowe's syndrome is a rare X-linked congenital disorder characterised by renal Fanconi syndrome (including low-molecular-weight proteinuria, hypercalciuria and aminoaciduria), congenital cataracts, mental retardation, maladaptive behaviour, rickets, hypotonia and areflexia [114,115]. Lowe's syndrome is exclusively caused by mutations in *OCRL* [1]. Missense mutations commonly occur in the 5-phosphatase, ASH, RhoGAP and Rab binding domains, disrupting folding, PtdIns(4,5)P_2 5-phosphatase catalytic activity, protein–protein interactions and/or reducing protein stability (Figure ure2) [109,111,113,116–122]. Nonsense mutations have been reported in the 3' region of the *OCRL* gene and result in expression of a truncated protein [1,123]. These mutations may lead to an absence of the protein or a complete loss of function [105]. Notably, regardless of the nature of the mutations, Lowe's fibroblasts exhibit reduced PtdIns(4,5)P_2 5-phosphatase activity [113].

13. Dent 2 disease

Dent 2 disease is also caused by mutations in the *OCRL* gene. Dent 2 disease is a rare X-linked disorder related to Lowe's syndrome. However, patients exhibit a less severe and predominantly renal restricted phenotype including renal Fanconi syndrome, mild mental retardation and rickets [124]. Missense mutations also occur in the *OCRL* 5-phosphatase domain in Dent 2 disease, but are distributed over the surface of the protein impairing 5-phosphatase activity and are unlikely to affect folding (Fig. 2) [105]. Interestingly, this is reminiscent of the localisation of Joubert syndrome mutations in *INPP5E* [34]. Nonsense and frameshift mutations have been reported in the N-terminal region of OCRL including the PH domain, which result in the expression of a catalytically functional truncated protein [105,124]. In contrast to Lowe's syndrome, Dent 2 disease is proposed to result from a partial loss of OCRL function.

14. Molecular mechanisms of Lowe's syndrome and Dent 2 disease

Despite the dramatic phenotypes exhibited by affected individuals with *OCRL* mutations, *Ocrl*$^{-/-}$ mice are viable, fertile and exhibit no phenotype [108]. This may be due to functional redundancy with another 5-phosphatase family member, namely *Inpp5b*, which has a similar domain structure, substrate specificity and shares common binding partners. *Inpp5b*$^{-/-}$ mice are viable but exhibit testicular degeneration post sexual maturity and infertility [108,125]. Significantly, *Ocrl*$^{-/-}$;*Inpp5b*$^{-/-}$ mice are embryonically lethal and no live embryos are detected at embryonic day (E) 9.5, suggesting functional redundancy during early development [108]. Early embryonic lethality is inconsistent with the ciliopathy mouse models, as mice with mutations in cilia-associated genes generally exhibit midgestation lethality at approximately E10.5 – E15.5 [126]. To generate an appropriate mouse model that accurately recapitulates the key features of Lowe's syndrome Bothwell et al. (2011) [127] generated *Ocrl*$^{-/-}$;*Inpp5b*$^{-/-}$ mice that express human *INPP5B*. These mice exhibit reduced growth, aminoaciduria and proteinuria and may provide key insights into Lowe's syndrome and Dent 2 disease pathogenesis in the future. Fibroblasts from Lowe's-affected individuals exhibit elevated PtdIns(4,5)P_2 signals, the preferred substrate of OCRL, compared to healthy controls [72,107,113]. The widely accepted view in the literature is that OCRL regulates PtdIns(4,5)P_2-dependent processes including actin cytoskeletal dynamics, cytokinesis and in particular vesicular trafficking, and that deregulation of these events accounts for the Lowe's syndrome phenotype [128–130].

OCRL binds to Rab family members Rab1, Rab5, Rab6, Rab14, Rab31, Rab35 and notably Rab8 [109,130,131]. Rab1, Rab6 and Rab31 mediate OCRL localisation to the TGN and Lowe's mutants which do not bind Rabs, do not localise to the endocytic network [132]. In vitro, Rab binding stimulates OCRL 5-phosphatase catalytic activity. Therefore OCRL is proposed to function on endomembranes to restrict PtdIns(4,5)P_2 and generate PtdIns(4)P signals and

thereby maintain organelle identity [109,132]. The OCRL PH and RhoGAP domains interact with clathrin and regulate multiple clathrin-dependent trafficking processes [110,112,133]. OCRL co-localises with clathrin, transferrin (Tf) and the cation-independent mannose-6-phosphate receptor (CI-MPR) on clathrin-coated vesicles [112]. Aberrant OCRL expression blocks retrograde trafficking, resulting in CI-MPR and adaptor protein-1 (AP-1) mislocalisation to endosomes [112,133]. Furthermore, OCRL regulates anterograde trafficking of the cation-dependent mannose-6-phosphate receptor (CD-MPR) [131]. Interestingly, Lowe's-affected individuals exhibit elevated serum lysosomal enzymes which may be due to altered MPR trafficking and thereby secretion of lysosomal hydrolases by default trafficking pathways [134]. OCRL also modulates TfR endocytosis at clathrin coated vesicles in association with clathrin and the adaptor AP-2 [112,135].

Defects in megalin and TrkA trafficking may explain the renal and neurological features of Lowe's syndrome respectively. Megalin is a scavenger receptor that mediates reabsorption of proteins and solutes from urine [136]. Megalin knockout mice and individuals with Lowe's syndrome both exhibit low molecular weight proteinuria. The TrkA receptor plays an important role in neuronal signalling [137]. OCRL interacts with the Rab5 effectors APPL1 and Ses1/2 on the early endosomes [111,122,138]. APPL1 binding bridges OCRL to [GAIP-interacting protein, C terminus] (GIPC), which is reported to regulate megalin and TrkA trafficking [111]. Reduced megalin shedding is detected in Lowe's urine, suggesting decreased kidney tubule plasma membrane megalin levels, which may result from defective megalin trafficking [139,140]. Additionally, ectopic early endosomal PtdIns(4,5)P_2 accumulates in Lowe's-affected renal cells and OCRL knockdown cells, leading to aberrant F-actin polymerisation and a block in megalin trafficking at early endosomes [141].

OCRL localises to the epithelial cell junctions in MDCK cells at the early stages of polarisation [142]. OCRL knockdown MDCK cells exhibit reduced height and mislocalisation of apical markers including ezrin, gp135 and F-actin. These cells fail to form cysts when grown in 3D culture, further supporting a polarity defect. Therefore OCRL is proposed to be essential for maturation of the polarising epithelium [142,143].

Although Lowe's syndrome does not fit the classical ciliopathy syndrome phenotype profile, Lowe's syndrome affects the same organs as ciliopathy syndromes, including brain, kidney and eye, and three recent studies have shown OCRL regulates ciliogenesis and trafficking to the cilia (Table 2) [47,79,143]. Lowe's syndrome-affected fibroblasts and OCRL knockdown NIH3T3 and hTERT-RPE cells exhibit reduced cilia number and cilia length in vitro [47,79]. However, cilia length is increased in OCRL knockdown MDCK cells, suggesting tissue specific defects in cilia function [143]. OCRL predominantly localises to the basal body and in a small proportion of cells at the cilia axoneme, however, Lowe's

Table 2
Comparison of *INPP5E* and *OCRL* associated ciliopathy syndrome with 'classical' ciliopathy syndromes.

	Classical Ciliopathy Syndrome	*INPP5E*	*OCRL*
Human disease	Joubert syndrome	Joubert syndrome	Lowe's Syndrome
	Meckel-Gruber syndrome	MORM	Dent 2 Disease
	COACH		
	Nephronophthisis		
	Senior–Løken syndrome		
	MORM		
	Orofacial digital syndrome		
	Cerebellar-ocular-renal syndrome		
	Dekaban-Arima syndrome		
	Cogan-type congenital oculomotor apraxia		
	Leber congenital amaurosis		
	Hydrolethalus		
	Acrocallosal		
Major tissues affected	Brain	Brain	Brain
	Eye	Eye	Eye
	Kidney	Kidney	Kidney
Pathology	Cerebellar vermis hypoplasia (MTS)	Cerebellar vermis hypoplasia (MTS)	Mental retardation
	Retinal degeneration		Congenital cataracts
	Nephronophthisis/polycystic kidneys		Renal Fanconi syndrome
Mouse models	Embryonic lethality	Embryonic/early post natal lethality	No phenotype
	Exencephaly/anencephaly/holoprosencephaly	Exencephaly/anencephaly	
	Cerebellar hypoplasia	Polydactyly	
	Neural tube patterning defects	Anophthalmos	
	Polydactyly	Skeletal abnormalities	
	Anophthalmia/microphthalmia/retinal degeneration	Polycystic kidneys	
	Skeletal abnormalities	Cleft palate	
	Craniofacial defects		
	Polycystic kidneys		
	Laterality defects		
	Male infertility		
	Obesity		
Zebrafish models	Curved tail	Not reported	Curved tail
	Cystic pronephroi		Cystic pronephroi
	Pigmentation defects		Pigmentation defects
	Laterality defects		Laterality defects
	Hydrocephalus		Oedema
	Abnormal ear otolith formation		Hydrocephalus
	Microphthalmia		Microphthalmia
Proposed molecular mechanism(s)	Cilia structure/function	Cilia stability	Trafficking (Megalin, TrkA)
	Trafficking to cilia		Cytoskeleton
	Cilia transition zone complex		Cytokinesis
	Cilia signalling		

mutant proteins fail to exhibit this distribution and localise to perinuclear puncta. Significantly, *ocrl* morpholino knockdown zebrafish exhibit mislocalised melanophores, laterality defects, curved tail and dilated cystic pronephroi with disorganised/longer cilia, characteristic of a ciliopathy phenotype [47,79,143]. Coon et al. (2012) [47] reported reduced Kupffer vesicle cilia number/length in ocrl knockdown zebrafish, whereas Rbaibi et al. (2012) [143] suggests Kupffer vesicle cilia are normal, therefore further studies will be required to fully define the extent of cilia dysfunction with loss of OCRL.

OCRL is proposed to be essential for ciliogenesis via regulation of trafficking. OCRL knockdown abrogates rhodopsin localisation to the primary cilia and OCRL forms a complex with Rab8 and Ses1/2, which is required for cilia assembly [47]. Rab8 mediates trafficking from the Golgi to the primary cilia, and Ses1/2 localises to the early endosomes and is required for endocytosis. Therefore OCRL is proposed to act in two independent trafficking pathways to the cilia; direct TGN to cilia trafficking in complex with Rab8 and cilia trafficking of endocytosed proteins with Ses1/2.

In the kidney OCRL plays an established role in megalin trafficking. Interestingly, megalin family members bind cilia signalling pathway ligands, Shh and Wnt, mediating endocytosis and downstream signalling [144–146]. Although the relevance of this observation remains to be shown, megalin mediated Shh endocytosis by astrocytes is essential for oligodendrocyte progenitor development and Lowe's syndrome-affected individuals show evidence of demyelination [131,147,148]. Therefore deregulated trafficking and ciliary signalling may potentially play a role in aspects of Lowe's pathogenesis. Trafficking, polarity and cilia structure/function are tightly linked processes and defects in one process may lead to abnormalities in the others, making it difficult to delineate the primary underlying defect. Many lines of evidence support a role for OCRL in trafficking irrespective of cell type, as trafficking precedes and is required for cell polarisation, specification and maintenance of cilia, dysregulated trafficking is a likely underlying molecular mechanism for the observed defects. Other typical cilia-associated proteins including IFT20, IFT57 and IFT88 have been implicated in extra-ciliary trafficking, suggesting global defects in trafficking may play a role in ciliopathy pathogenesis [50]. However, whether cilia dysfunction is pathogenic in Lowe's syndrome remains to be determined. Therefore, Lowe's syndrome may potentially represent a novel ciliopathy or 'ciliopathy associated' syndrome (Table 2).

The phosphoinositide-binding proteins Tulp3 and the BBSome localise to the primary cilia and the Tulp3 PtdIns(4,5)P_2, PtdIns(3,4)P_2 and PtdIns(3,4,5)P_3 binding site is essential for MCHR1 trafficking to the primary cilia [84,85]. The BBSome binds PtdIns(3,4)P_2 and the formation of coated profiles on liposomes is enhanced by PtdIns(3,4)P_2 [85]. Therefore, ciliary phosphoinositides may regulate the spatial and temporal activity of specific effector proteins. Under basal conditions phosphoinositides may act as docking sites to anchor proteins such as Tulp3 or the BBSome to the cilia membrane and upon stimulation, a different phosphorylated phosphoinositide species may recruit/activate a specific subset of lipid binding proteins. In this model mutations in INPP5E and OCRL which decrease 5-phosphatase activity (via reduced expression, enzyme activity or mislocalisation), could disrupt local cilia phosphoinositide content and/or turnover and thereby the localization and/or activity of phosphoinositide binding, cilia localised proteins.

15. Conclusions

INPP5E and OCRL exhibit overlapping substrate specificity, localisation to the primary cilia and regulate cilia function. However, Lowe's-affected individuals do not exhibit the classical ciliopathy phenotype. Therefore Lowe's may represent a novel class of 'ciliopathy-associated' syndromes. Future studies will be required to determine the molecular processes by which INPP5E and OCRL regulate cilia function and how mutations in these 5-phosphtases lead to human diseases.

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