

Review

# Phosphoinositides in Retinal Function and Disease

Theodore G. Wensel 

Verna and Marrs McLean Department of Biochemistry and Molecular Biology, Baylor College of Medicine, Houston, TX 77030, USA; twensel@bcm.edu

Received: 1 March 2020; Accepted: 30 March 2020; Published: 2 April 2020

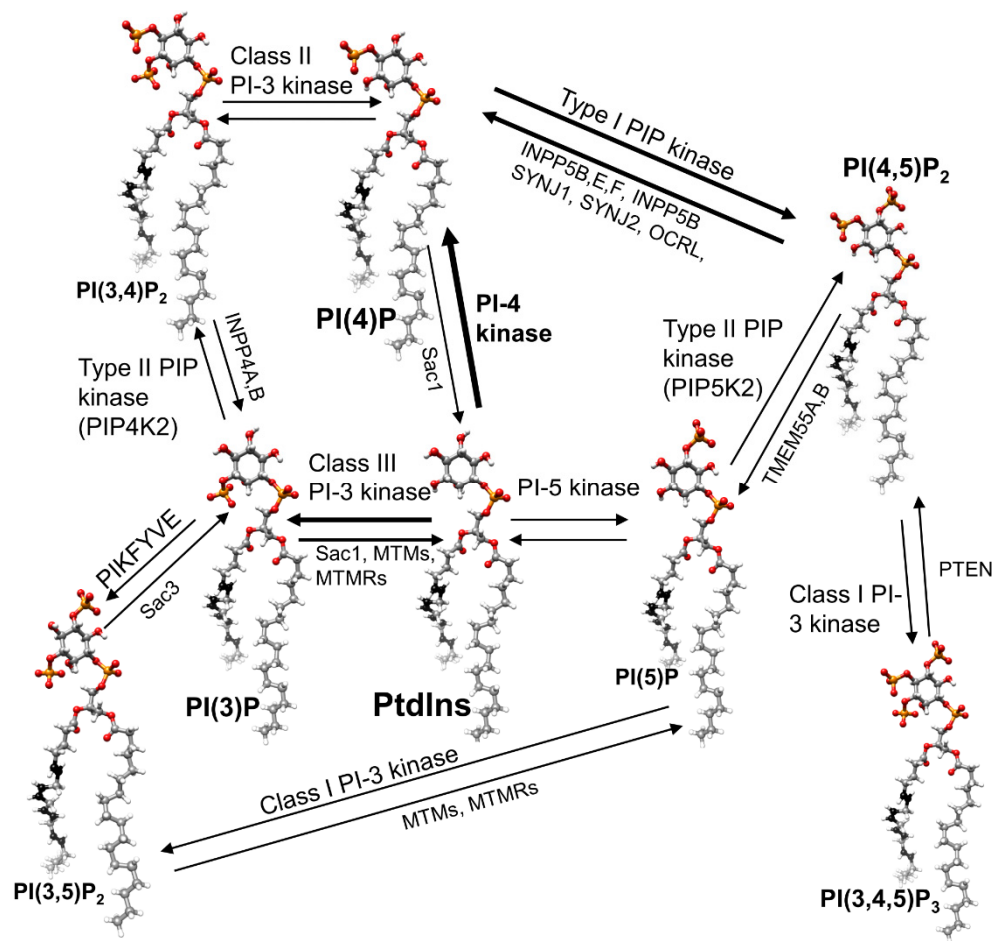


**Abstract:** Phosphatidylinositol and its phosphorylated derivatives, the phosphoinositides, play many important roles in all eukaryotic cells. These include modulation of physical properties of membranes, activation or inhibition of membrane-associated proteins, recruitment of peripheral membrane proteins that act as effectors, and control of membrane trafficking. They also serve as precursors for important second messengers, inositol (1,4,5) trisphosphate and diacylglycerol. Animal models and human diseases involving defects in phosphoinositide regulatory pathways have revealed their importance for function in the mammalian retina and retinal pigmented epithelium. New technologies for localizing, measuring and genetically manipulating them are revealing new information about their importance for the function and health of the vertebrate retina.

**Keywords:** phosphoinositides; retinal lipids; membrane trafficking

## 1. Introduction

Phosphoinositides are membrane phospholipids with the six-member cyclic polyol *myo*-inositol, (CHOH)<sub>6</sub>, or O-phosphorylated forms of inositol, as their headgroup (Figure 1). The phosphorylated forms are of low abundance in eukaryotic cells of all types, generally comprising 1% or less of total phospholipid. Nevertheless, they play critical roles in cellular regulation, and defects in their synthesis and regulation lead to devastating diseases [1–6]. The retina is clearly no exception to this generality, but surprisingly few details have been worked out in what is arguably one of the most extensively studied tissues in our bodies, about the regulation and regulatory roles of retinal phosphoinositides. Recent technological advances make it possible to make substantial advances in this field in the next few years.



**Figure 1.** Structures of the cellular phosphoinositides and enzymes responsible for their synthesis and interconversion. Phosphoinositides (PI) species are shown with the acyl chains most commonly found on phosphatidylinositol, which is the starting point for all the others, arachidonic acid (20:4) and stearic acid (C18). Relative font sizes correlate with relative abundance.

## 2. Chemical Structures of Phosphoinositides

Phosphoinositides (abbreviated here as “PI”) include phosphatidylinositol (PtdIns), in which the 1'-position of the inositol ring is attached via a phosphodiester bond to the *sn*-3 position of (1, 2) diacyl glycerol, and derivatives of PtdIns with one, two, or three phosphates attached in various combinations to the 4', 5' or 3' hydroxyls of PtdIns. Including PtdIns, a total of eight different PI head groups are commonly found in eukaryotic cells (Figure 1) [4,5].

## 3. Phosphatidylinositol Content in the Retina and RPE

PtdIns is a relatively substantial component of the membranes of most cells in metazoans, with mole fractions ranging from ~4%–20% of total phospholipid [4]. Early reports stated that retina phospholipids contained 4.4%–6.4% PtdIns across six different mammalian species [7–9]. Interestingly, rod outer segment (ROS) membranes were found to have much lower levels, 1.5% to 2.5% in bovine and 2.1% in frog [10–13]. Retinal pigment epithelial cells (RPE), in contrast, have higher levels of PtdIns, at 6.5% of total phospholipid [14], while ER membranes isolated from bovine retinas contain 9.6% PtdIns [10]. The general picture that emerges is that total PtdIns content in total retinal membranes outside of outer segments and that of RPE are more or less “normal” as compared to other tissues and cell types, consistent with the notion that widespread roles of PI are likely to be conserved in many retinal cell types. In contrast, ROS have an unusually low PtdIns content, suggesting different roles

for this lipid class in that organelle. This idea is consistent with findings discussed below, indicating different lipid compositions in plasma membranes as compared to ciliary membranes.

#### 4. Content of Minor Phosphoinositides in the Retina and RPE

As a negatively charged lipid, which typically contains one polyunsaturated side chain fatty acid, such as arachidonic acid [8], PtdIns has a major impact on the physical properties of the membrane domains containing it. In contrast, the phosphorylated forms are much less abundant, and exert their influence on cell physiology largely through interactions with proteins with high-affinity and high-specificity PI-binding domains [15–17]. There have been few measurements of phosphorylated PI in retina or cells isolated from retina, although there have been several papers addressing the turnover of PtdIns and other PI, or activity of enzymes involved in PI metabolism [18–21]. The likely reason for the absence of information on PI levels is their low abundance and the lack of sensitivity provided by conventional methods for lipid analysis. More sensitive techniques have been developed recently, including one based on recombinant phosphoinositide-binding domains fused to an epitope tag, allowing sensitive detection by enzyme-linked immunosorbent assays (ELISAs) and measurement of chemiluminescence [22]. This technique was used to quantify PI(3)P and PI(3,4,5)P<sub>3</sub> in preparations of rod cells that contain both outer segments and fragments of the inner segments and demonstrated levels of PI(3)P at 0.0035 mol% of total phospholipid under illumination conditions that yielded the highest levels of that lipid, and at least 10-fold lower (i.e., undetectable) levels of PI(3,4,5)P<sub>3</sub>. PI(4)P and PI(4,5)P<sub>2</sub> are, in general, found at much higher levels than the 3-phosphorylated PI, but even those appear to be present in rods at very low levels, which are only about 10-fold higher than the levels of PI(3)P, i.e., on the order of 0.04 mol% (He and Wensel, unpublished observations).

##### *Comparison to Other Tissues and Cell Types*

These numbers are comparable to those found in other eukaryotic cells, reported as PtdIns3P, 0.002% of phospholipid mass; PtdIns4P, 0.05%; PtdIns5P, 0.002%; PtdIns(4,5)P, 0.05%; PtdIns(3,4)P, 0.0001%; PtdIns(3,5)P, 0.0001% [17], see also references in [23]. A more recent mass spectrometry study reported PI(3,4,5)P<sub>3</sub> levels as 50-fold or more lower than those of the more common PIs in mammalian U87MG cells [24]. An interesting observation derived from measurements of PI levels in cultured cells is that, generally, they do not change greatly upon activation with extracellular stimuli; for the more common forms, PtdIns, PI(4)P, PI(4,5)P<sub>2</sub> and PI(3)P, the change is generally less than 30% [17]. The implication, for PI(4,5)P<sub>2</sub>, which is rapidly degraded to form InsP<sub>3</sub> and diacylglycerol upon activation of phospholipase C isozymes by G-protein-coupled receptors or growth factor receptors [25,26], is that homeostatic mechanisms are in place to regenerate rapidly the pools of both PI(4,5)P<sub>2</sub> and its precursor PI(4)P upon PLC activation. In contrast, PI(3,4,5)P<sub>3</sub> level changes due to receptor stimulation are generally too low to have a major impact on levels of its precursor, PI(4,5)P<sub>2</sub>.

#### 5. Importance of PI Generally

Despite their low abundance, phosphoinositides play major roles in regulation of cell signaling and membrane dynamics, and are essential for control of a wide range of processes including development, proliferation and differentiation, membrane excitability, exocytosis, phagocytosis, cell motility, and detection of extracellular signals [4]. These functional roles are primarily mediated by a plethora of enzymes, scaffold proteins and complex-nucleating proteins containing phosphoinositide-binding domains of high affinity and high specificity. Genetic defects in the enzymes responsible for their regulation are, in most cases, lethal at the embryo stage, except for some cases of redundancy (i.e., more than one gene encoding enzymes or PI-binding proteins with similar activities). Cell-type specific deletion of these enzymes leads to more specific pathologies, e.g., neurodegeneration in the case of the type III PI-3 kinase, Vps34 (also known as PIK3C3) [27,28]. Some of these enzymes, such as type I PI-3 kinases, can act as oncogenes when mutations disrupt their regulation, and are considered prime targets for cancer chemotherapy, whereas others, such as the phosphoinositide phosphatase, PTEN,

are considered tumor suppressor genes [29]; these therapeutic targets are present in the retina, where their roles in retinal function, and any effects of drugs targeting them are unknown.

#### *Importance of Phosphoinositides for Dynamics and Functions of Membranes in Retina and RPE*

Among the most important roles of phosphoinositides and their protein effectors are those mediating intracellular membrane traffic, by directing membrane proteins and lipids from one compartment to another in response to cellular needs and changing environments. For example, PI(3)P is found in early and recycling endosomes, and is important for recruiting key proteins that regulate trafficking to these compartments [30]. It is also important for autophagy, a survival-promoting pathway leading to the lysosomal degradation of organelles [31]. PI(4)P is enriched in the Golgi apparatus, and is thought to be important for membrane trafficking through the Golgi compartments and from the Golgi to the plasma membrane and other subcellular compartments [32], likely including disk membranes. PI(4,5)P<sub>2</sub> plays a key role in clathrin-mediated endocytosis, and serves to direct many effector proteins to the plasma membrane where it is primarily found [33].

PI(4,5)P<sub>2</sub> and other phosphoinositides directly regulate the activity of ion channels, transporters and enzymes in membranes [34,35]. In addition, PI(4,5)P<sub>2</sub> serves as the substrate for phosphoinositide-specific phospholipase C, leading to production of the important second messengers, inositol (1,4,5) trisphosphate (InsP<sub>3</sub>) and diacylglycerol [25,26,36,37]. Phosphoinositides are also critically important for regulating interactions between membranes and cytoskeletal elements [38,39]. Changes in these interactions are critical for cell growth and mobility, and for remodeling of intracellular structures. They may well play a role in cytoskeleton-dependent disk morphogenesis in rods.

### **6. Membrane Trafficking in Retina and RPE**

Every aspect of retinal biology depends heavily on the correct organization and composition of highly specialized membranes, from the unique disc membranes of the photoreceptor sensory cilia, to the ribbon synapses of rods, cones, and bipolar cells, to the apical processes of RPE (retinal pigmented epithelium) cells, uniquely tuned to the detection and engulfment of shed outer segment fragments. The formation, maintenance, and functions of these membranes rely heavily on the phosphorylated phosphoinositides [2–4,40]. Despite the intense interest in phosphoinositide research in recent decades, surprisingly little is known about their regulation and functional roles in the retina, although it is known that disruption of phosphoinositide regulation can lead to blindness in human patients and animal models [41–48]. The membranes and pathways they regulate are known to be essential for the function and health of the retina as well as for disease processes and cellular responses to disease states.

One of the reasons for the dearth of knowledge has been a lack of tools for studying these very low-abundance lipids within the multiple cell types of the retina and the adjacent retinal pigment epithelium. Recently, tools developed by the broader PI field have begun to be applied to the unique challenges and opportunities posed by the retina [22,49]. Doing so will have enormous impact on our understanding of the cell biology of the retina and its disruption in disease. This can help to inform the design and optimization of therapies aimed at treating and preventing retinal dysfunction and degeneration.

### **7. Features of the Retina that Make It Ideal for Studies of Phosphoinositide Regulation In Vivo**

The field of phosphoinositide regulation has long been dominated by studies in cultured immortalized cell lines, giving rise to a critical need for elucidation of their physiological regulation in terminally differentiated neurons. For this reason, in vivo studies have broad significance for this field. There are several features of the retina that make it particularly amenable to studies of phosphoinositide regulation in vivo. These include the ability to assay both structure and function non-invasively, the ease of making cell-type-specific knockouts, the ability to isolate rod cells for either biochemical analysis or ultrastructure determination, an extensive understanding of biochemistry and cell biology,

especially of rods, which exceeds that of any of other vertebrate neurons, and a wealth of knowledge of RPE cell biology.

## 8. Importance of Phosphoinositides for Membrane Trafficking in Retina

Despite years of study, no convincing evidence has accumulated for an important role for phosphoinositides in the phototransduction cascade. In contrast, a steady stream of evidence supports a central role for these lipids in membrane trafficking and sorting in all mammalian cell types, just as a critical role in photoreceptors for membrane sorting and trafficking has long been established [3,50,51]. A review article in 2011 covered advances in understanding the roles of phosphoinositides in photoreceptors [6]. It is highly likely that events such as endocytosis and exocytosis, endosomal sorting, membrane budding, post-Golgi vesicle trafficking, and disk morphogenesis all depend on phosphoinositide dynamics, and published reports support a role for PI(3)P and PI(4,5)P<sub>2</sub> in rhodopsin trafficking [52,53]. For example, PI(4,5)P<sub>2</sub>-binding proteins, ezrin and moesin, were reported to colocalize with Rac1 and Rab8 on rhodopsin transport carrier vesicles at the site of their fusion with the plasma membrane. A recent report suggesting the involvement of actin-nucleating proteins Arp2/Arp3 in basal disc extension [54] potentially implicates local pools of PI(4,5)P<sub>2</sub>, which are known to be critical for their function [55,56].

In cone photoreceptors, ablation of a type I PI-3 kinase leads to enhanced sensitivity to light damage [57]. Mutations in the phosphoinositide phosphatase, synaptojanin 1 lead to defects in synaptic vesicle trafficking in cone cells [44].

## 9. Retinal Cilia and Phosphoinositides

Phosphoinositides, and especially PI(4,5)P<sub>2</sub> and PI(4)P, have been proposed to play important roles in assembly, disassembly, and regulation of primary cilia [52,58–62]. The lipid content of cilia is different from that of the plasma membrane, and a membrane diffusion barrier surrounding the cilium has been demonstrated (see [63] for a review). Two PI-5-phosphatases, INPP5E and OCRL, essential for cilium function have been reported to be localized to the cilium [41,64–66]

### *Phosphoinositides and the BBSome*

The BBSome, a heterooctameric protein complex involved in ciliary trafficking, whose defects lead to the blinding ciliopathy, Bardet–Biedl syndrome, binds to membranes, and shows a preference for acidic lipids, including phosphoinositides [67,68], and isolated BBS5 which contains pleckstrin homology domains, binds to phosphoinositides, especially PI(3)P [68]. More recently, it was shown that a core BBSome complex containing BBS 1, 4, 5, 8, 9 and 18 and a smaller sub-complex lacking BBS1 and BBS5 bind phosphoinositides with similar specificities. A caveat for these studies is that the commercial “PIP strips” used have local surface densities of phosphoinositides that far exceed anything found under physiological conditions, so further investigation of phosphoinositide-binding of the BBSome and its sub-complexes is warranted.

## 10. Autophagy and other Stress Responses Involving Redirection of Membrane Traffic and Phosphoinositides

It has been reported that light exposure induces elements of the autophagy pathway in rods and that autophagy plays an important role in photoreceptor homeostasis [69–73]. This pathway has been suggested to be a neuroprotective one that forestalls apoptosis under conditions of stress [69,74]. This process may be part of a more general neuroprotective response involving re-direction of membrane traffic and phosphoinositides. As discussed below, Synaptojanin-1 has been implicated in autophagy in zebrafish cones [75].



## 11. Evidence for Effects of Light on Phosphoinositide Metabolism

A number of early reports in the 1980s suggested that light had measurable impacts on PI metabolism in photoreceptors or the retina generally. Based on measurement of  $^{32}\text{P}$ i incorporated into PtdIns by metabolic labeling, it was reported that exposure of isolated frog retina to light decreased levels of  $\text{PIP}_2$  by 14% after 5 s and 37% after 15 s, while levels of  $\text{PI}(4)\text{P}$ , PtdIns and other acidic lipids remained essentially constant [76]. Subsequent publications from the same group reported increased levels of  $^3\text{H}$  inositol and  $^{32}\text{P}$  into phosphoinositides upon illumination [77]. They also reported  $\text{PI}(4,5)\text{P}_2$ -specific phospholipase C (PLC) activity in frog photoreceptors, and PLC immunoreactivity in bovine rod outer segments [78,79], as well as PI-kinase and PIP-kinase activities in frog ROS [19]. Another group found that exposure of rat retinas to light led to decreased staining of rod outer segments with anti- $\text{PI}(4,5)\text{P}_2$  antibodies [80,81]. The caveats of those experiments are that it is known that physical properties of outer segment membranes and their protein composition are altered by bright light exposure, and that it is difficult to establish the specificity of such antibody staining. In addition to light, reports on regulation of photoreceptor PLC by  $\text{Ca}^{2+}$  [82] or by subunits of the phototransduction G protein, transducin [83], were published, also suggesting a possible influence of light exposure, which is known to control levels of  $\text{Ca}^{2+}$  and active and inactive forms of transducin subunits.

In contrast, another group [84] reported that bovine rod outer segments have very little PIP kinase activity as compared to the rest of the retina (consistent with the previously reported low level of  $\text{PI}(4,5)\text{P}_2$  in outer segment membranes), and that light adaptation had no measurable effect on phosphoinositide metabolism as compared to in vivo dark adaptation. Yet another group, using metabolic labeling with [ $^3\text{H}$ ]inositol, reported that light led to decreases in  $\text{PIP}_2$  levels without generation of  $\text{InsP}_3$ , suggesting light-dependent activity of a phosphatase rather than of phospholipase C [85]. In vitro studies demonstrated that the presence of  $\text{PI}(4,5)\text{P}_2$  in membranes could affect the activity of components of the phototransduction cascade [86,87], including the cGMP-gated cation channel and the cGMP phosphodiesterase-transducin complex. The physiological relevance of effects of  $\text{PI}(4,5)\text{P}_2$  on phototransduction or of effects of light on  $\text{PI}(4,5)\text{P}_2$  metabolism remains untested, and it seems to be possible to explain the entire time-course of rod light responses without invoking any participation by phosphoinositide metabolism [88]. Antibodies specific for isoforms of phospholipase C or  $\text{G}_{\alpha\text{q}/11}$  PLC-coupled subunits revealed the presence of  $\text{PLC}\beta_4$  and  $\text{G}_{\alpha\text{q}/11}$  in rod outer segments, and  $\text{G}_{\alpha\text{q}}$  and other PKC isoforms elsewhere in the retina [89]. The functional roles of these proteins in outer segments are not known. There have been suggestions that slower effects of prolonged light exposure, such as arrestin translocation from the inner to outer segments of rod cells, may be mediated by a phospholipase C cascade [90].

### *Light Regulation of PI-3 Kinase*

Interest has turned toward Type I PI-3 kinase and  $\text{PI}(3,4,5)\text{P}_3$ , with reports of effects of light on the activity of this enzyme in bovine rod outer segments [91,92], which were reported to be mediated by light-stimulated activation and tyrosine phosphorylation of the insulin receptor [93–95]. Deletion of the  $\text{p85}\alpha$  regulatory subunit of Type I PI-3 kinase in cone cells resulted in progressive degeneration of cones, without observable effects on rod survival [57]. Likewise, cone-specific inactivation of the gene encoding the  $\text{p110}\alpha$  catalytic subunit also resulted in defects in cone survival [96].

In contrast, Type I PI-3 kinase and its product,  $\text{PI}(3,4,5)\text{P}_3$ , seem to be much less important for rod function. Rod-specific ablation of the  $\text{p85}\alpha$  gene using two different rod-specific Cre transgenes yielded no obvious defects in retinal morphology or rod cell survival [22,97], although modest effects on kinetics of light response recovery and arrestin translocation were reported in one case [97]. Quantitative analysis of  $\text{PI}(3,4,5)\text{P}_3$  levels in rods isolated from dark-adapted or light-adapted retinas revealed levels of this phosphoinositide of more than one order magnitude lower than those found for  $\text{PI}(3)\text{P}$  in the light, or at least two orders of magnitude lower than light-stimulated levels of  $\text{PI}(4,5)\text{P}_2$  [22].

## 12. PI(4,5)P<sub>2</sub> and Phospholipase C in Intrinsically Photosensitive Ganglion Cells

In addition to image-forming light detection mediated by rods and cones, the vertebrate retina also contains intrinsically photosensitive retinal ganglion cells. These contain phototransduction cascades reminiscent of that found in invertebrate rhabdomeric photoreceptors [98–104]. Light activates melanopsin, encoded by the *Opn4* gene, a visual pigment which is more closely related to invertebrate opsins than to vertebrate opsin [105]. In M1-type ganglion cells, melanopsin photoisomerization leads to activation of a G<sub>αq/11/14</sub> class G-protein, which activates the phosphoinositide-specific phospholipase C isoform, PLCβ4; the phospholipase presumably acts on PI(4,5)P<sub>2</sub> as in other cell types, including *Drosophila* photoreceptors, which contain a homologous phospholipase, to produce diacylglycerol and InsP<sub>3</sub>. PI(4,5)P<sub>2</sub> hydrolysis, in turn, leads to the activation of the cation channels TRPC6 and TRPC7 [104]. In M4 ganglion cells, a different phototransduction cascade involving cyclic nucleotides and cyclic nucleotide-regulated HCN channels, whereas in M2 ganglion cells, both of these cascades operate [102].

## 13. Studies of PI Metabolism in the RPE

A variety of extracellular stimuli acting on tyrosine kinase-associated receptors or G protein-coupled-receptors have been reported to stimulate release of inositol phosphates in cultured RPE cells, presumably derived from PLC action of PI(4,5)P<sub>2</sub>, on a timescale of tens of minutes; effective stimuli included fetal bovine serum, agonists for muscarinic, histamine, and serotonin, peptides, including bradykinin, arginine vasopressin, bombesin and oxytocin, [106–109]. The physiological relevance of these observations was not explored, but an *in vivo* study using frogs demonstrated dramatic acceleration of inositol phosphate release, especially of InsP<sub>3</sub>, following stimulation by light [21]. Acutely isolated rat RPE cells were reported to release InsP<sub>3</sub> in response to induction of phagocytosis by addition of isolated rod outer segments [110]; this InsP<sub>3</sub> release was not observed in cells from Royal College of Surgeon (RCS) rats, which have a defect in OS phagocytosis due to a deficiency in the receptor tyrosine kinase, MERTK [111]. As in many other cell types, insulin has been reported to stimulate activity of Type I PI-3 kinase to produce PI(3,4,5)P<sub>3</sub> [95,112,113]. Responses to hypoxia [112,114,115] and elevated glucose [116,117] are also reported to involve this pathway in RPE.

A number of important processes in RPE are known to rely on phosphoinositides, but how they are regulated in these cells is not well understood. Phagocytosis, autophagy, endocytosis and endosome processing, establishment of epithelial cell polarity and extension of microvilli membranes are all known to critically depend on phosphoinositides. For example, both autophagy and phagocytosis involve the recruitment of the ubiquitin-like protein, LC3 [118–120], whose recruitment to membranes depends on PI(3)P. Phagocytosis is also thought to require PI(4,5)P<sub>2</sub> and lysosomal fusion may involve other phosphoinositides such as PI(3,5)P<sub>2</sub> and PI(5)P [22,121–125].

## 14. Phosphoinositide Kinases and Phosphatase

In mammals, there are 47 genes encoding 19 PI-kinase and PIP-kinases and 28 PIP phosphatases [126].

### 14.1. Kinases

The kinase isoforms are divided into three major families: PI 4-kinases (PI4Ks), the PI 3-kinases (PI3Ks), and PIP (PIP) kinases (PIPKs) [127]. The nomenclature for these is a bit confusing, as some enzymes termed “PI-kinases” actually act primarily as PIP kinases. For example, Type I PI-3 kinases primarily use PI(4,5)P<sub>2</sub> as their substrate to produce PI(3,4,5)P<sub>3</sub>, and there is little evidence for a substantial portion of cellular PI(3)P being formed by these enzymes. When the Type III PI-3 kinase, Vps34, was knocked out in mouse rod cells and phosphoinositide levels measured, the results suggested complete ablation of PI(3)P despite the presence of the Type I enzyme [22]. Several of these have been reported to be expressed in retina or RPE at the level of protein, mRNA or enzyme activity and most,

if not all, are likely present at some level; however, as far as their functions, only the Type I and Type III PI-3 kinase have been studied using gene knockouts in the retina and RPE [22,49,57,128]. Global knockouts have been produced for the  $\alpha$ ,  $\beta$ , and  $\gamma$  isoforms of Type I PIP-kinases, which are the major source of PI(4,5)P<sub>2</sub> in most cells [16]. Of these, the  $\gamma$  isoform seems to have the highest expression in the retina [129] and in other neurons [130,131] and leads to severe neuronal phenotypes and early postnatal mortality when knocked out [132]. Type II PIP-kinases have been observed in retina and are reported to be regulated by tyrosine phosphorylation [133]. The proteins encoded by the mouse genes, Pip4k2a, Pip4k2b, Pip4k2c, Pip5k1a, and Pip5k1c were all observed in a proteomic study of mouse retina [134].

#### 14.2. Phosphatases

The phosphoinositide phosphatases encoded by Inpp1, Inpp4a, Inpp4b, Inpp5e, Mtmr2 and Synj1 (synaptojanin-1) have also been detected in retina by proteomics [134]. As noted below, defects in synaptojanin-1 and INPP5E are associated with retinal defects, as is the phosphoinositide 5-phosphatase, OCRL (oculocerebrorenal syndrome of Lowe) [135,136]. Among the other enzymes detected, almost none were enriched in the rod outer segment fraction as compared to the rest of the retina, consistent with the relatively low PI content of that organelle. One exception was Pip4k2c, the PI(5)P-4-kinase Type II  $\gamma$  isoform. Inactivation of the mouse *Pip4kc2* gene was found to lead to hyperactivation of the immune system, but the retinal phenotype was not examined [137].

### 15. Retinal Phenotypes of Genetic Defects in Genes Related to Phosphoinositide Metabolism and Signaling

Rods and cones have a very high rate of metabolism and biosynthesis of membrane components, due to the energetic demands of the phototransduction cascade and the daily shedding of ~10% of the disk membranes (based on observation of a rate of 9%–13% in the rhesus monkey [138], which have to be engulfed and recycled by the RPE. As highly polarized cells, their function and health depend critically on efficient and accurate transport of the correct proteins and lipids to the correct compartments. A host of human blinding diseases have been linked to defects in membrane transport and sorting [139,140]. In RPE cells, massive amounts of membrane traffic are associated with their role as professional phagophores. Defects in RPE phagocytosis, as in MERTK deficiency [111,141] and Bestrophin deficiency [142–145], cause retinal degeneration in humans and animal models and have been proposed to play a role in age-related macular degeneration [146].

#### 15.1. Phosphatases and Inherited Retinopathies

Inherited defects in the phosphoinositide phosphatase, INPP5E, are associated with the multi-syndromic ciliopathies, Joubert syndrome and Bardet–Biedl syndrome [147–150], and with retinal degeneration. The substrates for this phosphatase are PI(4,5)P<sub>2</sub> and PI(3,4,5)P<sub>3</sub>, and its critical role in the cilia suggests that regulating levels of PI(4,5)P<sub>2</sub> may be important in ciliogenesis and cilium stability.

Synaptojanins are phosphoinositide phosphatases associated with synaptic function [151–153], including vesicle uncoating and endocytosis. Synaptojanin-1 deficiency causes severe cone defects in zebrafish and has been implicated in the regulation of autophagy in cones [45,46,75].

Defects in another phosphoinositide phosphatase, OCRL, are associated with a severe ciliopathy, oculocerebrorenal syndrome of Lowe [136]. Symptoms of this disease include glaucoma, a disease of the retina.

#### 15.2. PI3NM3

The phosphatidyl inositol transfer protein PIT3NM3 (aka CCL118) is the mammalian homologue of the *Drosophila* retinal degeneration gene, *rdgB*, and defects in it are associated with autosomal dominant cone-rod dystrophy CORD5 [154–159]. The protein has also been implicated in cancer



metastasis [160]. In zebrafish, the Class I phosphatidylinositol transfer protein  $\beta$  isoform, Pitpnb, is essential for biogenesis and maintenance of double cones [161].

### 15.3. PI Binding Proteins

Proteins with phosphoinositide-binding domains have also been associated with retinal disease. These include the product of the *tub/TUB* gene [162,163] and a related protein, TULP1 [47,164–166]. Tub was discovered as the protein encoded by a gene whose mutation in *tubby* mice causes obesity, deafness and blindness. The widely expressed members of the *tubby* family, including TULP1–TULP4, have a characteristic carboxyl-terminal *tubby* domain consisting of an alpha helix surrounded by a beta barrel which has been shown to bind to specific phosphoinositides [167]. Both Tub and Tulp1 are expressed in the retina, and TULP1 mutations cause retinitis pigmentosa [47,168].

## 16. Conclusions

While the overall field of phosphoinositide regulation and signaling has made dramatic advances in recent years, our understanding of specific regulatory pathways in specific cell types of the retina remains limited. The emergence of new technologies for cell-type-specific gene manipulation, along with imaging techniques for subcellular localization of phosphoinositides, their regulatory enzymes and their effector proteins, and the development of more sensitive methods for measuring PI levels, bodes well for rapid progress in understanding the roles of retinal phosphoinositides in the coming years.

**Funding:** The author's research in this area has been supported by NIH grants R01-EY007981, R01-EY025218 and the Robert A. Welch Foundation, Q0035.

**Conflicts of Interest:** The author declares no conflicts of interest relevant to this paper.

## References

- Phan, T.K.; Williams, S.A.; Bindra, G.K.; Lay, F.T.; Poon, I.K.H.; Hulett, M.D. Phosphoinositides: Multipurpose cellular lipids with emerging roles in cell death. *Cell Death Differ.* **2019**, *26*, 781–793. [[CrossRef](#)] [[PubMed](#)]
- Dickson, E.J.; Hille, B. Understanding phosphoinositides: Rare, dynamic, and essential membrane phospholipids. *Biochem. J.* **2019**, *476*, 1–23. [[CrossRef](#)] [[PubMed](#)]
- Schink, K.O.; Tan, K.W.; Stenmark, H. Phosphoinositides in Control of Membrane Dynamics. *Annu. Rev. Cell Dev. Biol.* **2016**, *32*, 143–171. [[CrossRef](#)] [[PubMed](#)]
- Balla, T. Phosphoinositides: Tiny lipids with giant impact on cell regulation. *Physiol. Rev.* **2013**, *93*, 1019–1137. [[CrossRef](#)]
- Maffucci, T. An introduction to phosphoinositides. *Curr. Top. Microbiol. Immunol.* **2012**, *362*, 1–42. [[CrossRef](#)]
- Brockerhoff, S.E. Phosphoinositides and photoreceptors. *Mol. Neurobiol.* **2011**, *44*, 420–425. [[CrossRef](#)]
- Broekhuysse, R.M. Phospholipids in tissues of the eye. I. Isolation, characterization and quantitative analysis by two-dimensional thin-layer chromatography of diacyl and vinyl-ether phospholipids. *Biochim. Biophys. Acta* **1968**, *152*, 307–315. [[CrossRef](#)]
- Anderson, R.E.; Feldman, L.S.; Feldman, G.L. Lipids of ocular tissues. II. The phospholipids of mature bovine and rabbit whole retina. *Biochim. Biophys. Acta* **1970**, *202*, 367–373. [[CrossRef](#)]
- Anderson, R.E. Lipids of ocular tissues. IV. A comparison of the phospholipids from the retina of six mammalian species. *Exp. Eye Res.* **1970**, *10*, 339–344. [[CrossRef](#)]
- Anderson, R.E.; Maude, M.B.; Zimmerman, W. Lipids of ocular tissues—X. Lipid composition of subcellular fractions of bovine retina. *Vision Res.* **1975**, *15*, 1087–1090. [[CrossRef](#)]
- Anderson, R.E.; Maude, M.B. Phospholipids of bovine outer segments. *Biochemistry* **1970**, *9*, 3624–3628. [[CrossRef](#)] [[PubMed](#)]
- Nielsen, N.C.; Fleischer, S.; McConnell, D.G. Lipid composition of bovine retinal outer segment fragments. *Biochim. Biophys. Acta* **1970**, *211*, 10–19. [[CrossRef](#)]
- Anderson, R.E.; Risk, M. Lipids of ocular tissues. IX. The phospholipids of frog photoreceptor membranes. *Vision Res.* **1974**, *14*, 129–131. [[CrossRef](#)]

14. Anderson, R.E.; Lissandrello, P.M.; Maude, M.B.; Matthes, M.T. Lipids of bovine retinal pigment epithelium. *Exp. Eye Res.* **1976**, *23*, 149–157. [[CrossRef](#)]
15. Balla, T. Inositol-lipid binding motifs: Signal integrators through protein-lipid and protein-protein interactions. *J. Cell Sci.* **2005**, *118*, 2093–2104. [[CrossRef](#)] [[PubMed](#)]
16. Choi, S.; Thapa, N.; Tan, X.; Hedman, A.C.; Anderson, R.A. PIP kinases define PI4,5P(2) signaling specificity by association with effectors. *Biochim. Biophys. Acta* **2015**, *1851*, 711–723. [[CrossRef](#)]
17. Lemmon, M.A. Membrane recognition by phospholipid-binding domains. *Nat. Rev. Mol. Cell Biol.* **2008**, *9*, 99–111. [[CrossRef](#)]
18. Anderson, R.E.; Maude, M.B.; Kelleher, P.A. Metabolism of phosphatidylinositol in the frog retina. *Biochim. Biophys. Acta* **1980**, *620*, 236–246. [[CrossRef](#)]
19. Choe, H.G.; Ghalayini, A.J.; Anderson, R.E. Phosphoinositide metabolism in frog rod outer segments. *Exp. Eye Res.* **1990**, *51*, 167–176. [[CrossRef](#)]
20. Gehm, B.D.; Mc Connell, D.G. Phosphoinositide synthesis in bovine rod outer segments. *Biochemistry* **1990**, *29*, 5442–5446. [[CrossRef](#)]
21. Rodriguez de Turco, E.B.; Gordon, W.C.; Bazan, N.G. Light stimulates in vivo inositol lipid turnover in frog retinal pigment epithelial cells at the onset of shedding and phagocytosis of photoreceptor membranes. *Exp. Eye Res.* **1992**, *55*, 719–725. [[CrossRef](#)]
22. He, F.; Agosto, M.A.; Anastassov, I.A.; Tse, D.Y.; Wu, S.M.; Wensel, T.G. Phosphatidylinositol-3-phosphate is light-regulated and essential for survival in retinal rods. *Sci. Rep.* **2016**, *6*, 26978. [[CrossRef](#)]
23. Stephens, L.R.; Jackson, T.R.; Hawkins, P.T. Agonist-stimulated synthesis of phosphatidylinositol(3,4,5)-trisphosphate: A new intracellular signalling system? *Biochim. Biophys. Acta* **1993**, *1179*, 27–75. [[CrossRef](#)]
24. Bui, H.H.; Sanders, P.E.; Bodenmiller, D.; Kuo, M.S.; Donoho, G.P.; Fischl, A.S. Direct analysis of PI(3,4,5)P3 using liquid chromatography electrospray ionization tandem mass spectrometry. *Anal. Biochem.* **2018**, *547*, 66–76. [[CrossRef](#)]
25. Kadamur, G.; Ross, E.M. Mammalian phospholipase C. *Annu. Rev. Physiol.* **2013**, *75*, 127–154. [[CrossRef](#)]
26. Trebak, M.; Lemonnier, L.; Smyth, J.T.; Vazquez, G.; Putney, J.W., Jr. Phospholipase C-coupled receptors and activation of TRPC channels. *Handb Exp. Pharmacol.* **2007**, 593–614.
27. Wang, L.; Budolfson, K.; Wang, F. Pik3c3 deletion in pyramidal neurons results in loss of synapses, extensive gliosis and progressive neurodegeneration. *Neuroscience* **2011**, *172*, 427–442. [[CrossRef](#)]
28. Zhou, X.; Wang, L.; Hasegawa, H.; Amin, P.; Han, B.X.; Kaneko, S.; He, Y.; Wang, F. Deletion of PIK3C3/Vps34 in sensory neurons causes rapid neurodegeneration by disrupting the endosomal but not the autophagic pathway. *Proc. Natl. Acad. Sci. USA* **2010**, *107*, 9424–9429. [[CrossRef](#)]
29. Carnero, A.; Blanco-Aparicio, C.; Renner, O.; Link, W.; Leal, J.F. The PTEN/PI3K/AKT signalling pathway in cancer, therapeutic implications. *Curr. Cancer Drug Targets* **2008**, *8*, 187–198. [[CrossRef](#)]
30. Carpentier, S.; N’Kuli, F.; Grieco, G.; Van Der Smissen, P.; Janssens, V.; Emonard, H.; Bilanges, B.; Vanhaesebroeck, B.; Gaide Chevronnay, H.P.; Pierreux, C.E.; et al. Class III phosphoinositide 3-kinase/VPS34 and dynamin are critical for apical endocytic recycling. *Traffic* **2013**, *14*, 933–948. [[CrossRef](#)]
31. Dall’Armi, C.; Devereaux, K.A.; Di Paolo, G. The role of lipids in the control of autophagy. *Curr. Biol.* **2013**, *23*, R33–R45. [[CrossRef](#)]
32. Lenoir, M.; Overduin, M. PtdIns(4)P signalling and recognition systems. *Adv. Exp. Med. Biol.* **2013**, *991*, 59–83. [[CrossRef](#)]
33. McLaughlin, S.; Wang, J.; Gambhir, A.; Murray, D. PIP(2) and proteins: Interactions, organization, and information flow. *Annu. Rev. Biophys. Biomol. Struct.* **2002**, *31*, 151–175. [[CrossRef](#)]
34. Falkenburger, B.H.; Jensen, J.B.; Dickson, E.J.; Suh, B.C.; Hille, B. Phosphoinositides: Lipid regulators of membrane proteins. *J. Physiol.* **2010**, *588*, 3179–3185. [[CrossRef](#)]
35. Hilgemann, D.W.; Feng, S.; Nasuhoglu, C. The complex and intriguing lives of PIP2 with ion channels and transporters. *Sci. STKE* **2001**, *2001*, re19. [[CrossRef](#)]
36. Fukami, K.; Inanobe, S.; Kanemaru, K.; Nakamura, Y. Phospholipase C is a key enzyme regulating intracellular calcium and modulating the phosphoinositide balance. *Prog. Lipid Res.* **2010**, *49*, 429–437. [[CrossRef](#)]
37. Vines, C.M. Phospholipase C. *Adv. Exp. Med. Biol.* **2012**, *740*, 235–254. [[CrossRef](#)]
38. Shewan, A.; Eastburn, D.J.; Mostov, K. Phosphoinositides in cell architecture. *Cold Spring Harb. Perspect. Biol.* **2011**, *3*, a004796. [[CrossRef](#)]

39. Yin, H.L.; Janmey, P.A. Phosphoinositide regulation of the actin cytoskeleton. *Annu. Rev. Physiol.* **2003**, *65*, 761–789. [[CrossRef](#)]
40. Hille, B.; Dickson, E.J.; Kruse, M.; Vivas, O.; Suh, B.C. Phosphoinositides regulate ion channels. *Biochim. Biophys. Acta* **2015**, *1851*, 844–856. [[CrossRef](#)]
41. Bielas, S.L.; Silhavy, J.L.; Brancati, F.; Kisseleva, M.V.; Al-Gazali, L.; Sztriha, L.; Bayoumi, R.A.; Zaki, M.S.; Abdel-Aleem, A.; Rosti, R.O.; et al. Mutations in INPP5E, encoding inositol polyphosphate-5-phosphatase E, link phosphatidylinositol signaling to the ciliopathies. *Nat. Genet.* **2009**, *41*, 1032–1036. [[CrossRef](#)]
42. Jacoby, M.; Cox, J.J.; Gayral, S.; Hampshire, D.J.; Ayub, M.; Blockmans, M.; Pernot, E.; Kisseleva, M.V.; Compere, P.; Schiffmann, S.N.; et al. INPP5E mutations cause primary cilium signaling defects, ciliary instability and ciliopathies in human and mouse. *Nat. Genet.* **2009**, *41*, 1027–1031. [[CrossRef](#)]
43. Saar, K.; Al-Gazali, L.; Sztriha, L.; Rueschendorf, F.; Nur, E.K.M.; Reis, A.; Bayoumi, R. Homozygosity mapping in families with Joubert syndrome identifies a locus on chromosome 9q34.3 and evidence for genetic heterogeneity. *Am. J. Hum. Genet.* **1999**, *65*, 1666–1671. [[CrossRef](#)] [[PubMed](#)]
44. George, A.A.; Hayden, S.; Holzhausen, L.C.; Ma, E.Y.; Suzuki, S.C.; Brockerhoff, S.E. Synaptojanin 1 is required for endolysosomal trafficking of synaptic proteins in cone photoreceptor inner segments. *PLoS ONE* **2014**, *9*, e84394. [[CrossRef](#)] [[PubMed](#)]
45. Holzhausen, L.C.; Lewis, A.A.; Cheong, K.K.; Brockerhoff, S.E. Differential role for synaptojanin 1 in rod and cone photoreceptors. *J. Comp. Neurol.* **2009**, *517*, 633–644. [[CrossRef](#)]
46. Van Epps, H.A.; Hayashi, M.; Lucast, L.; Stearns, G.W.; Hurley, J.B.; De Camilli, P.; Brockerhoff, S.E. The zebrafish nrc mutant reveals a role for the polyphosphoinositide phosphatase synaptojanin 1 in cone photoreceptor ribbon anchoring. *J. Neurosci.* **2004**, *24*, 8641–8650. [[CrossRef](#)]
47. Hagstrom, S.A.; North, M.A.; Nishina, P.L.; Berson, E.L.; Dryja, T.P. Recessive mutations in the gene encoding the tubby-like protein TULP1 in patients with retinitis pigmentosa. *Nat. Genet.* **1998**, *18*, 174–176. [[CrossRef](#)]
48. Jacobson, S.G.; Cideciyan, A.V.; Huang, W.C.; Sumaroka, A.; Roman, A.J.; Schwartz, S.B.; Luo, X.; Sheplock, R.; Dauber, J.M.; Swider, M.; et al. TULP1 mutations causing early-onset retinal degeneration: Preserved but insensitive macular cones. *Invest. Ophthalmol. Vis. Sci.* **2014**, *55*, 5354–5364. [[CrossRef](#)]
49. He, F.; Nichols, R.M.; Kailasam, L.; Wensel, T.G.; Agosto, M.A. Critical Role for Phosphatidylinositol-3 Kinase Vps34/PIK3C3 in ON-Bipolar Cells. *Invest. Ophthalmol. Vis. Sci.* **2019**, *60*, 2861–2874. [[CrossRef](#)]
50. Hammond, G.R.; Hong, Y. Phosphoinositides and Membrane Targeting in Cell Polarity. *Cold Spring Harb. Perspect. Biol.* **2018**, *10*. [[CrossRef](#)]
51. Mayinger, P. Phosphoinositides and vesicular membrane traffic. *Biochim. Biophys. Acta* **2012**, *1821*, 1104–1113. [[CrossRef](#)] [[PubMed](#)]
52. Chuang, J.Z.; Zhao, Y.; Sung, C.H. SARA-regulated vesicular targeting underlies formation of the light-sensing organelle in mammalian rods. *Cell* **2007**, *130*, 535–547. [[CrossRef](#)] [[PubMed](#)]
53. Deretic, D.; Traverso, V.; Parkins, N.; Jackson, F.; Rodriguez de Turco, E.B.; Ransom, N. Phosphoinositides, ezrin/moesin, and rac1 regulate fusion of rhodopsin transport carriers in retinal photoreceptors. *Mol. Biol. Cell* **2004**, *15*, 359–370. [[CrossRef](#)] [[PubMed](#)]
54. Spencer, W.J.; Lewis, T.R.; Phan, S.; Cady, M.A.; Serebrovskaya, E.O.; Schneider, N.F.; Kim, K.Y.; Cameron, L.A.; Skiba, N.P.; Ellisman, M.H.; et al. Photoreceptor disc membranes are formed through an Arp2/3-dependent lamellipodium-like mechanism. *Proc. Natl. Acad. Sci. USA* **2019**. [[CrossRef](#)]
55. Bucki, R.; Wang, Y.H.; Yang, C.; Kandy, S.K.; Fatunmbi, O.; Bradley, R.; Pogoda, K.; Svitkina, T.; Radhakrishnan, R.; Janmey, P.A. Lateral distribution of phosphatidylinositol 4,5-bisphosphate in membranes regulates formin- and ARP2/3-mediated actin nucleation. *J. Biol. Chem.* **2019**, *294*, 4704–4722. [[CrossRef](#)]
56. Daste, F.; Walrant, A.; Holst, M.R.; Gadsby, J.R.; Mason, J.; Lee, J.E.; Brook, D.; Mettlen, M.; Larsson, E.; Lee, S.F.; et al. Control of actin polymerization via the coincidence of phosphoinositides and high membrane curvature. *J. Cell Biol.* **2017**, *216*, 3745–3765. [[CrossRef](#)]
57. Ivanovic, I.; Anderson, R.E.; Le, Y.Z.; Fliesler, S.J.; Sherry, D.M.; Rajala, R.V. Deletion of the p85alpha regulatory subunit of phosphoinositide 3-kinase in cone photoreceptor cells results in cone photoreceptor degeneration. *Invest. Ophthalmol. Vis. Sci.* **2011**, *52*, 3775–3783. [[CrossRef](#)]
58. Xu, W.; Jin, M.; Huang, W.; Wang, H.; Hu, R.; Li, J.; Cao, Y. Apical PtdIns(4,5)P2 is required for ciliogenesis and suppression of polycystic kidney disease. *FASEB J.* **2019**, *33*, 2848–2857. [[CrossRef](#)]
59. Phua, S.C.; Nihongaki, Y.; Inoue, T. Autonomy declared by primary cilia through compartmentalization of membrane phosphoinositides. *Curr. Opin. Cell Biol.* **2018**, *50*, 72–78. [[CrossRef](#)]

60. Park, J.; Lee, N.; Kavoussi, A.; Seo, J.T.; Kim, C.H.; Moon, S.J. Ciliary Phosphoinositide Regulates Ciliary Protein Trafficking in *Drosophila*. *Cell Rep.* **2015**, *13*, 2808–2816. [[CrossRef](#)]
61. Garcia-Gonzalo, F.R.; Phua, S.C.; Roberson, E.C.; Garcia, G., 3rd; Abedin, M.; Schurmans, S.; Inoue, T.; Reiter, J.F. Phosphoinositides Regulate Ciliary Protein Trafficking to Modulate Hedgehog Signaling. *Dev. Cell* **2015**, *34*, 400–409. [[CrossRef](#)] [[PubMed](#)]
62. Vieira, O.V.; Gaus, K.; Verkade, P.; Fullekrug, J.; Vaz, W.L.; Simons, K. FAPP2, cilium formation, and compartmentalization of the apical membrane in polarized Madin-Darby canine kidney (MDCK) cells. *Proc. Natl. Acad. Sci. USA* **2006**, *103*, 18556–18561. [[CrossRef](#)] [[PubMed](#)]
63. Nachury, M.V.; Seeley, E.S.; Jin, H. Trafficking to the ciliary membrane: How to get across the periciliary diffusion barrier? *Annu. Rev. Cell Dev. Biol.* **2010**, *26*, 59–87. [[CrossRef](#)] [[PubMed](#)]
64. Luo, N.; West, C.C.; Murga-Zamalloa, C.A.; Sun, L.; Anderson, R.M.; Wells, C.D.; Weinreb, R.N.; Travers, J.B.; Khanna, H.; Sun, Y. OCRL localizes to the primary cilium: A new role for cilia in Lowe syndrome. *Hum. Mol. Genet.* **2012**, *21*, 3333–3344. [[CrossRef](#)] [[PubMed](#)]
65. Coon, B.G.; Hernandez, V.; Madhivanan, K.; Mukherjee, D.; Hanna, C.B.; Barinaga-Rementería Ramirez, I.; Lowe, M.; Beales, P.L.; Aguilar, R.C. The Lowe syndrome protein OCRL1 is involved in primary cilia assembly. *Hum. Mol. Genet.* **2012**, *21*, 1835–1847. [[CrossRef](#)] [[PubMed](#)]
66. Humbert, M.C.; Weihbrecht, K.; Searby, C.C.; Li, Y.; Pope, R.M.; Sheffield, V.C.; Seo, S. ARL13B, PDE6D, and CEP164 form a functional network for INPP5E ciliary targeting. *Proc. Natl. Acad. Sci. USA* **2012**, *109*, 19691–19696. [[CrossRef](#)] [[PubMed](#)]
67. Jin, H.; White, S.R.; Shida, T.; Schulz, S.; Aguiar, M.; Gygi, S.P.; Bazan, J.F.; Nachury, M.V. The conserved Bardet-Biedl syndrome proteins assemble a coat that traffics membrane proteins to cilia. *Cell* **2010**, *141*, 1208–1219. [[CrossRef](#)]
68. Nachury, M.V.; Loktev, A.V.; Zhang, Q.; Westlake, C.J.; Peranen, J.; Merdes, A.; Slusarski, D.C.; Scheller, R.H.; Bazan, J.F.; Sheffield, V.C.; et al. A core complex of BBS proteins cooperates with the GTPase Rab8 to promote ciliary membrane biogenesis. *Cell* **2007**, *129*, 1201–1213. [[CrossRef](#)]
69. Chinskey, N.D.; Zheng, Q.D.; Zacks, D.N. Control of Photoreceptor Autophagy after Retinal Detachment: The Switch from Survival to Death. *Invest. Ophthalmol. Vis. Sci.* **2014**, *55*, 688–695. [[CrossRef](#)]
70. Reme, C.; Drinker, C.K.; Aeberhard, B. Modification of autophagic degradation by medium- and illumination conditions in frog visual cells in vitro. *Doc. Ophthalmol.* **1984**, *56*, 377–383. [[CrossRef](#)]
71. Reme, C. Autophagy in rods and cones of the vertebrate retina. *Dev. Ophthalmol.* **1981**, *4*, 101–148.
72. Reme, C.E.; Sulser, M. Diurnal variation of autophagy in rod visual cells in the rat. *Albrecht Von Graefes Arch. Klin. Exp. Ophthalmol.* **1977**, *203*, 261–270. [[CrossRef](#)]
73. Chen, Y.; Sawada, O.; Kohno, H.; Le, Y.Z.; Subauste, C.; Maeda, T.; Maeda, A. Autophagy protects the retina from light-induced degeneration. *J. Biol. Chem.* **2013**, *288*, 7506–7518. [[CrossRef](#)] [[PubMed](#)]
74. Besirli, C.G.; Chinskey, N.D.; Zheng, Q.D.; Zacks, D.N. Autophagy activation in the injured photoreceptor inhibits fas-mediated apoptosis. *Invest. Ophthalmol. Vis. Sci.* **2011**, *52*, 4193–4199. [[CrossRef](#)] [[PubMed](#)]
75. George, A.A.; Hayden, S.; Stanton, G.R.; Brockerhoff, S.E. Arf6 and the 5'phosphatase of synaptojanin 1 regulate autophagy in cone photoreceptors. *Bioessays* **2016**, *38* (Suppl. 1), S119–S135. [[CrossRef](#)]
76. Ghalayini, A.; Anderson, R.E. Phosphatidylinositol 4,5-bisphosphate: Light-mediated breakdown in the vertebrate retina. *Biochem. Biophys. Res. Commun.* **1984**, *124*, 503–506. [[CrossRef](#)]
77. Anderson, R.E.; Maude, M.B.; Pu, G.A.; Hollyfield, J.G. Effect of light on the metabolism of lipids in the rat retina. *J. Neurochem.* **1985**, *44*, 773–778. [[CrossRef](#)] [[PubMed](#)]
78. Tarver, A.P.; Anderson, R.E. Phospholipase C activity and substrate specificity in frog photoreceptors. *Exp. Eye Res.* **1988**, *46*, 29–35. [[CrossRef](#)]
79. Ghalayini, A.J.; Tarver, A.P.; Mackin, W.M.; Koutz, C.A.; Anderson, R.E. Identification and immunolocalization of phospholipase C in bovine rod outer segments. *J. Neurochem.* **1991**, *57*, 1405–1412. [[CrossRef](#)]
80. Das, N.D.; Yoshioka, T.; Samuelson, D.; Shichi, H. Immunocytochemical localization of phosphatidylinositol-4,5-bisphosphate in dark- and light-adapted rat retinas. *Cell Struct. Funct.* **1986**, *11*, 53–63. [[CrossRef](#)]
81. Das, N.D.; Yoshioka, T.; Samuelson, D.; Cohen, R.J.; Shichi, H. Immunocytochemical evidence for the light-regulated modulation of phosphatidylinositol-4,5-bisphosphate in rat photoreceptor cells. *Cell Struct. Funct.* **1987**, *12*, 471–481. [[CrossRef](#)] [[PubMed](#)]



82. Panfoli, I.; Morelli, A.; Pepe, I. Calcium ion-regulated phospholipase C activity in bovine rod outer segments. *Biochem. Biophys. Res. Commun.* **1990**, *173*, 283–288. [[CrossRef](#)]
83. Grigorjev, I.V.; Grits, A.I.; Artamonov, I.D.; Baranova, L.A.; Volotovskii, I.D. betagamma-Transducin stimulates hydrolysis and synthesis of phosphatidylinositol 4,5-bisphosphate in bovine rod outer segment membranes. *Biochim. Biophys. Acta* **1996**, *1310*, 131–136. [[CrossRef](#)]
84. Van Rooijen, L.A.; Bazan, N.G. The inositide cycle in bovine photoreceptor membranes. *Life Sci.* **1986**, *38*, 1685–1693. [[CrossRef](#)]
85. Millar, F.A.; Fisher, S.C.; Muir, C.A.; Edwards, E.; Hawthorne, J.N. Polyphosphoinositide hydrolysis in response to light stimulation of rat and chick retina and retinal rod outer segments. *Biochim. Biophys. Acta* **1988**, *970*, 205–211. [[CrossRef](#)]
86. He, F.; Mao, M.; Wensel, T.G. Enhancement of phototransduction G protein-effector interactions by phosphoinositides. *J. Biol. Chem.* **2004**, *279*, 8986–8990. [[CrossRef](#)]
87. Womack, K.B.; Gordon, S.E.; He, F.; Wensel, T.G.; Lu, C.C.; Hilgemann, D.W. Do phosphatidylinositides modulate vertebrate phototransduction? *J. Neurosci.* **2000**, *20*, 2792–2799. [[CrossRef](#)]
88. Gross, O.P.; Pugh, E.N., Jr.; Burns, M.E. Spatiotemporal cGMP dynamics in living mouse rods. *Biophys. J.* **2012**, *102*, 1775–1784. [[CrossRef](#)]
89. Peng, Y.W.; Rhee, S.G.; Yu, W.P.; Ho, Y.K.; Schoen, T.; Chader, G.J.; Yau, K.W. Identification of components of a phosphoinositide signaling pathway in retinal rod outer segments. *Proc. Natl. Acad. Sci. USA* **1997**, *94*, 1995–2000. [[CrossRef](#)]
90. Orisme, W.; Li, J.; Goldmann, T.; Bolch, S.; Wolfrum, U.; Smith, W.C. Light-dependent translocation of arrestin in rod photoreceptors is signaled through a phospholipase C cascade and requires ATP. *Cell Signal.* **2010**, *22*, 447–456. [[CrossRef](#)]
91. Guo, X.; Ghalayini, A.J.; Chen, H.; Anderson, R.E. Phosphatidylinositol 3-kinase in bovine photoreceptor rod outer segments. *Invest. Ophthalmol. Vis. Sci.* **1997**, *38*, 1873–1882. [[PubMed](#)]
92. Guo, X.X.; Huang, Z.; Bell, M.W.; Chen, H.; Anderson, R.E. Tyrosine phosphorylation is involved in phosphatidylinositol 3-kinase activation in bovine rod outer segments. *Mol. Vis.* **2000**, *6*, 216–221. [[PubMed](#)]
93. Rajala, R.V.; McClellan, M.E.; Chan, M.D.; Tsiokas, L.; Anderson, R.E. Interaction of the retinal insulin receptor beta-subunit with the p85 subunit of phosphoinositide 3-kinase. *Biochemistry* **2004**, *43*, 5637–5650. [[CrossRef](#)] [[PubMed](#)]
94. Rajala, R.V.; Anderson, R.E. Light regulation of the insulin receptor in the retina. *Mol. Neurobiol.* **2003**, *28*, 123–138. [[CrossRef](#)]
95. Rajala, R.V.; McClellan, M.E.; Ash, J.D.; Anderson, R.E. In vivo regulation of phosphoinositide 3-kinase in retina through light-induced tyrosine phosphorylation of the insulin receptor beta-subunit. *J. Biol. Chem.* **2002**, *277*, 43319–43326. [[CrossRef](#)] [[PubMed](#)]
96. Rajala, R.V.; Ranjo-Bishop, M.; Wang, Y.; Rajala, A.; Anderson, R.E. The p110alpha isoform of phosphoinositide 3-kinase is essential for cone photoreceptor survival. *Biochimie* **2015**, *112*, 35–40. [[CrossRef](#)] [[PubMed](#)]
97. Ivanovic, I.; Allen, D.T.; Dighe, R.; Le, Y.Z.; Anderson, R.E.; Rajala, R.V. Phosphoinositide 3-kinase signaling in retinal rod photoreceptors. *Invest. Ophthalmol. Vis. Sci.* **2011**, *52*, 6355–6362. [[CrossRef](#)]
98. Detwiler, P.B. Phototransduction in Retinal Ganglion Cells. *Yale J. Biol. Med.* **2018**, *91*, 49–52.
99. Graham, D.M.; Wong, K.Y.; Shapiro, P.; Frederick, C.; Pattabiraman, K.; Berson, D.M. Melanopsin ganglion cells use a membrane-associated rhabdomic phototransduction cascade. *J. Neurophysiol.* **2008**, *99*, 2522–2532. [[CrossRef](#)]
100. Hardie, R.C. Photosensitive TRPs. *Handb. Exp. Pharmacol.* **2014**, *223*, 795–826. [[CrossRef](#)]
101. Isoldi, M.C.; Rollag, M.D.; Castrucci, A.M.; Provencio, I. Rhabdomic phototransduction initiated by the vertebrate photopigment melanopsin. *Proc. Natl. Acad. Sci. USA* **2005**, *102*, 1217–1221. [[CrossRef](#)] [[PubMed](#)]
102. Jiang, Z.; Yue, W.W.S.; Chen, L.; Sheng, Y.; Yau, K.W. Cyclic-Nucleotide- and HCN-Channel-Mediated Phototransduction in Intrinsically Photosensitive Retinal Ganglion Cells. *Cell* **2018**, *175*, 652–664 e612. [[CrossRef](#)]
103. Montell, C. Drosophila visual transduction. *Trends Neurosci.* **2012**, *35*, 356–363. [[CrossRef](#)] [[PubMed](#)]
104. Xue, T.; Do, M.T.; Riccio, A.; Jiang, Z.; Hsieh, J.; Wang, H.C.; Merbs, S.L.; Welsbie, D.S.; Yoshioka, T.; Weissgerber, P.; et al. Melanopsin signalling in mammalian iris and retina. *Nature* **2011**, *479*, 67–73. [[CrossRef](#)] [[PubMed](#)]
105. Arendt, D. Evolution of eyes and photoreceptor cell types. *Int. J. Dev. Biol.* **2003**, *47*, 563–571. [[PubMed](#)]



106. Kuriyama, S.; Ohuchi, T.; Yoshimura, N.; Honda, Y. Growth factor-induced cytosolic calcium ion transients in cultured human retinal pigment epithelial cells. *Invest. Ophthalmol. Vis. Sci.* **1991**, *32*, 2882–2890.
107. Osborne, N.N.; FitzGibbon, F.; Schwartz, G. Muscarinic acetylcholine receptor-mediated phosphoinositide turnover in cultured human retinal pigment epithelium cells. *Vision Res.* **1991**, *31*, 1119–1127. [[CrossRef](#)]
108. Feldman, E.L.; Randolph, A.E.; Johnston, G.C.; DelMonte, M.A.; Greene, D.A. Receptor-coupled phosphoinositide hydrolysis in human retinal pigment epithelium. *J. Neurochem.* **1991**, *56*, 2094–2100. [[CrossRef](#)]
109. York, N.; Halbach, P.; Chiu, M.A.; Bird, I.M.; Pillers, D.M.; Pattnaik, B.R. Oxytocin (OXT)-stimulated inhibition of Kir7.1 activity is through PIP2-dependent Ca(2+) response of the oxytocin receptor in the retinal pigment epithelium in vitro. *Cell Signal.* **2017**, *37*, 93–102. [[CrossRef](#)]
110. Heth, C.A.; Marescalchi, P.A. Inositol triphosphate generation in cultured rat retinal pigment epithelium. *Invest. Ophthalmol. Vis. Sci.* **1994**, *35*, 409–416.
111. D’Cruz, P.M.; Yasumura, D.; Weir, J.; Matthes, M.T.; Abderrahim, H.; LaVail, M.M.; Vollrath, D. Mutation of the receptor tyrosine kinase gene Mertk in the retinal dystrophic RCS rat. *Hum. Mol. Genet.* **2000**, *9*, 645–651. [[CrossRef](#)] [[PubMed](#)]
112. Treins, C.; Giorgetti-Peraldi, S.; Murdaca, J.; Semenza, G.L.; Van Obberghen, E. Insulin stimulates hypoxia-inducible factor 1 through a phosphatidylinositol 3-kinase/target of rapamycin-dependent signaling pathway. *J. Biol. Chem.* **2002**, *277*, 27975–27981. [[CrossRef](#)] [[PubMed](#)]
113. Geraldès, P.; Yagi, K.; Ohshiro, Y.; He, Z.; Maeno, Y.; Yamamoto-Hiraoka, J.; Rask-Madsen, C.; Chung, S.W.; Perrella, M.A.; King, G.L. Selective regulation of heme oxygenase-1 expression and function by insulin through IRS1/phosphoinositide 3-kinase/Akt-2 pathway. *J. Biol. Chem.* **2008**, *283*, 34327–34336. [[CrossRef](#)]
114. Mwaikambo, B.R.; Yang, C.; Chemtob, S.; Hardy, P. Hypoxia up-regulates CD36 expression and function via hypoxia-inducible factor-1- and phosphatidylinositol 3-kinase-dependent mechanisms. *J. Biol. Chem.* **2009**, *284*, 26695–26707. [[CrossRef](#)]
115. Yang, X.M.; Wang, Y.S.; Zhang, J.; Li, Y.; Xu, J.F.; Zhu, J.; Zhao, W.; Chu, D.K.; Wiedemann, P. Role of PI3K/Akt and MEK/ERK in mediating hypoxia-induced expression of HIF-1 $\alpha$  and VEGF in laser-induced rat choroidal neovascularization. *Invest. Ophthalmol. Vis. Sci.* **2009**, *50*, 1873–1879. [[CrossRef](#)]
116. Kim, D.I.; Lim, S.K.; Park, M.J.; Han, H.J.; Kim, G.Y.; Park, S.H. The involvement of phosphatidylinositol 3-kinase/Akt signaling in high glucose-induced downregulation of GLUT-1 expression in ARPE cells. *Life Sci.* **2007**, *80*, 626–632. [[CrossRef](#)]
117. Qin, D.; Zhang, G.M.; Xu, X.; Wang, L.Y. The PI3K/Akt signaling pathway mediates the high glucose-induced expression of extracellular matrix molecules in human retinal pigment epithelial cells. *J. Diabetes Res.* **2015**, *2015*, 920280. [[CrossRef](#)]
118. Ferguson, T.A.; Green, D.R. Autophagy and phagocytosis converge for better vision. *Autophagy* **2014**, *10*, 165–167. [[CrossRef](#)]
119. Kim, J.Y.; Zhao, H.; Martinez, J.; Doggett, T.A.; Kolesnikov, A.V.; Tang, P.H.; Ablonczy, Z.; Chan, C.C.; Zhou, Z.; Green, D.R.; et al. Noncanonical autophagy promotes the visual cycle. *Cell* **2013**, *154*, 365–376. [[CrossRef](#)]
120. Muniz-Feliciano, L.; Doggett, T.A.; Zhou, Z.; Ferguson, T.A. RUBCN/rubicon and EGFR regulate lysosomal degradative processes in the retinal pigment epithelium (RPE) of the eye. *Autophagy* **2017**, *13*, 2072–2085. [[CrossRef](#)]
121. Shaw, J.D.; Hama, H.; Sohrabi, F.; DeWald, D.B.; Wendland, B. PtdIns(3,5)P2 is required for delivery of endocytic cargo into the multivesicular body. *Traffic* **2003**, *4*, 479–490. [[CrossRef](#)]
122. Ketel, K.; Krauss, M.; Nicot, A.S.; Puchkov, D.; Wieffer, M.; Muller, R.; Subramanian, D.; Schultz, C.; Laporte, J.; Haucke, V. A phosphoinositide conversion mechanism for exit from endosomes. *Nature* **2016**, *529*, 408–412. [[CrossRef](#)]
123. Isobe, Y.; Nigorikawa, K.; Tsurumi, G.; Takemasu, S.; Takasuga, S.; Kofuji, S.; Hazeki, K. PIKfyve accelerates phagosome acidification through activation of TRPML1 while arrests aberrant vacuolation independent of the Ca<sup>2+</sup> channel. *J. Biochem.* **2019**, *165*, 75–84. [[CrossRef](#)]
124. Ikononov, O.C.; Sbrissa, D.; Shisheva, A. Localized PtdIns 3,5-P2 synthesis to regulate early endosome dynamics and fusion. *Am. J. Physiol. Cell Physiol.* **2006**, *291*, C393–C404. [[CrossRef](#)]

125. Dong, X.P.; Shen, D.; Wang, X.; Dawson, T.; Li, X.; Zhang, Q.; Cheng, X.; Zhang, Y.; Weisman, L.S.; Delling, M.; et al. PI(3,5)P(2) controls membrane trafficking by direct activation of mucolipin Ca(2+) release channels in the endolysosome. *Nat. Commun.* **2010**, *1*, 38. [[CrossRef](#)]
126. Sasaki, T.; Takasuga, S.; Sasaki, J.; Kofuji, S.; Eguchi, S.; Yamazaki, M.; Suzuki, A. Mammalian phosphoinositide kinases and phosphatases. *Prog. Lipid Res.* **2009**, *48*, 307–343. [[CrossRef](#)]
127. Brown, J.R.; Auger, K.R. Phylogenomics of phosphoinositide lipid kinases: Perspectives on the evolution of second messenger signaling and drug discovery. *BMC Evol. Biol.* **2011**, *11*, 4. [[CrossRef](#)]
128. Azadi, S.; Brush, R.S.; Anderson, R.E.; Rajala, R.V. Class I Phosphoinositide 3-Kinase Exerts a Differential Role on Cell Survival and Cell Trafficking in Retina. *Adv. Exp. Med. Biol.* **2016**, *854*, 363–369. [[CrossRef](#)]
129. Sakagami, H.; Katsumata, O.; Hara, Y.; Tamaki, H.; Fukaya, M. Preferential localization of type I phosphatidylinositol 4-phosphate 5-kinase gamma at the periaxial zone of mouse photoreceptor ribbon synapses. *Brain Res.* **2014**, *1586*, 23–33. [[CrossRef](#)]
130. Wenk, M.R.; Pellegrini, L.; Klenchin, V.A.; Di Paolo, G.; Chang, S.; Daniell, L.; Arioka, M.; Martin, T.F.; De Camilli, P. PIP kinase Igamma is the major PI(4,5)P(2) synthesizing enzyme at the synapse. *Neuron* **2001**, *32*, 79–88. [[CrossRef](#)]
131. Wright, B.D.; Loo, L.; Street, S.E.; Ma, A.; Taylor-Blake, B.; Stashko, M.A.; Jin, J.; Janzen, W.P.; Frye, S.V.; Zylka, M.J. The lipid kinase PIP5K1C regulates pain signaling and sensitization. *Neuron* **2014**, *82*, 836–847. [[CrossRef](#)]
132. Di Paolo, G.; Moskowitz, H.S.; Gipson, K.; Wenk, M.R.; Voronov, S.; Obayashi, M.; Flavell, R.; Fitzsimonds, R.M.; Ryan, T.A.; De Camilli, P. Impaired PtdIns(4,5)P2 synthesis in nerve terminals produces defects in synaptic vesicle trafficking. *Nature* **2004**, *431*, 415–422. [[CrossRef](#)]
133. Huang, Z.; Guo, X.X.; Chen, S.X.; Alvarez, K.M.; Bell, M.W.; Anderson, R.E. Regulation of type II phosphatidylinositol phosphate kinase by tyrosine phosphorylation in bovine rod outer segments. *Biochemistry* **2001**, *40*, 4550–4559. [[CrossRef](#)]
134. Zhao, L.; Chen, Y.; Bajaj, A.O.; Eblimit, A.; Xu, M.; Soens, Z.T.; Wang, F.; Ge, Z.; Jung, S.Y.; He, F.; et al. Integrative subcellular proteomic analysis allows accurate prediction of human disease-causing genes. *Genome Res.* **2016**, *26*, 660–669. [[CrossRef](#)]
135. Prosseda, P.P.; Luo, N.; Wang, B.; Alvarado, J.A.; Hu, Y.; Sun, Y. Loss of OCRL increases ciliary PI(4,5)P2 in Lowe oculocerebrorenal syndrome. *J. Cell Sci.* **2017**, *130*, 3447–3454. [[CrossRef](#)]
136. Attree, O.; Olivos, I.M.; Okabe, I.; Bailey, L.C.; Nelson, D.L.; Lewis, R.A.; McInnes, R.R.; Nussbaum, R.L. The Lowe’s oculocerebrorenal syndrome gene encodes a protein highly homologous to inositol polyphosphate-5-phosphatase. *Nature* **1992**, *358*, 239–242. [[CrossRef](#)]
137. Shim, H.; Wu, C.; Ramsamoj, S.; Bosch, K.N.; Chen, Z.; Emerling, B.M.; Yun, J.; Liu, H.; Choo-Wing, R.; Yang, Z.; et al. Deletion of the gene Pip4k2c, a novel phosphatidylinositol kinase, results in hyperactivation of the immune system. *Proc. Natl. Acad. Sci. USA* **2016**, *113*, 7596–7601. [[CrossRef](#)]
138. Young, R.W. The renewal of rod and cone outer segments in the rhesus monkey. *J. Cell Biol.* **1971**, *49*, 303–318. [[CrossRef](#)]
139. Adams, N.A.; Awadein, A.; Toma, H.S. The retinal ciliopathies. *Ophthalmic Genet.* **2007**, *28*, 113–125. [[CrossRef](#)]
140. Wheway, G.; Parry, D.A.; Johnson, C.A. The role of primary cilia in the development and disease of the retina. *Organogenesis* **2013**, *10*, 69–85. [[CrossRef](#)]
141. Gal, A.; Li, Y.; Thompson, D.A.; Weir, J.; Orth, U.; Jacobson, S.G.; Apfelstedt-Sylla, E.; Vollrath, D. Mutations in MERTK, the human orthologue of the RCS rat retinal dystrophy gene, cause retinitis pigmentosa. *Nat. Genet.* **2000**, *26*, 270–271. [[CrossRef](#)]
142. Marmorstein, A.D.; Johnson, A.A.; Bachman, L.A.; Andrews-Pfannkoch, C.; Knudsen, T.; Gilles, B.J.; Hill, M.; Gandhi, J.K.; Marmorstein, L.Y.; Pulido, J.S. Mutant Best1 Expression and Impaired Phagocytosis in an iPSC Model of Autosomal Recessive Bestrophinopathy. *Sci Rep.* **2018**, *8*, 4487. [[CrossRef](#)]
143. Strauss, O.; Reichhart, N.; Gomez, N.M.; Muller, C. Contribution of Ion Channels in Calcium Signaling Regulating Phagocytosis: MaxiK, Cav1.3 and Bestrophin-1. *Adv. Exp. Med. Biol.* **2016**, *854*, 739–744. [[CrossRef](#)]
144. Muller, C.; Mas Gomez, N.; Ruth, P.; Strauss, O. CaV1.3 L-type channels, maxiK Ca(2+)-dependent K(+) channels and bestrophin-1 regulate rhythmic photoreceptor outer segment phagocytosis by retinal pigment epithelial cells. *Cell Signal.* **2014**, *26*, 968–978. [[CrossRef](#)]

145. Xiao, Q.; Hartzell, H.C.; Yu, K. Bestrophins and retinopathies. *Pflugers Arch.* **2010**, *460*, 559–569. [[CrossRef](#)]
146. Strauss, O. The retinal pigment epithelium in visual function. *Physiol. Rev.* **2005**, *85*, 845–881. [[CrossRef](#)]
147. Luo, N.; Lu, J.; Sun, Y. Evidence of a role of inositol polyphosphate 5-phosphatase INPP5E in cilia formation in zebrafish. *Vision Res.* **2012**, *75*, 98–107. [[CrossRef](#)]
148. Travaglini, L.; Brancati, F.; Silhavy, J.; Iannicelli, M.; Nickerson, E.; Elkhartoufi, N.; Scott, E.; Spencer, E.; Gabriel, S.; Thomas, S.; et al. Phenotypic spectrum and prevalence of INPP5E mutations in Joubert syndrome and related disorders. *Eur. J. Hum. Genet.* **2013**, *21*, 1074–1078. [[CrossRef](#)]
149. Plotnikova, O.V.; Seo, S.; Cottle, D.L.; Conduit, S.; Hakim, S.; Dyson, J.M.; Mitchell, C.A.; Smyth, I.M. INPP5E interacts with AURKA, linking phosphoinositide signaling to primary cilium stability. *J. Cell Sci.* **2015**, *128*, 364–372. [[CrossRef](#)]
150. Xu, W.; Jin, M.; Hu, R.; Wang, H.; Zhang, F.; Yuan, S.; Cao, Y. The Joubert Syndrome Protein Inpp5e Controls Ciliogenesis by Regulating Phosphoinositides at the Apical Membrane. *J. Am. Soc. Nephrol.* **2017**, *28*, 118–129. [[CrossRef](#)]
151. Verstreken, P.; Koh, T.W.; Schulze, K.L.; Zhai, R.G.; Hiesinger, P.R.; Zhou, Y.; Mehta, S.Q.; Cao, Y.; Roos, J.; Bellen, H.J. Synaptojanin is recruited by endophilin to promote synaptic vesicle uncoating. *Neuron* **2003**, *40*, 733–748. [[CrossRef](#)]
152. Chi, Y.; Zhou, B.; Wang, W.Q.; Chung, S.K.; Kwon, Y.U.; Ahn, Y.H.; Chang, Y.T.; Tsujishita, Y.; Hurley, J.H.; Zhang, Z.Y. Comparative mechanistic and substrate specificity study of inositol polyphosphate 5-phosphatase *Schizosaccharomyces pombe* Synaptojanin and SHIP2. *J. Biol. Chem.* **2004**, *279*, 44987–44995. [[CrossRef](#)]
153. Chang-Ileto, B.; Frere, S.G.; Chan, R.B.; Voronov, S.V.; Roux, A.; Di Paolo, G. Synaptojanin 1-mediated PI(4,5)P<sub>2</sub> hydrolysis is modulated by membrane curvature and facilitates membrane fission. *Dev. Cell* **2011**, *20*, 206–218. [[CrossRef](#)] [[PubMed](#)]
154. Lev, S.; Hernandez, J.; Martinez, R.; Chen, A.; Plowman, G.; Schlessinger, J. Identification of a novel family of targets of PYK2 related to *Drosophila* retinal degeneration B (rdgB) protein. *Mol. Cell Biol.* **1999**, *19*, 2278–2288. [[CrossRef](#)]
155. Tian, D.; Lev, S. Cellular and developmental distribution of human homologues of the *Drosophila* rdgB protein in the rat retina. *Invest. Ophthalmol. Vis. Sci.* **2002**, *43*, 1946–1953.
156. Kohn, L.; Kadzhaev, K.; Burstedt, M.S.I.; Haraldsson, S.; Hallberg, B.; Sandgren, O.; Golovleva, I. Mutation in the PYK2-binding domain of PITPNM3 causes autosomal dominant cone dystrophy (CORD5) in two Swedish families. *Eur. J. Hum. Genet.* **2007**, *15*, 664–671. [[CrossRef](#)]
157. Kohn, L.; Kadzhaev, K.; Burstedt, M.S.I.; Haraldsson, S.; Sandgren, O.; Golovleva, I. Mutation in the PYK2-binding domain of PITPNM3 causes autosomal dominant cone dystrophy (CORD5) in two Swedish families. *Recent Adv. Exp. Med. Biol.* **2008**, *613*, 229–234. [[CrossRef](#)]
158. Kohn, L.; Kohl, S.; Bowne, S.J.; Sullivan, L.S.; Kellner, U.; Daiger, S.P.; Sandgren, O.; Golovleva, I. PITPNM3 is an uncommon cause of cone and cone-rod dystrophies. *Ophthalmic Genet.* **2010**, *31*, 139–140. [[CrossRef](#)]
159. Bakhoun, M.F.; Sengillo, J.D.; Cui, X.; Tsang, S.H. Autoimmune retinopathy in a patient with a missense mutation in PITPNM3. *Retin Cases Brief. Rep.* **2018**, *12* (Suppl. 1), S72–S75. [[CrossRef](#)]
160. Lin, Z.; Li, W.; Zhang, H.; Wu, W.; Peng, Y.; Zeng, Y.; Wan, Y.; Wang, J.; Ouyang, N. CCL18/PITPNM3 enhances migration, invasion, and EMT through the NF-kappaB signaling pathway in hepatocellular carcinoma. *Tumour Biol.* **2016**, *37*, 3461–3468. [[CrossRef](#)]
161. Ile, K.E.; Kassen, S.; Cao, C.; Vihtehlic, T.; Shah, S.D.; Mousley, C.J.; Alb, J.G., Jr.; Huijbregts, R.P.; Stearns, G.W.; Brockerhoff, S.E.; et al. Zebrafish class 1 phosphatidylinositol transfer proteins: PITPbeta and double cone cell outer segment integrity in retina. *Traffic* **2010**, *11*, 1151–1167. [[CrossRef](#)] [[PubMed](#)]
162. Chang, B.; Hawes, N.L.; Hurd, R.E.; Davisson, M.T.; Nusinowitz, S.; Heckenlively, J.R. Retinal degeneration mutants in the mouse. *Vision Res.* **2002**, *42*, 517–525. [[CrossRef](#)]
163. Borman, A.D.; Pearce, L.R.; Mackay, D.S.; Nagel-Wolfrum, K.; Davidson, A.E.; Henderson, R.; Garg, S.; Waseem, N.H.; Webster, A.R.; Plagnol, V.; et al. A homozygous mutation in the TUB gene associated with retinal dystrophy and obesity. *Hum. Mutat.* **2014**, *35*, 289–293. [[CrossRef](#)] [[PubMed](#)]
164. Hagstrom, S.A.; Watson, R.F.; Pauer, G.J.; Grossman, G.H. Tulp1 is involved in specific photoreceptor protein transport pathways. *Adv. Exp. Med. Biol.* **2012**, *723*, 783–789. [[CrossRef](#)] [[PubMed](#)]
165. Xi, Q.; Pauer, G.J.; Traboulsi, E.I.; Hagstrom, S.A. Mutation screen of the TUB gene in patients with retinitis pigmentosa and Leber congenital amaurosis. *Exp. Eye Res.* **2006**, *83*, 569–573. [[CrossRef](#)] [[PubMed](#)]

166. Xi, Q.; Pauer, G.J.; West, K.A.; Crabb, J.W.; Hagstrom, S.A. Retinal degeneration caused by mutations in TULP1. *Adv. Exp. Med. Biol.* **2003**, *533*, 303–308. [[CrossRef](#)]
167. Mukhopadhyay, S.; Jackson, P.K. The tubby family proteins. *Genome Biol.* **2011**, *12*, 225. [[CrossRef](#)]
168. Hagstrom, S.A.; Duyao, M.; North, M.A.; Li, T. Retinal degeneration in *tulp1*<sup>-/-</sup> mice: Vesicular accumulation in the interphotoreceptor matrix. *Invest. Ophthalmol. Vis. Sci.* **1999**, *40*, 2795–2802.



© 2020 by the author. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<http://creativecommons.org/licenses/by/4.0/>).