
Article:
Ong, A.C.M. and Harris, P.C. (2015) A polycystin-centric view of cyst formation and disease: the polycystins revisited. Kidney International, 88 (4). pp. 699-710. ISSN 0085-2538

https://doi.org/10.1038/ki.2015.207

Published in final edited form as:
Kidney Int. 2015 October ; 88(4): 699–710. doi:10.1038/ki.2015.207.

A polycystin-centric view of cyst formation and disease: the polycystins revisited

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Abstract

It is 20 years since the identification of *PKD1,* the major gene mutated in autosomal dominant polycystic kidney disease (ADPKD), followed closely by the cloning of *PKD2.* These major breakthroughs have led in turn to a period of intense investigation into the function of the two proteins encoded, polycystin-1 and polycystin-2 and how defects in either protein lead to cyst formation and non-renal phenotypes. In this review, we summarise the major findings in this area and present a current model of how the polycystin proteins function in health and disease.

Keywords

ADPKD; PKD1; PKD2; polycystin-1; polycystin-2; TRPP2; primary cilia; cysts

Introduction

Autosomal dominant polycystic kidney disease (ADPKD) is the fourth ranked cause of kidney failure and the most common inherited nephropathy. Beyond the kidney, the major organs affected include the liver, pancreas, heart and intracerebral arteries. Although long considered an untreatable disease, the availability of new treatments that could alter its natural history are becoming a reality[1, 2].

Mutations in two genes, *PKD1* and *PKD2*, cause ADPKD, with the existence of '*PKD3*' in doubt following reanalysis of the reported unlinked cases[3]. In typical renal clinic populations, PKD1 accounts for 80-85% of cases with PKD2 accounting for the remainder. Although PKD1 and PKD2 patients have overlapping renal and extra-renal features, truncating *PKD1* mutations are associated with the poorest renal survival whereas *PKD2* mutations have the best outcomes; non-truncating *PKD1* mutations display an intermediate spectrum[4].

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Disclosure: None declared

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PKD1 and *PKD2* encode the proteins, polycystin-1 (PC1) and polycystin-2 (PC2), respectively [5]. Early studies showed that tissue expression of both proteins was largely overlapping although not identical[6, 7]. In addition, *Pkd2* expression appeared more constant while that of *Pkd1* was developmentally regulated[8]. Biochemical studies indicate that both proteins interact to form a polycystin (PC) complex[9-11]. However this needs to be reconciled with the non-overlapping subcellular location/s of both proteins, especially the predominant localisation of PC2 in the ER[12] where it may function as a Ca^{2+} release channel[13-15].

ADPKD disease mechanism

There is agreement that ADPKD is associated with loss of function; null *Pkd1* or *Pkd2* mouse models are lethal and develop cysts by ~E13.5[16, 17]. Disagreement has centred on whether a complete loss of the normal allele is required (two hit hypothesis) or whether cysts can develop once the level of function protein falls below a specific level (threshold hypothesis)[18]. Consistent with the need for two hits, inactivating and base pair somatic mutations have been identified in ADPKD renal and liver cystic epithelium, and cysts are clonal and so may be derived from a single cell[19-21]. The hypermutable *Pkd2* allele (WS25), develops cysts following spontaneous loss of the normal allele[22] and induced mutation in conditional models shows that loss of the second allele causes cystogenesis. However, the timing of this event significantly influences disease severity; before P13, cysts rapidly develop, while later loss results in slowly progressive disease[23, 24]. The timing of somatic mutation thus significantly influences growth rates, possibly due to the basal level of proliferation or a critical developmental window. Somatic mutation could explain the focal nature of cyst development, found in a limited number of nephrons. It has also been suggested that PKD1 is a more severe disease than PKD2 due to *PKD1* being a larger mutational target[25].

On the other hand, hypomorphic models indicate that cysts can develop even if low levels of normal PC1 (15-20%) are present[26, 27] and cysts in $Pkd1^{+/+}$; $Pkd1^{-/-}$ chimeric mice initially comprise cells of both genotypes, only later (and associated with histological changes) being all $Pkd1^{-/-}$[28]. *PKD2* somatic mutations in PKD1 cysts and vice versa[29, 30], plus other karyotypic changes in developing cysts[31] also indicate complexity in cyst development, rather than due simply to the loss of both alleles[18].

A threshold model of cystogenesis in ADPKD

The data presented above and recent evidence that different types of *PKD1* mutation (truncating and non-truncating) are associated with different disease severity[4], that humans and mice with two incompletely penetrant alleles can be viable (severe to typical disease), and that *in utero* onset ADPKD can be due to biallelic *PKD1* or *PKD2* mutations (inactivating plus hypomorphic or two hypomorphic)[32-36] suggests that a threshold or dosage model best explains cystogenesis in ADPKD (Figure 1). In patients with a 50% reduction of functional PC1 or PC2 (typical patients with an inactivating mutation), cysts can occur if the level of functional PC falls below the cystogenic threshold. This may occur by somatic mutation to the other allele, but stochastic cellular variability of expression of the remaining ADPKD allele[37, 38] and other factors, such as renal damage (which has been

shown to promote cystogenesis in mice), may determine if a cyst develops[39, 40]. It is possible that this minimum threshold itself could vary between animals, by nephron segment, developmental stage, tissue and even cell type[23, 41, 42]. In mice, slowly progressive disease occurs if the level of functional PC1 is ~40%, but rapidly progressive disease occurs with ~20% functional PC1, highlighting the influence of dosage[36] (Figure 1). Since the level of functional PC seems linked to renal disease severity, treatments that can promote that level may help to slow disease progression.

Once initiated, further genetic events at the disease locus and elsewhere, similar to tumour development in cancer, plus other environmental influences, may favour growth and survival of a cyst. Of note, even in hypomorphic models, cyst development is focal[36] suggesting that factors in addition to the level of the functional protein are important but that once tipped into a cystogenic cascade, possibly irreversible. In conditional knockouts with low levels of induced deletion of the normal allele during adulthood, cyst development is slow but later cysts cluster around early ones, indicating that paracrine cystogenic factors may diffuse from developed cysts, although the non-randomness of Cre-inactivation should also be considered [43].

Mutation to the transcription factor HNF1B leads to a diverse range of kidney phenotypes including renal agenesis, dysplasia and renal malformations but most commonly cysts, occasionally phenocopying ADPKD as the Renal Cystic and Diabetes Syndrome (RCAD)[44]. Both *PKD2* and *PKHD1,* the autosomal recessive PKD (ARPKD) gene, are under the transcriptional control of HNF1B[45], and a combination of *PKD1* and *HNF1B* pathogenic alleles may cause *in utero* onset PKD [34]. This may be the result of the combination of altered regulation of HNF1B targets and the *PKD1* mutation.

The microRNA-17 (miRNA17) binds to the 3′UTR of *PKD2* and regulates the stability of *PKD2* mRNA and its translation. Transgenic overexpression of miRNA17 leads to a cystic phenotype in *Xenopus* and mice, through down-regulating *Pkd2* mRNA, confirming the importance of gene dosage[46]. A transgenic model with two miRs targeting *Pkd1* also resulted in a slowly progressive PKD model[47]. The RNA-binding protein, Bicaudal C (Bicc1), is mutated in several mouse models of PKD (*bpk, jcpk*) and competes with miRNA17 for binding to *Pkd2* mRNA: *Pkd2* levels are reduced with *Bicc1* mutation[48].

Disease mechanisms in non-renal tissues

A striking finding from *Pkd1* and *Pkd2* null animals is the uniform lack of liver cysts, common pancreatic cysts and variable expression of vascular abnormalities[16, 17, 49]. These findings indicate that each tissue may have a different threshold for disease onset and expression. An unusual feature of the liver phenotype is the strong female predisposition to develop polycystic liver disease[50]. This is the converse of the modest male predisposition to develop larger polycystic kidneys [25] and earlier ESRD [4], which implies different modifiers of this phenotype.

The prevalence of intracranial aneurysms (ICA) in ADPKD varies between 6-16% with evidence of familial clustering[51, 52]. ICA rupture can occur in younger individuals and before the onset of hypertension, suggesting a primary link between ICA formation and

polycystin function[53, 54]. ICAs have been reported in only a few *Pkd1* mice and these have tended to be hypomorphic, transgenic or challenged heterozygous animals[55-57] rather than vascular-specific knockouts[58]. These findings suggest that gene dosage is important in the genesis of ICAs but that disease penetrance is determined by other factors such as genetic background and environmental 'stress'. An early predisposing factor could be endothelial dysfunction, detected in resistance arteries of normotensive non-cystic heterozygous mice[59].

A common polycystin pathway for cystogenesis

Genetic interaction between cystogenes

Consistent with a dosage model of ADPKD cystogenesis, human and mouse studies have shown genetic interaction between cystogenes (Figure 2). Contiguous deletion of *PKD1* and the adjacent tuberous sclerosis gene (*TSC2*) results in much more severe PKD than a *PKD1* or *TSC2* mutation alone[60, 61]. The mechanism may be related to overlap between their downstream signalling pathways involving mTOR and possibly others[62, 63], but a direct interaction between PC1 and the TSC2 protein, tuberin, may also be relevant[64].

Early-onset PKD foetuses with co-inheritance of mutations in *PKD2* and *PKHD1* have also been reported, suggesting another potential genetic interaction[34] (Figure 2). The ARPKD protein, fibrocystin (FPC), may bind to PC2 and regulate its Ca^{2+} permeability[65]. Genetic studies in mice have also shown a genetic interaction between *Pkd1* and *Pkhd1*[41]. In one family, patients with digenic *PKD1* and *PKD2* mutations had ESRD ~20 years earlier than single mutations to either gene[66, 67] and digenic mouse studies with hypermutable (*Pkd2*) and hypomorphic (*Pkd1*) alleles showed a similar dose dependent, synergistic phenotypic enhancement[68].

Studies of conditional kidney inactivation of polycystic liver disease (PCLD) genes (*Prkcsh, Sec63*) or *Pkhd1* with the ADPKD genes provide further evidence of cystogenic interaction and a dosage dependence of *Pkd1,* where the level of PC1 plays a central role[41] (Figure 2). In this model, *Pkd2* cannot substitute for *Pkd1* but is required for *Pkd1* function suggesting that the PC1-PC2 complex is essential. In PCLD, the disease proteins are involved in glycosylation or translocation of membrane proteins into the ER, plus ER quality control[69, 70] and hence, involved with processing the large and complex PC1 or PC2. It is not clear if PLCD is restricted to the liver because this organ is more dosage sensitive for these proteins or if somatic mutations occur more frequently in the liver[41].

Polycystin structure and function

Polycystin-1

The 3D structure of PC1 remains unresolved and continues to prove challenging in view of the size, and complexity of the protein. Nonetheless, the modular domain structure of the protein has stimulated study of isolated domains. Figure 3 depicts our current view of the structure of the protein.

The GAIN domain—A major advance has been the crystallisation of the GPCR-Autoproteolysis Inducing (GAIN) regulatory domain[71], a 320 residue region which includes

the 50 residue G protein-coupled receptor proteolysis site (GPS) motif which mediates *cis*-autoproteolysis of PC1 to generate a 320kDa (unglycosylated) N-terminal product (NTP) and a 140kDa C-terminal product (CTP) which remain non-covalently bound[72]. The GAIN domain is evolutionarily conserved and found in all 33 cell-adhesion GPCRs, orphan receptors with no known ligands, as well as all 5 PC1-like proteins[71] (Figure 3). The functional role of this cleavage is not clear but may be a mechanism of stabilising protein folding and hence trafficking. An unanswered question is whether the uncleaved form of PC1 is functional since the extent of cleavage of the endogenous protein varies in different cells. A *Pkd1* GPS cleavage mouse mutant (*Pkd1*$^{V/V}$, T3041V) escapes embryonic lethality but develops rapidly progressive post-natal PKD[72], suggesting a role for the uncleaved form during development. The interaction of PC1 with PC2 has been suggested as required for efficient GPS cleavage[73]. However, recent data indicates that PC1 is efficiently cleaved even in *Pkd2* null cells and in mutant PC1 with the C-tail deleted[68, 74]. An abundant, surface expressed cleaved NTP, detached from the CTP, of unknown function has been reported[75].

The PKD domain—An extracellular region that comprises 30% of PC1 (16 copies) is the Polycystic Kidney Disease (PKD) domain, which has similar topology to Ig-like and fibronectin type III domains[76]. The first PKD domain is separated from the other 15, which exist in tandem (Figure 3). This arrangement of tandem Ig-like domains is reminiscent of proteins with structural and mechanical roles such as titin, fibronectin and NCAM. PKD domains have been identified in surface layer proteins of some archaeobacteria where they may mediate the formation of multicellular structures. The crystal structure of a *Methanosarcina* PKD domain shows the highest similarity to the NMR structure of PKD domain 1, revealing its possible role in evolution from unicellular to multicellular organisms[77].

Biophysical studies have shown that the PC1 extracellular domain is highly extensible through the folding and unfolding of the PKD domains[78, 79]. In addition, the PKD domains (human and archae) appear to be stabilised by force-induced formation of a stable intermediate state[80]. These studies are consistent with a role for PC1 in mechanical coupling between cells, e.g. in maintaining normal tubular lumen diameter under flow. Indeed, a functional role for the PC1 extracellular domains (including the PKD domains) in mediating cell adhesion and/or cell junction formation has been demonstrated in mammalian cells from several species[81-83], likely via *trans*-homophilic interactions of the PKD domains and *cis*-heterophilic interactions with E-cadherin[81].

The PLAT domain—The Polycystin-1 Lipoxygenase Alpha-Toxin (PLAT) domain is considered a signature domain of the PC1-like proteins[84, 85] (Figure 3), and is identified in over 1000 different proteins. The PLAT domain crystal structure determined from murine Rab6-interacting protein 1 (Rab6IP1) and white sea coral 11*R*-lipooxgenase[86, 87] show a β sandwich with two sheets of four strands each. Sequence homology to PC1 PLAT is however low (20%). Genetic studies of LOV-1, the *C.elegans* PC1 homologue, have implicated PLAT in mediating male mating behaviour in worms[88], but the domain structure and function of worm and human PC1 are clearly divergent. Recent NMR studies of human PC1 PLAT show discrete binding motifs to acidic phospholipids and Ca^{2+} and that it is

phosphorylated (Ong ACM, submitted). It is likely that PC1 PLAT functions as a lipid/protein binding scaffold to integrate cell signalling and PC1 trafficking.

The C-terminal tail—The best studied region of PC1 is the ~200aa C-terminal tail although its 3D structure is still unknown. This contains several functional motifs including a coiled-coil domain (aa4220-4251) which mediates binding to PC2 and a G-protein binding and activation sequence (aa4111-4184) for heterotrimeric G proteins. It can be phosphorylated *in vitro* and has been shown to bind protein phosphatases which regulate PC1 and PC2 phosphorylation [89, 90]. Other key signalling proteins or effectors (eg. mTOR, Wnt, Jak/Stat) may be similarly regulated [91-93] (see below).

Polycystin-2

A strong body of evidence indicates that PC2 functions primarily as a high conductance non-selective Ca^{2+} permeable channel [13, 94, 95] and specific missense mutations (eg D511V) abolish Ca^{2+} permeability in the mutant protein [13, 14]. Sequence homology to other TRP channels supports this hypothesis: PC2 is also known as TRPP2 [96]. What is less clear is where its primary site of action resides (or whether there are multiple sites of action) and whether channel opening is directly regulated by PC1, Ca^{2+} binding (via its EF-hand) and/or phosphorylation (see below). However it is predicted that mutation of either *PKD1* or *PKD2* leads to lower cytoplasmic Ca^{2+} concentrations (reduced entry and/or release) resulting in dysregulated cAMP levels and downstream signalling [97].

A second coiled coil domain (CC2)—A second coiled coil domain (CC2) distal to the original, CC1, mediates oligomerisation of the PC2 C-terminus (CT2) (to form dimers or trimers), an event essential for recognition and binding of the PC1 C-terminus (CT1) to form a functional PC1/PC2 protein complex[14, 98] (Figure 3). The binding region in CT1 involves the coiled coil domain, although the precise stoichiometry of the complex is still debated.

Other oligomerisation motifs—Native PC2 forms higher order oligomers (tetramers, others) consistent with the likely tetrameric structure of other TRP channels [11, 99]. An N-terminal dimerization motif and a single cysteine residue (C632), which mediates disulphide bonding, likely contribute to the formation of PC2 tetramers[100,101].

EF-hand—Invertebrate PC2 homologues have two canonical EF hands (EF1, EF2), whereas vertebrate homologues have a single functional Ca^{2+} binding motif (EF2) due to a 4aa deletion in the Ca^{2+} binding loop of EF1[102]. The functional effect of Ca^{2+} binding may favour monomer over dimer formation[103] and/or regulate certain Ca^{2+} dependent interactions, rather than directly impact channel open probability[104].

Membrane targeting motifs—The detection of discrete ciliary and plasma membrane (PM) pools of PC2 has led to a search for distinct targeting signals for each compartment. Conserved ciliary targeting (^{6}RVxP^{9}) and PM (^{572}KxxxF^{576}) export motifs have been reported[105, 106]. Mutation of the RVxP motif does not abolish localisation of PC2 to nodal cilia or its function in left-right determination [107] but the functionality of the KxxxF motif has not been tested *in vivo*. It has been postulated that PC2 could be directed from the *cis*-

Golgi without transversing the *trans*-Golgi to the cilia or PM, independently of PC1[106]. Two different PC1 sequences (aa4296-4302; aa4100-4204) have been proposed as required for ciliary localisation by heterologous expression[108, 109]. Several other pathways have been reported to regulate the surface expression of mammalian PC2. These include GSK3, PKA and CAMK-dependent pathways[90, 110, 111]. However, it is not known if these signals are independent of PC1 or the targeting motifs reported.

Post-translational modification

Phosphorylation and Dephosphorylation

Although multiple phosphorylated residues have been identified from MS analysis, functional evidence for a regulatory role is limited. The best evidence comes from studies of five serine residues (S76, S80, S801, S812, S829) in PC2, each phosphorylated by a different kinase (GSK3, PrKD1, CK2, PKA)[90, 110, 112, 113]. These appear to regulate a number of key steps such as forward and retrograde trafficking, surface localisation, Ca^{2+} permeability and Ca^{2+} regulation of PC2[90, 110, 112-114]. An important link to PC1 was the striking finding that S829, a PKA activated site in PC2, remains constitutively phosphorylated in the absence of PC1[90]. The mechanism appears due to loss of protein phosphatase-1 action (PP1 binds to CT1)[89, 90]. PC1 is reported to bind to several receptor tyrosine phosphatases but it is unclear whether endogenous PC1 or PC2 are substrates for tyrosine kinases[115].

The NEK8 kinase is mutated in patients with nephronophthisis (NPHP9), in the spontaneous *jck* cystic mouse and the Lewis polycystic kidney (*lpk*) rat[116-118]. In *jck* kidneys, PC2 appears to be hyperphosphorylated[119]. NEK8 is known to act on other substrates such as ANKS1 but there is no evidence yet that PC2 is a substrate[120].

Ubiquitination and proteosomal degradation

Both PC1 and PC2 are subject to ubiquitin-dependent proteosomal degradation through the binding of different E3 ubiquitin ligases, Siah-1 and TAZ[121, 122]. *Taz* mutant mice develop predominant glomerular cysts and are associated with lower PC2 levels[123]. Nek1 in turn has been shown to phosphorylate TAZ leading to its degradation and increased PC2 levels, possibly leading to cystogenesis[124]. TAZ is known to mediate both Hippo signalling and canonical Wnt responses through regulating the degradation of β-catenin[125]. ER associated degradation (ERAD) of PC2 can be regulated by PRKCSH [126, 127]. These pathways may be especially important during nephrogenesis where the dosage of both proteins is critical for tubular elongation or in the adult kidney for appropriate repair following injury [128, 129].

PC1 proteolytic cleavage

Additional CT1 cleavage (following GPS cleavage) generating two CT1 cleavage products (CCP) of differing length (17, 34 kDa) may occur[130, 131] with these products acting as co-activators of several transcriptional pathways (Stat, Wnt, CHOP), independent of the NTP[130, 131]. A third reported cleavage event generating a P100 CCP might regulate store-operated Ca^{2+} entry independently of PC2 through inhibiting translocation of the ER Ca sensor STIM-1[132].

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Is ADPKD a ciliopathy?

Accumulated data over the past 15 years has implicated functional defects in primary cilia in ADPKD pathogenesis but there is also conflicting information[133].

Primary cilia involved in PKD

Most cell types have a primary cilium whose role is sensory/mechanosensory. The cilium is rooted in the basal body and has a specific mechanism, intraflagellar transport (IFT), for distributing proteins anterograde and retrograde, which is essential for cilia formation and resorption[134]. The cilium is a partially separate compartment with the transition zone and transition fibers acting as a ciliary gate. In epithelial cells, the cilium extends from the apical surface into the tubule lumen. Cilia are essential for certain developmental signaling pathways, most notably sonic hedgehog (Shh), and mechanosensory functions, like detecting flow; functional cilia are essential for normal development[135].

The initial evidence that PKD (ADPKD) is a ciliopathy came from the determination that homologous proteins to PC1 (lov1) and PC2 (pkd2) in *C. elegans* are localized to sensor cilia and loss of either results in defective mating behaviour[136, 137]. Next, a mouse model defective for the IFT protein, IFT88, was found to develop PKD[138, 139]. Subsequently, both PC1 and PC2 were localized to cilia in mammalian cells[140, 141]; recent data has emphasized this localization and interaction of these proteins in cilia[68, 74]. Another study showed that knocking out *Kif3A* (an IFT motor subunit) in the collecting duct resulted in PKD in this segment[142]. While structural cilia abnormalities are found in some ciliopathies, including ARPKD[143], cilia from *Pkd1* or *Pkd2* mutations were considered normal. Recently, study of the $Pkd1^{RC/RC}$ and $Pkd1^{RC/null}$ hypomorphic models has revealed longer cilia, with cilia length associated with the level of functional PC1[36]. It is unclear if the length difference is directly associated with the reduced level of PC1 or compensation for reduced cilia signalling[144].

Recessively inherited developmental disorders with renal defects from PKD to nephronophthisis (NPHP), Meckel syndrome (MKS), Joubert syndrome (JBTS) and Bardet Biedl syndrome (BBS) are ciliopathies[135]. The cilia link includes localization of the proteins to the transition zone, other regions of the cilia, the basal body or to a protein complex termed the BBSome shown to be important for localizing membrane associated proteins to the cilium[145, 146]. Cilia in these mutants have altered protein composition. Many of the extra-renal phenotypes observed in these disorders are also consistent with ciliary defects: retinal defects (connecting cilium are required to form the outer segment), polydactyly (cilia dependent Shh is involved in limb bud development), *situs inversus* (defects in cilia in the embryonic node), anosmia (defective olfactory cilia) and infertility (due to sperm flagella defects)[135]. It seems likely but not proven that the cystic defects in these pleotropic disorders are due to mislocalization/function of the PC-complex and FPC.

Role of the PC complex on cilia—Although there is good evidence that the PC complex is found on cilia and that cilia are associated with cyst development, the precise role of the PC complex on the cilium is more controversial. It is known that cilia can act as a flow sensor and that changes in flow or mechanical movement of the cilium induces an

influx of Ca^{2+} [147]. Cells null for *Pkd1,* or blocked for PC2, have been shown to lose the Ca^{2+} influx in response to flow, suggesting that the PC complex is a ciliary flow receptor[148, 149]. Additional evidence suggests that PC2 may be involved in flow detection in the cilia, but in combination with a different TRP channel, TRPV4[150]. In the embryonic node, PC2 also plays a role in flow detection, but this time in combination with the PC1-like protein, PC1L1, with the PC2/ PC1L1 complex sensing nodal flow[151-153] (Figure 3). This is consistent with *Pkd2* but not *Pkd1* mice having *situs inversus*[154, 155]. A non-dimerizing PC2 mutant (PC2-4M) that cannot bind to PC1 but still has the ability to function as an ER-located Ca^{2+} release channel and can partially rescue LR asymmetry in a *pkd2* zebrafish model, may be associated with this role for PC2[14]. However, inactivation of *Trpv4* or *Pkd111* is not associated with cyst development, questioning the link between ciliary flow sensing and PKD.

Polycystins and ciliary calcium regulation—Recently, the concept that the PC1/2 complex regulates the level of ciliary Ca^{2+} has also been thrown into doubt with the PC1L1/ PC1L2 complex implicated in that task[156, 157] (Figure 3). Furthermore, the authors argue that a change in Ca^{2+} concentration in the cilium is insufficient to trigger a global cytoplasmic Ca^{2+} response. Nevertheless, given the likely involvement of the PC1/2 complex in Ca^{2+} regulation and the links to cilia and PKD, this issue is incompletely resolved. It is possible that a stimulus other than flow (ligand/s) may be important to activate the PC complex. In addition, localized differences in Ca^{2+} concentration, such as around the ciliary base and/or additional signal amplification, e.g. through cAMP[158, 159], should be considered as ways that a cilia cue could be perpetuated to the cell.

Cilia, polycystins and other signalling—PC1 and PC2 are secreted at high levels in exosomes and may be involved in mediating distal nephron signalling possibly by interacting with cilia[160-162]. Other signalling pathways likely involving cilia have also been implicated in PKD. Changes in oriented cell division (OCD) in elongating tubules were found in the PCK rat model of ARPKD[163]. Planar cell polarity (PCP) which is linked to functional cilia, regulates this process, suggesting a role for PCP in controling tubule dilatation[164]. PC1 deficient cells also appear to lack directional movement in relation to a stimulus possibly reflecting a PCP defect[165]. However, evidence of an essential role of abnormal OCD in cyst formation in ADPKD is conflicting[166, 167]. A role for PCP more generally in ciliopathies is also questioned by findings of normal classical PCP processes, such as orientation of motile cilia and asymmetric expression of Vangl1 during inner ear development, in an MKS animal model, *bpck*[168]. An alternative explanation involves the related process, convergent-extension, which controls cell movements during tubular elongation [169]; which is dysregulated in *Pkd1* mice[170].

Recently, a role for Shh signaling in PKD was been suggested with mutation to an IFT component IFT139 that results in abnormal Shh signaling causing cyst development, as well as other ciliopathy phenotypes[171]. Interestingly, inhibition of Shh in kidney organ culture resulted in reduced cystogenesis in a *Pkd1* model[172]. Mutations in the Kruppel-like zinc finger transcription factor, Gli-similar 3 (*Glis3*), result in neonatal diabetes, hypothyroidism and PKD in humans and mice[173, 174]. GLIS3 has been localised to primary cilia and

interacts with the transcriptional co-regulator protein, WWtr1/Taz, and *Glis3* mutant kidneys have lower *Pkd1* mRNA levels, indicating that GLIS3 may regulate *Pkd1* transcription[174].

Cell cycle regulation and centrosome duplication—PC1 and PC2 appear to regulate the transcription of the cyclin-dependent kinase inhibitor p21, via JAK2-STAT3 signalling[93]. This could explain in part, the increased proliferation rate observed in non-cystic tubules and the exaggerated proliferative response following renal injury[128, 175]. In addition, PC2 may further regulate the nuclear translocation of p21 through its cytoplasmic retention by binding to the Id2 protein[176]. PC1 and PC2 deficient cells also have an abnormal increase in centrosome number, which could lead to abnormalities in proliferation control or result in apoptosis[177]. It is not clear whether this represents a primary effect of centrosomal duplication or is secondary to abnormal cell cycle regulation.

Cilium signalling promotes cyst growth—A surprising study in conditional knockout models of *Pkd1* and *Pkd2*, and genes essential for cilia formation, *Ift88* and *Ift20*, showed that elimination of cilia as well as loss of the PC resulted in much milder disease than loss of the PC alone[178]. This has been interpreted as the presence of a growth-promoting stimulus from cilia that is normally suppressed by the PC complex. However, while it is know that ciliary signalling can have a growth stimulating effect through regulation of the cell/centrosome cycles, direct linkage with the PC complex seems less certain.

Non-cilia functions of polycystins

Regulation of stretch-activated channels

In mesenteric arteries, a mechanism involving PC2 in suppressing stretch activated currents (SAC) has been proposed which does not involve its channel activity[179]. The role of PC1 is to titrate the amounts of PC2. PC1 and PC2 also regulate the opening of stretch-activated K (2P) channels in kidney cells conferring protection against apoptosis induced by mechanical stress: a mechanism that may be operational during cyst growth[180].

Basolateral localisation function and polarity

The proposed basolateral location of PC1 fits well with evidence that PC1 regulates or mediates cell-cell or cell-matrix adhesion[82]. Results from a recent study supports this idea showing a remarkable suppression of the *Pkd1* cystic phenotype when combined with deletion of β1 integrin[181].

Abnormalities in apicobasal polarity are an inconsistent finding in PC1 and PC2 deficient cells but abnormalities in cell-cell junction formation are commonly found[182, 183]. Alterations in the basolateral trafficking of E-cadherin have been linked to misregulation of components of the exocyst complex (sec6, sec8), which are important in the establishment of the basolateral domain of epithelial cells[184]. PC2 has also been shown to bind to Sec10, although this has been linked to cilia rather than basolateral trafficking of PC2[185]. It is conceivable that the role of PC1 in mediating cell-cell adhesion, through *trans*-homophilic interactions, and to recruit E-cadherin through *cis*-heterophilic interactions, could regulate

this process[81]. Changes in intercellular adhesion are paralleled by changes in cell-matrix adhesion especially to collagen I[186].

Functions of other polycystins

We have discussed the role of PC1L1 with PC2 in the embryonic node and PC1L1 and PC2L1 in regulating ciliary calcium, but other members also have diverse functions (Figure 3). PC1REJ has been shown to mediate the sperm acrosome reaction[187] and PC1L3 to be the sour taste (H^+) detector[188]. The role of PC1L2 is less clear but up-regulation in mice results in chronic neuromuscular impairment[189] while PC2L2 has been implicated in spermatogenesis[190]. In addition to what is presently known, other combinations between PC1 and PC2 paralogs likely mediate other cilia related and unrelated functions.

Polycystin complex formation, maturation and trafficking

The localisation of both PC1 and PC2 to different subcellular compartments (cilia, PM, ER and exosomes) has led to uncertainty whether the trafficking of both proteins is co-dependent, the nature of the targeting, export or retrieval motifs, and the functional site/s of action to prevent PKD.

Ciliary and PM complexes

PC2 is most abundantly found in the ER, consistent with the normal appearance of only an immature (EndoH sensitive) glycoform[12]. PC1 generates mature (EndoH resistant; NTR, CTR) and immature (EndoH sensitive; NTS, CTS) glycoforms[11] with NTR found on the PM, cilia and exported via the multivesicular pathway in exosomes[36, 68, 74, 75, 161] (Figure 4). In contrast, NTS likely remains in the ER along with any unGPS-cleaved PC1. PC1 binding to PC2 is absolutely dependent on PC2 oligomerisation via its C-terminus [14] and PC1 maturation and localization requires PC2 in a dose-dependent manner[68, 74]. PC1 cleavage at the GPS/GAIN domain is a requirement for PC1 maturation and the generation of PC1 NTR[68, 74]. A PC1 NTP unlinked to the PC1 CTP has been reported at the plasma membrane[75] but transgenic expression an NTP-like protein (F3043X) could not rescue the phenotype of GPS cleavage–deficient *Pkd1*$^{v/v}$ (T3041V) mice[75]. It is unclear if the isolated PC1-CTP is functional but one study has shown that expression of the transgene is stabilised by PC2 binding[109].

Both PC1 and PC2 are present in the *cis*-Golgi, but at this point it is uncertain whether they continue to be co-transported through the Golgi for maturation and export to cilia. It has been suggested that they become uncoupled at the *cis*-Golgi and undergo independent trafficking at this point and recouple in a post-Golgi compartment[106]. However, recent evidence of a cilia localized EndoH-resistant (mature) form of PC2 suggests that they may traffic together to that organelle[74]. Transport of PC2 and PC1 to PM membranes may be similarly co-dependent[73, 74, 191]. The low level of surface labelling of PC2 compared to PC1, questions whether PM PC1 may interact with ER PC2 in membrane subdomains[14, 68], possibly in cooperation with IP3 receptors[15].

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In conclusion

In 20 years, extensive information about the mechanism of disease in ADPKD, the structure of the polycystins and where they are localized has been determined. The challenges now are to determine exactly what the PC1/2 complex does in the cilium, if PC1/2 localization elsewhere is significant to pathogenesis and whether PC1/2 levels are rate-limiting for the onset of PKD with other cystoproteins. Answers to these questions would stimulate new therapeutic options to target cyst initiation in ADPKD and other cystic diseases.

Acknowledgements

Work in the author's laboratories was supported by grants from the Wellcome Trust, Medical Research Council, Research Councils UK, Kidney Research UK, PKD Foundation, European Union (EU-FP7/2007-2013, grant agreement no. 317246, TranCYST) and NIH/NIDDK (DK058816 and DK090728). We thank past and present members of the Ong and Harris laboratories for significant contributions to this work and for many stimulating discussions.

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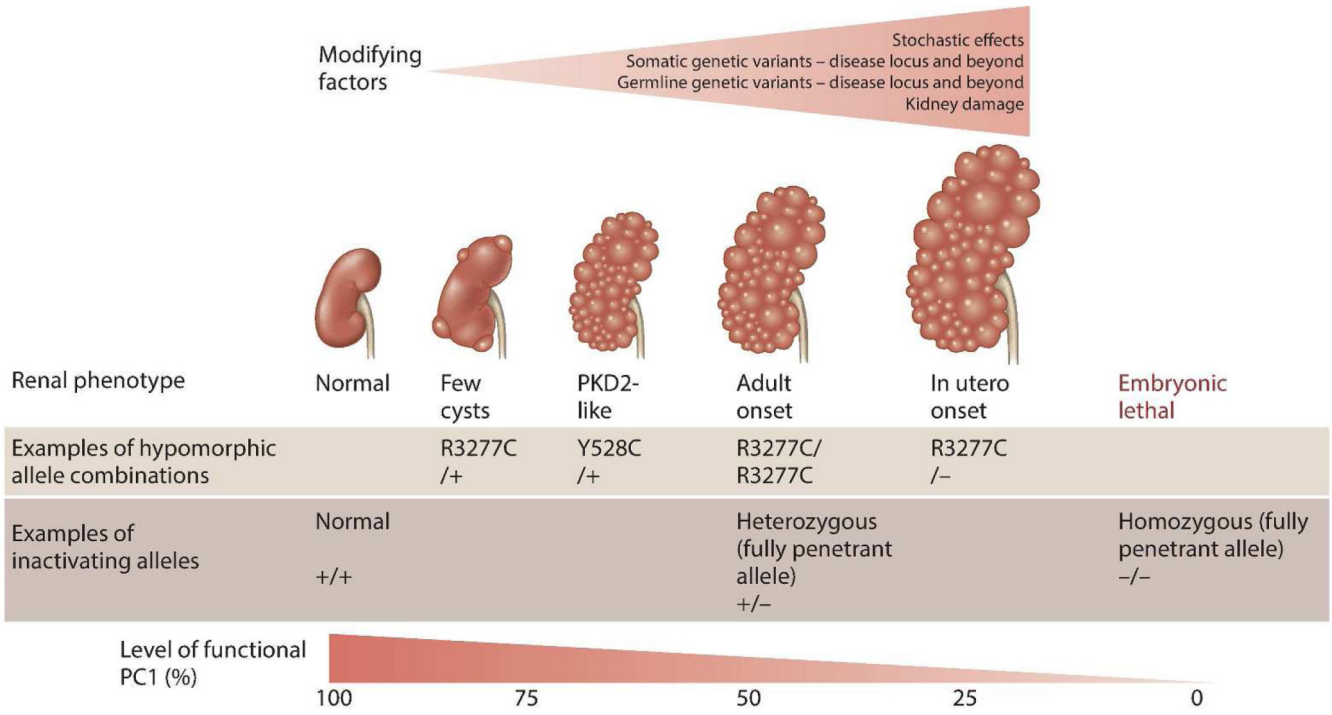

Figure 1. Dosage dependent disease mechanism in PKD1

The level of functional PC1 (bottom) directly influences the renal phenotype with a ~50% reduction (haploinsufficiency due to a single inactivating allele) associated with adult onset disease and no PC1 incompatible with life. Incompletely penetrant (hypomorphic) PC1 alleles of different strengths and combinations can significantly influence the renal phenotype. The PC1 allele p.Y528C has a phenotype similar to PKD2[67] while p.R3277C can result in a few cysts, adult onset disease or early onset disease depending on the *in trans* combination[32, 36]. Additional mutations/variants at the disease locus and elsewhere (somatic and germline), along with chance and environmental factors influence the disease course by determining the frequency of cyst development.

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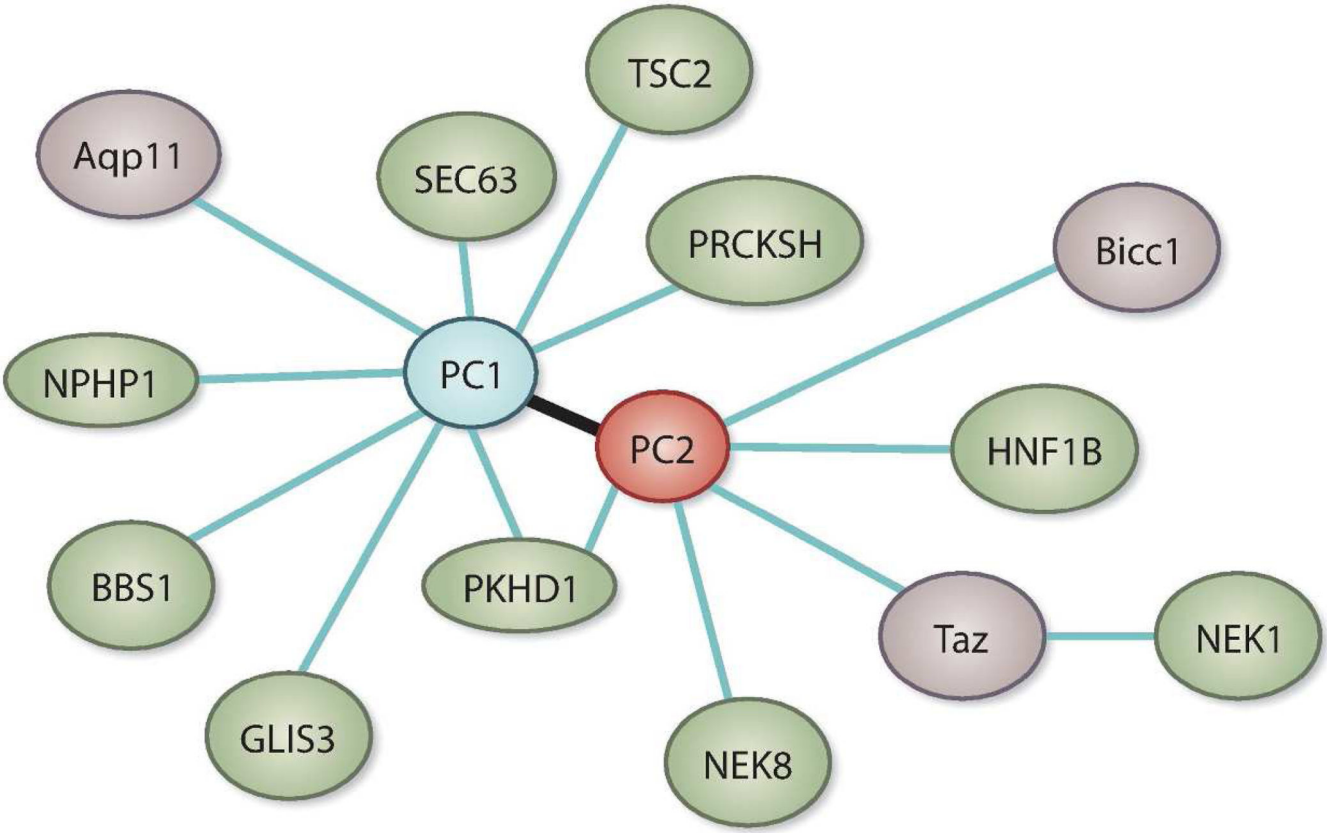
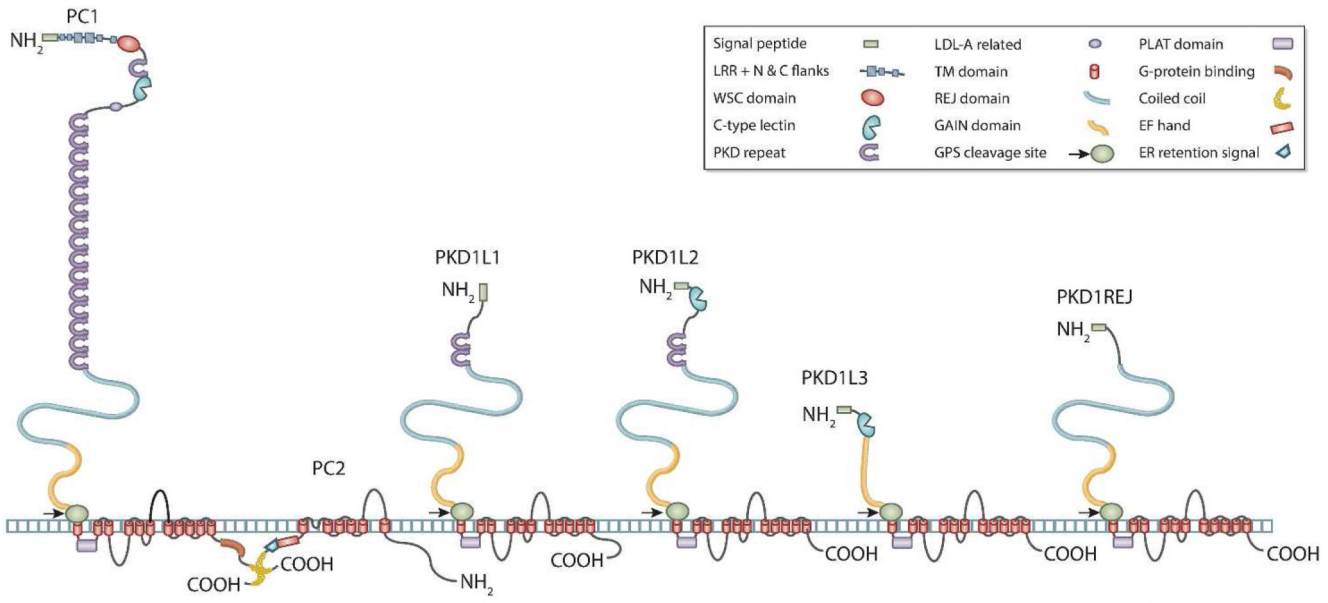


Figure 2. Genetic and biochemical interactions between known cystoproteins

Genetic and/or biochemical interactions are shown as solid lines. The murine cystoproteins shaded in grey (Aqp11, Bicc1, Taz) represent those where a human PKD phenotype has not yet been reported[123, 192, 193]. Biochemical interactions between PC1 and NPHP1 and BBS1 have been reported[194, 195].



PC1 protein	PC1	PKD1L1		PKD1L2	PKD1L3	PKD1REJ
Binding partner	PC2	PC2	PKD2L1	??	PKD2L1	PC2 and PKD2L1
Localization	Cilia, cell surface, exosomes	Embryonic node cilia	Cilia	Skeletal muscle	Taste buds	Sperm
Role	Cilia sensor, mechanosensor?	Establishes left-right asymmetry	Cilia calcium concentration	Neuro-muscular disease: mouse overexpression	Sour (H^+) detector	Regulating acrosome reaction

Figure 3. Structure and functions of PC1 and related polycystin-like proteins, plus PC2

The Key shows the different domains and other motifs found in these proteins. PC2 is shown complexed with PC1 via PC2 CC2 and the PC1 coiled coil region. A high degree of similarity between PC1 paralogs is found in the transmembrane regions but with more variation in the N-terminal ectodomains and the cytoplasmic tails. The structure of PC2L1 and PC2L2 are similar to PC2 but PC2L2 does not have an EF-hand.

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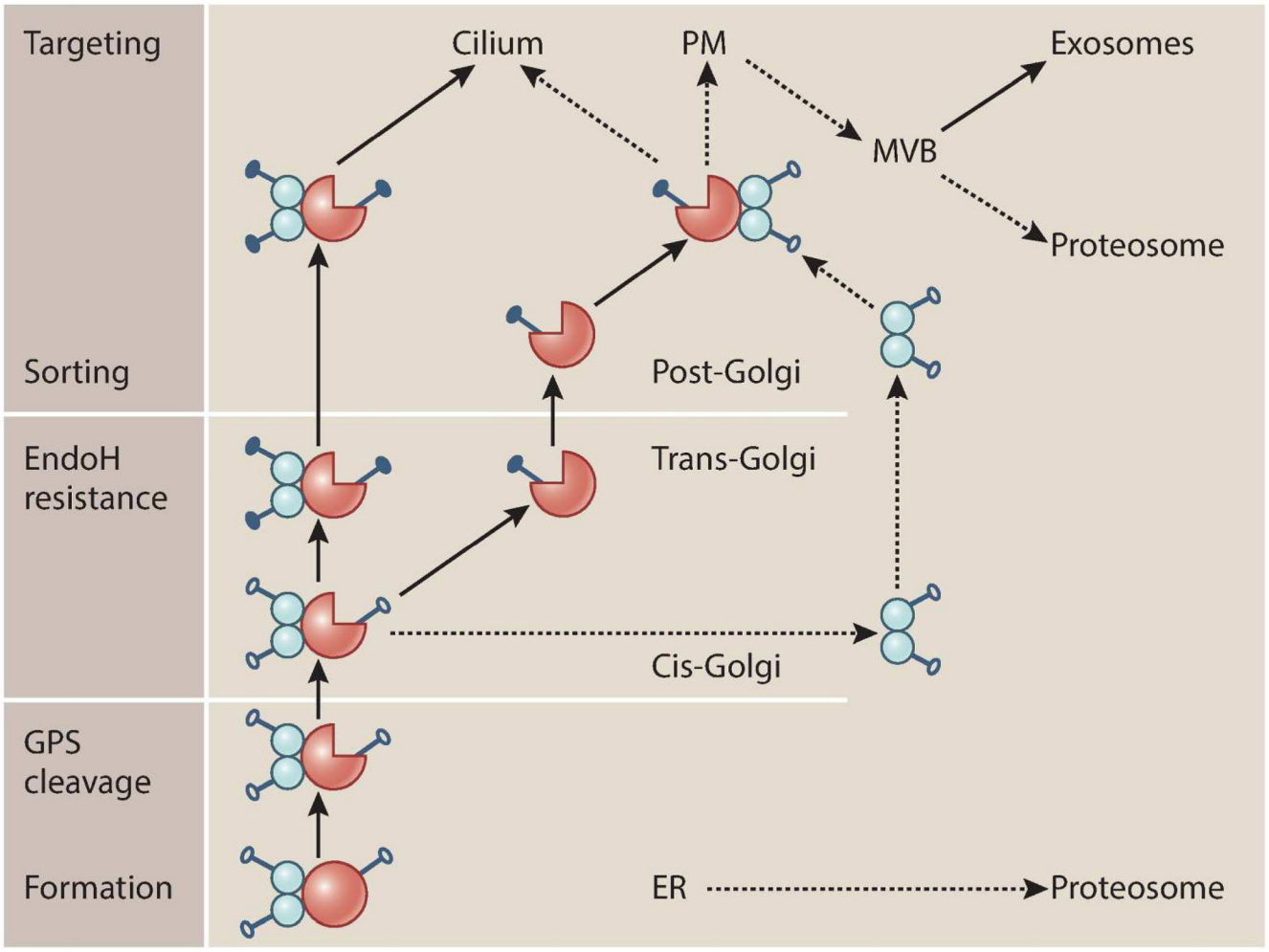

Figure 4. Models of the biosynthesis, maturation and trafficking of the polycystin complex

PC1 (red) binds to PC2 (blue) shown as a putative dimer in the ER prior to undergoing GPS cleavage. At this stage, both proteins are expressed as EndoH-sensitive glycoforms (empty circles). EndoH-resistance (filled circles) is acquired with passage through the *trans*-Golgi with a small pool of an EndoH-resistant complex detectable in primary cilia. An alternative model proposes that EndoH-sensitive PC2 exits the *cis*-Golgi and traffics independently of PC1 which undergoes normal Golgi maturation, acquiring Endo H-resistance. The broken lines indicate other regulatory pathways which could determine the levels of both proteins, complex formation and subcellular localisation.