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REVIEW

Polycystin-1 cleavage and the regulation of transcriptional pathways

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Abstract Autosomal dominant polycystic kidney disease (ADPKD) is the most common genetic cause of end-stage renal disease, affecting approximately 1 in 1,000 people. The disease is characterized by the development of numerous large fluid-filled renal cysts over the course of decades. These cysts compress the surrounding renal parenchyma and impair its function. Mutations in two genes are responsible for ADPKD. The protein products of both of these genes, polycystin-1 and polycystin-2, localize to the primary cilium and participate in a wide variety of signaling pathways. Polycystin-1 undergoes several proteolytic cleavages that produce fragments which manifest biological activities. Recent results suggest that the production of polycystin-1 cleavage fragments is necessary and sufficient to account for at least some, although certainly not all, of the physiological functions of the parent protein.

Keywords Autosomal dominant polycystic kidney disease · Transcription · Proliferation · Apoptosis · Wnt · CHOP · Proteolytic cleavage

Molecular pathogenesis of autosomal dominant polycystic kidney disease

Autosomal dominant polycystic kidney disease (ADPKD) affects approximately 1 in 1,000 people and is the most common potentially lethal genetic disease [1–3]. ADPKD is marked by massive enlargement of the kidneys that is attributable to an abundance of large fluid-filled cysts. These cysts develop over the span of decades, and their expansion destroys adjacent renal parenchyma, leading to end-stage renal disease in approximately 50 % of cases. ADPKD is also associated with cardiovascular, musculoskeletal, and gastrointestinal abnormalities [4]. This condition is caused by mutations in the *PKD1* and *PKD2* genes that encode polycystin-1 (PC1) and polycystin-2 (PC2), respectively. Most ADPKD cases (approx. 85 %) are due to mutations in *PKD1*, while mutations in *PKD2* account for almost all of the remaining cases.

A great deal of effort has focused on elucidating the mechanisms responsible for the autosomal pattern of inheritance in ADPKD. Elegant studies of the genetic material associated with individual cysts suggest that loss of heterozygosity may account for a substantial fraction of cyst development [5]. According to this scenario, cysts arise when "second hit" somatic mutations occur in individual renal epithelial cells that carry one germline mutant *PKD1* or *PKD2* allele. Cells that lose their wild-type copies of *PKD1* or *PKD2* go on to manifest the hyperproliferative and secretory phenotypes that characterize the cyst-lining epithelial cells. In this case, each cyst can be thought of as essentially a benign tumor, and the *PKD1* and *PKD2* genes can be seen to function as benign tumor suppressors. A second model posits that individual cysts may arise as a consequence of stressful stimuli in the context of *PKD1* or *PKD2* haploinsufficiency. The reduced levels of PC1 or PC2 expression associated with heterozygosity might predispose renal epithelial cells to respond to conditions of stress, such as those associated with renal injury, by manifesting the cystic phenotype [6, 7]. These models are not mutually exclusive, and both of them can account for the slow acquisition of cysts over the space of many years that characterizes the natural history of ADPKD.

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Structure, function, and localization of PC1 and PC2

Polycystin 1 is an extremely large protein, with a mass exceeding 460 kDa and 11 predicted transmembrane spans [8, 9]. It is predicted to possess a large (approx. 3,000 amino acid)

extracellular N terminal domain and a short (approx. 200 amino acid) C terminal domain that faces the cytoplasm. The massive PC1 extracellular N terminal domain includes 16 copies of an immunoglobulin (Ig)-like sequence known as the polycystin repeat. It also embodies a number of interesting molecular motifs [10–12] that can participate in protein–protein interactions, supporting the suggestion that PC1 may participate in cell–cell or cell–matrix associations [12–16]. The extracellular domains of PC1 and PC2 may also sense fluid flow and pressure in the kidney [17]. Relatives of PC1 and PC2 (PC1L3 and PC2L1) respond to acidic pH and may contribute to sour taste detection by the tongue [18–20], suggesting that PC1 and PC2 may similarly possess chemosensory properties. PC1 is implicated in a variety of pathways tied to proliferation, including G-protein signaling and the Wnt, AP-1, NFAT [21], and JAK-STAT cascades [22–28]. Moreover, depletion of PC1 increases the rate of cell growth, while its overexpression slows this process, indicating that PC1 may negatively regulate proliferation [29, 30].

PC2 has a molecular weight of approximately 110 kDa and six putative membrane spanning regions [31, 32]. It is a Ca^{2+} permeable cation channel belonging to the transient receptor potential (TRP) family [33, 34]. PC2 mediates the release of Ca^{2+} from intracellular stores and transduces mechanostimulatory signals from the primary cilium [35]. The C terminal cytoplasmic tail of PC1 contains a coiled coil domain that mediates its interaction with PC2 [36, 37]. PC1 and PC2 associate with one another in renal epithelial cells, but little is known about what regulates that association [38]. PC2 may be involved in several signaling pathways [39, 40], including some of the same growth-suppression pathways that have been attributed to PC1 [27]. The PC1 and PC2 proteins interact physically with one another and with numerous other proteins that may modulate their trafficking properties or their involvement in signal transduction [41].

Subsets of the populations of the PC1 and PC2 proteins are associated with the primary cilium [42, 43], where they appear to participate in mechanosensory or chemosensory processes. PC1 and PC2 may also be shed in exosome-like vesicles that can interact with the primary cilium [44]. ADPKD is the most prevalent member of the "ciliopathies", which is a recently defined class of genetic disorders that result from mutations in genes that encode proteins associated with cilium or the basal body [45]. While these disorders are characterized by a variety of pathologies, many of them are notable for the presence of renal cysts [46]. To elucidate the pathogenesis of ADPKD, as well as to understand the function of PC1 and PC2, it will be necessary to develop a thorough insight into the roles of these proteins in the primary cilium and of the mechanisms that control their association with this intriguing organelle.

PC1 cleavage

Polycystin 1 is cleaved at sites in both its – and C-terminal domains [47]. The N-terminal cleavage takes place at the G protein-coupled receptor proteolytic site (GPS), close to the beginning of the first transmembrane domain [48]. This *cis*-autoproteolytic cleavage occurs as PC1 traverses the secretory pathway [48] and is stimulated by PC2 [49]. The cleaved N-terminus appears to remain non-covalently attached to the membrane-bound C-terminal fragment [50]. Mutant forms of PC1 that cannot undergo GPS cleavage are not able to rescue the PKD phenotype in *PKD1*$^{-/-}$ mice [51]. More importantly, a comparable missense mutation is sufficient to cause human ADPKD [48, 51, 52]. A PC1 mutant that cannot undergo GPS cleavage does not reach the cell surface [49].

At least three other cleavages liberate portions of the cytoplasmic C-terminal tail (CTT) of PC1 (Fig. 1). One of these cleavages releases an approximately 35-kDa soluble portion of the tail that accumulates in the nucleus in response to decreased fluid flow in the murine kidney [53, 54]. Low et al. [28, 55] found a more distal cleavage that releases a 17-kDa fragment that interacts with the transcriptional activators STAT3 and STAT6 and the co-activator p100. Flow cessation increased this

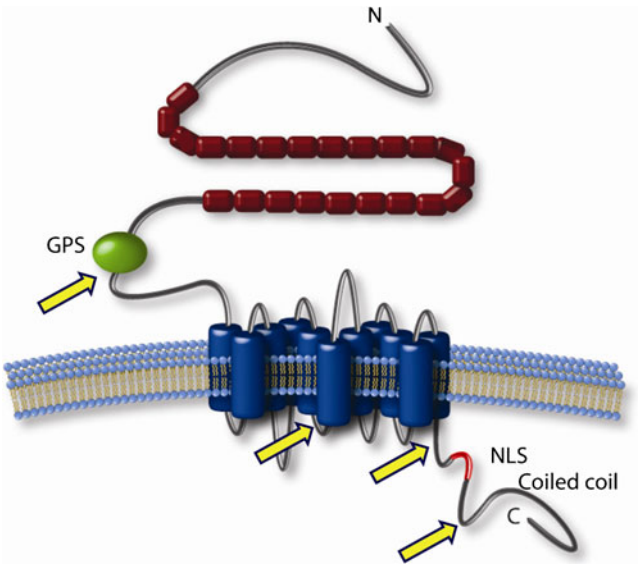

Fig. 1 Schematic diagram of polycystin-1 (PC1) structure and cleavages. PC1 is a massive polypeptide that is predicted to possess a large N terminal extracellular domain (*N*), 11 transmembrane segments (*blue*), and a short cytoplasmic C terminal tail (*C*). The N terminal domain includes 16 copies of the immunologulin (Ig)-like polycystin repeat (*brown*). PC1 undergoes several proteolytic cleavages (*yellow arrows*), including an autocatalytic cleavage at the G protein-coupled receptor proteolytic site (*GPS*) (*green*) that releases the N terminal domain, which remains non-covalently attached to the transmembrane domains. A cleavage in a cytosolic loop segment produces a fragment of approximately 100 kDa [47], and at least two cleavages release portions of the C terminus that enter the nucleus and influence transcriptional pathways [53, 55]. *NLS* Nuclear localization signal/sequence

cleavage as well as the nuclear translocation of both the PC1 tail [53] and STAT6 [28, 55]. A fragment with six transmembrane domains that regulates store-operated calcium entry [47] has also been identified. Although the sizes of these three fragments have been determined and their production is apparently regulated, the amino acid sequences of their cleavage sites and the enzymes and signals that selectively activate each cleavage process have yet to be determined. The C-terminal tail of PC1 contains a PEST sequence, which may facilitate its ubiquitin-mediated degradation [55, 56].

These observations suggest the existence of novel signaling pathways in which CTT fragments of PC1 carry messages from the cell surface to the nucleus. Nuclear translocation of PC1 CTT fragments raises a series of obvious, but nonetheless fascinating questions, namely: "What are the PC1 CTT fragments doing there? Whom do they talk to and what do they say?". Recent studies indicate that nuclear CTT interacts with transcription factors and proteins that modulate gene expression. These studies illuminate a new pathway through which the PC1 CTT influences the activities of several transcription factors whose targets have been linked with PC1 function [57]. It is important to stress, however, that cleavage is one of many physiological processes in which PC1 appears to participate. Cleavage certainly does not account for all of PC1's functional properties, and cleavage-independent PC1 activities are without doubt critically important aspects of the PC1 protein's biology.

To characterize fully the proteolytic events that release PC1 CTT fragments, it will be necessary to ascertain whether and how these cleavages are predicated upon one another [47, 48, 50, 55], to determine which enzymes are responsible, and to establish the sites of action of these enzymes within the PC1 protein. Recent data indicate that γ-secretase plays an obligate role in releasing the 35-kDa PC1 CTT and that the phenotype of wild-type cultured renal epithelial cells subjected to γ-secretase inhibition resembles that of *PKD1*$^{-/-}$ cells [57].

PC1 cleavage and the regulation of the Wnt pathway

Proliferation and apoptosis are prominent among the many cellular processes that are perturbed when expression of the polycystin proteins is disrupted [2, 41]. Cyst-lining epithelial cells appear to be hyper-proliferative [1] and, at least in some models, to manifest high rates of apoptosis [58]. A number of pro-proliferative pathways appear to be activated in the cells that line ADPKD cysts. A gene expression analysis performed on human ADPKD cyst epithelial cells revealed that a number of targets of the Wnt signaling pathway are upregulated in this tissue [59].

The Wnt signaling cascade controls the quantity and activity of β-catenin [60], which is a soluble cytoplasmic polypeptide which interacts with adhesion molecules at sites of cell–cell contact and helps to nucleate the assembly of the submembranous cytoskeleton. When β-catenin is released from cell adhesion complexes it can enter the nucleus, where it binds to and activates the T-cell factor (TCF) transcription factor, which in turn directs the expression of genes whose products drive proliferation. Prior to reaching the nucleus, β-catenin can be recognized by a "destruction complex" that phosphorylates it and targets it for degradation in the proteasome. The binding of extracellular Wnt proteins to the plasma membrane receptor of β-catenin leads to the inactivation of the destruction complex and allows β-catenin to co-activate pro-proliferative pathways. Like many transcription factors, TCF depends upon an interaction with the transcriptional co-activator p300 in order to mediate the transcription of its target genes [61]. The approximately 35-kDa PC1-CTT fragment binds to TCF and prevents it from interacting with p300 [57]. Thus, this PC1 cleavage product acts a profound inhibitor of TCF-mediated gene expression. At least some component of the anti-proliferative influence of PC1 expression, therefore, may be attributable to the ability of a PC1 C terminal tail fragment to suppress the downstream effectors of the Wnt signaling pathway.

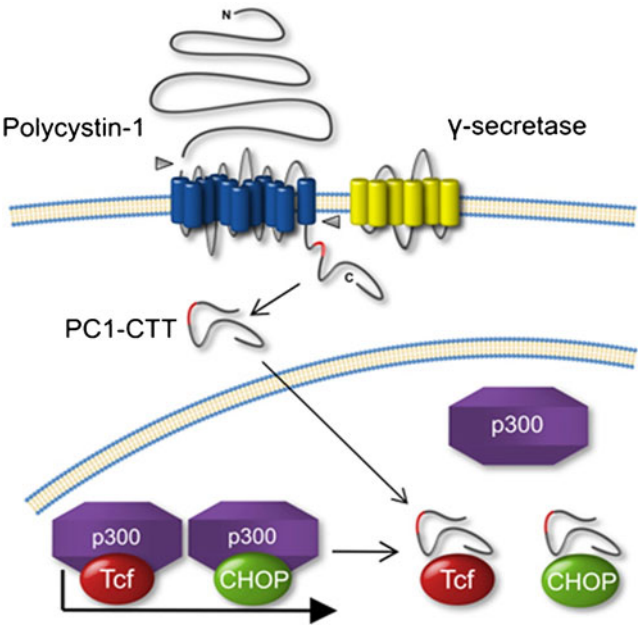

Fig. 2 γ-Secretase-mediated cleavage of PC1 produces fragments that modulate the activity of the T-cell factor (*TCF*) and C/EBP homologous protein (*CHOP*) transcription factors. Data from recent studies [57] indicate that γ-secretase activity participates in generating PC1 cleavage fragments that influence the activity of the TCF and CHOP transcription factors, which in turn modulate proliferation and apoptosis, respectively. Both TCF and CHOP require an interaction with the p300 transcriptional co-activator in order to regulate transcription of their target genes. The C terminal tail of PC1 can interact with TCF and CHOP and prevent interactions between these transcription factors and p300. Thus, γ-secretase-dependent cleavage of PC1 can generate a fragment or fragments that reduce the activities of the TCF and CHOP transcriptional pathways. Reproduced with permission from Merrick et al. [57]

PC1 cleavage and the regulation of the C/EBP homologous protein pathway

A high-throughput screen has been performed to identify additional transcription factors whose functions might be modulated by PC1 CTT fragments [57]. This effort revealed that activity of the C/EBP homologous protein (CHOP) transcription factor is inhibited by the expression of a construct whose sequence corresponds to the C terminal 200 amino acid residues of the PC1 protein. CHOP (also known as Ddit3 and GADD153) is involved in the propagation of apoptosis in response to endoplasmic reticulum (ER) stress [62, 63] that occurs upon accumulation of unfolded or mis-folded proteins [64]. The initial cellular responses to ER stress involve efforts to reduce the incoming load of proteins into the ER [65], to upregulate the expression of chaperones to assist in protein folding, and to eject mis-folded proteins from the ER for destruction by the ubiquitin–proteasome system [66, 67]. If these measures are not sufficient to clear unfolded proteins from the ER, the cell commits to apoptosis [68]. Three signaling pathways are employed in the initiation of apoptosis: transcriptional activation of CHOP, activation of the JNK pathway by the Ire1-TNF/ASK1 complex [68], and activation of ER-associated caspace-12 [69].

C/EBP homologous protein is a 29-kDa protein containing an N-terminal transcriptional activation domain and a C-terminal basic-leucine zipper (bZIP) domain, which is essential for CHOP-induced apoptosis [63, 70]. Under normal physiological conditions, CHOP is ubiquitously expressed at very low levels, but its expression is highly upregulated upon induction of ER stress [71]. While much progress has been made in elucidating the signaling pathways that regulate CHOP activation, relatively little is known about the downstream targets of CHOP. Overexpression of CHOP leads to cell cycle arrest and apoptosis [63, 72], whereas $CHOP^{-/-}$ mice demonstrate reduced cellular apoptosis in response to ER stress [73].

Like TCF, CHOP requires an interaction with the p300 transcriptional co-activator in order to function [61, 74]. The approximately 35-kDa fragment of PC1 binds to CHOP and prevents it from assembling with p300 [57]. In keeping with this behavior, overexpression of a construct that corresponds to the approximately 35-kDa C terminal tail fragment of PC1 reduces CHOP activity, as measured by transcriptional reporter assays. More significantly, overexpression of this PC1-CTT fragment also dramatically reduces the high rate of apoptosis that is observed in $Pkd1^{-/-}$ cells grown in culture. Thus, PC1 fragments produced as a consequence of PC1 cleavage appear to interact with and suppress the activities of pro-proliferative and pro-apoptotic transcription factors through very similar mechanisms (see Fig. 2).

Signaling by PC1 cleavage fragments in vivo

The in vitro experiments discussed in the preceding sections suggest that C terminal tail fragments of the PC1 protein possess biological activity and that they are able to influence transcriptional pathways that are relevant to aspects of the ADPKD phenotype. Confirmation of the relevance of PC1 C terminal cleavage to the prevention or development of ADPKD, however, will require demonstrations that these processes are necessary and sufficient to account for at least some of the functions of the PC1 protein in vivo.

Zebrafish express two *Pkd1* orthologs, *Pkd1a* and *Pkd1b*. The simultaneous morpholino-induced knockdown of *Pkd1a* and *Pkd1b* expression in zebrafish embryos produces a number of phenotypes, including pronephric duct cysts, hydrocephalus, and skeletal abnormalities [75]. One of the most robust and readily quantifiable of these phenotypes is the development of upward-facing tail curvature. It is interesting to note that a similar tail curvature is also observed in zebrafish embryos that have been treated with inhibitors of γ-secretase [76]. While the γ-secretase-dependent pathway that is responsible for this effect has not been fully elucidated, its similarity to the *Pkd1a* and *Pkd1b* morphant phenotype suggests that these two interventions may influence the same process. Support for this hypothesis derives from the observation that transgenic expression of a construct encoding the C terminal 200 amino acid residues of PC1 is sufficient to at least partially rescue the tail curvature phenotypes that are produced by both *Pkd1a* and *Pkd1b* knockdown and by γ-secretase inhibition [57]. These data lend in vivo support to the concept that PC1 C terminal tail cleavage is required for this protein to fulfill its biological functions and that a released fragment of the PC1 C terminal tail is sufficient to recapitulate at least some of those functions.

Conclusions

Autosomal dominant polycystic kidney disease is a complex disease. Its pathogenesis is attributable to mutations in two genes whose products localize to a number of cellular structures and participate in a number of cellular signaling pathways. Both PC1 and PC2 localize to the primary cilium, and this fascinating organelle clearly plays a critical role in governing processes that, when perturbed, participate in the development of renal cysts. Much remains to be learned about the nature of these processes and about the cellular machinery through which they are actuated. PC1 protein undergoes several proteolytic cleavages, and the products of these cleavages possess important biological activities. The production of at least some of these fragments appears to be a prerequisite in order for PC1 to fulfill its complete range of physiological

functions. Furthermore, these fragments appear to be capable of mediating some of these functions even when expression of the full-length parent protein is suppressed or absent. Future research will be required to understand how and where PC1is cleaved and to determine whether and how these cleavages are obligate aspects of the biology of the polycystins and polycystic kidney disease.

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