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Mini Review

Interaction of Gα12 and Polycystin-1 in Autosomal Dominant Polycystic Kidney Disease

Frank Z. Xu, Tianqing Kong#* and Tzongshi Lu#

Renal Division, Brigham and Women's Hospital, Harvard Medical School, USA

#Both authors contribute equally

***Corresponding author**

Tianqing Kong, Renal Division, Harvard Institutes of Medicine, Rm# 550, 77 Avenue Louis Pasteur, Boston, MA 02115, USA, Tel: 617-525-5812; Fax: 617-525-5830; Email: tqkong@gmail.com

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Abstract

Polycystin-1 (PC1) is a large cell membrane protein. Its mutation is responsible for the majority of autosomal dominant polycystic kidney disease (ADPKD). PC1 complexes are localized in kidney apical and baso-lateral regions. It affects polarity, cell-cell contact and cell-matrix adhesion. Heterotrimeric G proteins are critical signaling molecules in renal cystogenesis in ADPKD. The activated status is regulated by G protein-coupled receptors (GPCRs) and non-GPCRs. PC1 has been thought as an unconventional GPCR, but the signaling pathways of PC1 and G proteins remain unclear. As a heterotrimeric G protein, Gα12 is essential for renal cystogenesis induced by Pkd1 knockout in mice. Deletion of *Pkd1* increases the activation of Gα12. Active Gα12 is involved in adherens junction, integrin-mediated cell-matrix adhesion, and stress fibers. It also promotes the activation of Adam10, which increases the shedding of E-cadherin, and changes the signaling pathways of Wnt/β-catenin. Additionally, active Γα12 promotes epithelial–mesenchymal transition (EMT) in kidney epithelial cells. Furthermore, active Gα12 affects the focal adhesion kinase (FAK) and paxillin functions, weakens the integrin-mediated cell-matrix adhesion, and strengthens stress fibers. The deletion of Gα12 disrupts the integrity of cell-cell contact and cell-matrix interaction. In conclusion, Gα12 is a key signaling molecule for PC1 in the pathogenesis of ADPKD. Inhibition of Gα12 activity could be used as an effective therapeutic target for ADPKD.

INTRODUCTION

ADPKD and G proteins

Autosomal dominant polycystic kidney disease (ADPKD) is characterized by gradual enlargement of multiple kidney cysts, which destroy the normal structure of nephrons and eventually causes end-stage renal disease (ESRD). Dialysis or kidney transplantation is the only option for these patients with ESRD. Mutation of *PKD1* (encoding PC1) or *PKD2* (encoding polycystin-2, PC2) causes 85% and 15% of all ADPKD cases, respective [1-3]. The cellular changes such as dysregulation of dedifferentiation [4], proliferation and apoptosis [5,6], disruption of cell polarity [7], altered interactions of cell-matrix interaction [8,9] and cell-cell contact [10], and chronic inflammation and collagen accumulation [11,12], are all observed in renal epithelial cells of ADPKD. Over the last few decades, extensive studies have been conducted and revealed much information about biological function of polycystins, particularly PC1. The PC1 signaling molecules consist of Ca2+, cAMP, JNK and AP-1 [13], mTOR [14], JAK/STAT [15], integrins [16,17], E-cadherin/Wnt [18], and G proteins [19,20].

G proteins (or heterotrimeric G proteins) play important roles in the signal transduction from external signals to intracellular action. Generally, the signaling transmission is involved with cell-surface G protein-coupled receptors (GPCR), which are stimulated by a variety of signals such as ions, photons, mechanical force, drugs, hormones or proteins. GPCRs are characterized by their seven trans-membrane spanning domains with outside N-terminus and the intracellular C-terminus. GPCRs are usually stimulated by their ligands or signals via the N-terminus and/or with a pocket formed by the extracellular and transmembrane domains. After stimulation, GPCRs undergo conformational changes and activate intracellular signaling networks via G proteins, which initiate related cellular responses [21,22]. There are four major families of G proteins based on their different α subunits: Gαs, Gαi/o, Gαq, and Gα12/13. The signal is processed through the GTP binding to Gα, which tseparates from from Gβγ, and activates downstream effectors. Finally, the hydrolysis of GTP to GDP on Gα terminates the signal [23].

Initially, a conserved heterotrimeric G-protein activation sequence was noticed in the cytoplasmic tail of PC1. Then, this sequence was found to bind to the heterotrimeric G protein: Gi/Go *in vitro* [19]. In addition, PC1 cytoplasmic tail specifically binds to Gα12 but not Gα13. This association is important in regulating the apoptosis of kidney epithelial cells via JNK/bcl2 pathway [24]. Through mutation analysis, a few amino acids in PC1 cytoplasmic tail are integral for the binding to Gα12 and this apoptosis signaling [25]. Polycystin-1 (PC1) could function as an atypical GPCR in renal epithelial cells, and controls the ion channel of polycystin-2 (PC2) [26,27], regulates activity of G-protein

subunits or its accessory proteins. As an accessory protein, G-protein signaling modulator 1 (GPSM1) is a GPCR-independent regulator of G proteins. It increases the proliferation of kidney epithelial cells in polycystic kidney disease [28]. In addition, knockout of GPSM1 enhances the development of kidney cysts in ADPKD mice [29].

Recently, Gα12 has been found to be an essential signaling molecule in pathogenesis of multiple kidney cysts induced by *Pkd1* knockout in mice [30]. These mice develop a large amount of kidney cysts after *Pkd1* gene is deleted. The pathogenesis of cysts in these mice is similar to the development of multiple kidney cysts in ADPKD patients. Multiple hepatic cysts are also observed. However, deletion of Gα12 in the ADPKD mice blocks the cystogenesis in kidneys but not in livers [30], which indicates that this Gα12-PC1 signaling pathway is specific in kidneys. Over the last few years, Gα12 has been reported to affect several biological functions in renal epithelial cells, which include integrin-mediated cell-matrix adhesion, cadherin/β-catenin signaling, focal inflammation and fibrosis. All of these are consistent with the pathological changes in cystic renal epithelial cells in ADPKD.

ADPKD AND CELL-MATRIX ADHESION

Alternated matrix adhesion is one of the major changes in renal epithelial cells in ADPKD. Integrins are the key parts in cell-matrix adhesion. Most of the interaction between renal epithelial cells and matrix are mediated via β1 integrin, which forms a heterodimer complex with different α subunits such as α1, α2, α3, α5 and α6. The distribution of intgerins is abnormal in the renal epithelial cells of both ADPKD and ARPKD [21]. In the renal tubule epithelia, integrins α2β1 and α6β1 are the most dominant. The collagen I and IV in the matrix are the ligands for α2β1. Laminin is the ligand for α6β1 and α6β4 [31,32]. Their binding elicits a series of changes in structure and function of epithelial cells, eventually leading to the change in its migration and morphology.

Some extracellular matrix metalloproteinase may also be involved in the renal cystogenese of ADPKD. For instance, matrix metalloproteinase 9 (MMP9) is altered [33,34]. Abnormal expression of basement membrane laminins also promote cystic growth in ADPKD [35,36]. Change in extracellular matrix composition and integrin profile causes the cystic growth of kidney epithelial cells [37].

The binding site between integrins and extracellular matrix (ECM) is called focal adhesion. It is located at the submembrane region where ECM interacts with cytoplasmic actin cytoskeleton. It is a huge complex that forms with integrins, vinculin, talin, paxillin, α-actinin, tensin and focal adhesion kinase (FAK). In kidney epithelial cells of ADPKD, these PC1-complexes are localized at the adhesion site with collagen [17,38].

Functional defects of several integrins are observed in renal epithelial cells in ADPKD. In the early stage of renal cystogenesis, the distribution of integrins α2, α3 and α6 is altered. In addition, the expression level of integrin α1 is increased specifically in the collecting ducts of ADPKD [39]. These early changes could directly result from the defect of PC1 in ADPKD patients. β1 integrin forms a functional heterodimer complex with each of the α subunits above. Therefore, β1 integrin is critical for the integrity of cell-matrix in the renal epithelial cells. Early studies show that specific β1-contained integrins are involved in the differentiation of different parts of nephron segments [40,41].

In a kidney epithelial cell line, activation of Gα12 causes the cystic growth of these cells in a collagen gel three dimensional cell culture system. Activation of Gα12 reduces the adhesion of the cell on collagen I, a ligand for α2β1 integrins. This change results from the modulation of the phosphorylation status of FAK and paxillin. There is no change in the expression level of α2β1 integrins on the cell surface [42]. In these cells, the function of α6β1 integrins is also altered after Gα12 is activated. The expression of α6 subunit is decreased significantly after Gα12 is activated. Therefore, the adhesion of cells on laminin-5 (ligand for α6β1 integrins) is reduced [43]. Gα12 is specifically associated with the cytoplastic tail of PC1 [24]. The effect of Gα12 is dependent on its binding to the cytoplasmic tail of PC1. The uncoupling mutations of the Gα12 binding sites in the cytoplasmic tail of PC1 abolish the decreasing effects of activated Gα12 on cell adhesion. Activation of Gα12 decreases some of phosphorylation sites of FAK and paxillin. Ectopic expression of PC1 increases focal adhesions but reduces stress fibers. Activated Gα12 decreases focal adhesions but promotes stress fibers [30]. These data indicate that PC1 negatively regulates Gα12 activation on cell-matrix adhesion.

It has been long reported that the interaction between α6β4 integrins and their ligand lamnin-5 are disrupted in polycystic kidney disease [44]. Recently, it has been reported that deletion of integrin β1 gene prevents the development of kidney cysts in ADPKD induced by loss of PC1. Deletion of integrin β1 not only affects the focal adhesions but also reduces the extracellular matrix proteins and focal fibrosis in kidney tissues of ADPDK mice [16]. This study provides a direct genetic evidence that integrin β1 is essential for the development of kidney cysts in ADPKD.

ADPKD AND CELL-CELL ADHESION

Cell-cell adhesion contains several protein complexes: tight junction, adherens junction, desmosome and gap junction. Among them, adherens junction is the most important in maintaining the integrity of cell polarity and morphology of renal epithelial cells. This adhesion system is also called E-cadherin-mediated intercellular junction. It is cytoskeleton-related communication system between two adjacent cells both in normal organ development and pathological processes. Classically, this complex is composed of E-cadherin/(α, β)-catenins/actin filaments, which is needed for cell aggregation [45]. Technological advances and more research reveal that the dynamic change of adherens junction is much complicated. There are two stages for adherens junction formation. Underneath the plasma membrane, cadherins and its associated proteins promote homophilic binding between two cadherin ectodomains and cell-cell contact. This process could lead to the formation of a typical adherens junction or keep cells in an immature state for less adhesion and easy migration in epithelial cells [46].

Abnormality and loss of E-cadherin function are observed in ADPKD [47,48]. In renal epithelial cells, both PC1 and PC2 are in E-cadherin complex and involved in the canonical signaling

pathway of Wnt/β-catenin [18,49-51] Gα12 is physically associated with PC1 [24,25,52]. Gα12 could have an impact on the PC1/Wnt/β-catenin signaling. Gα12 has recently been reported to be a key regulator for E-cadherin. First, in kidney epithelial cells, active Gα12 promotes the activation of a disintegrin and metalloproteinase domain-containing protein (ADAM)10 [53]. ADAM10 is a family of cell surface metallopeptidase with functions as sheddase. It cleaves cell surface proteins and extracellular matrix including E-cadherin and TNF, and is involved in cell-cell and cell matrix adhesion [54]. Activation of Gα12 increases the shedding of E-cadherin, which is dependent on the ADAM10 activity. The cleavage of E-cadherin causes β-catenin to translocate into nucleus, and triggers the Wnt signaling pathway and affects cell-cell adhesion and cell polarity [53]. In addition, loss of PC1 and activation of Gα12 promote the early form of N-cadherin in renal epithelial cells [55]. In epithelial cells, there are two forms of N-cadherin. Its early form is dominated when cells grow loosely without cell-cell contacts, which favors cell proliferation. Whereas, the late form of N-cadherin is mainly present when the cell growth reaches very dense state, and cell-cell adhesions and polarity are established. At this stage, the late form of N-cadherin prohibits cell proliferation [55].

Epithelial–mesenchymal transition (EMT) is a series of changes in epithelial cells such as loss of epithelial characters, loss of cell-cell adhesion, and increase of cell motility [56]. During the pathological process of renal cyst development, tubular epithelial cells undergo EMT [57]. Interstitial fibrosis in kidney tissue is one of the changes in PKD, which is also one of the main features of EMT. In ADPKD patients, EMT is responsible for the cystogenesis and progression of the kidney cysts [58,59]. The hallmark of EMT is the E-cadherin to N-cadherin switch. In certain tumor cells, the aggressive growth is correlated with this E-cadherin/N-cadherin switch with decreased expression of E-cadherin and increased level of N-cadherin [60]. In colon cancer epithelial cells, both PC1 and PC2 is involved in EMT and promoting the malignant growth [61]. By use of virtual-tissue computer simulations, the initiation and development of renal cysts, the change in cell adhesion and proliferation is required. The epithelial cells undergo decreased cell-cell contact inhibition and increased cell proliferation. Loss of cell-cell adhesion due to cadherin switch is enough to drive renal cystogenesis [62]. We have found that activated Gα12 cleaves the extracellular domain of E-cadherin, and promotes the early form N-cadherin [30,53]. These data indicate that deletion of *Pkd1* or activation of Gα12 induces EMT of kidney epithelial cells, which favors the change of polarity and morphology of renal epithelial cells in ADPKD.

CONCLUSION

Gα12 is essential for renal cystogenesis in ADPDK. It functions as a key signaling molecule in the PC1 complex that regulates adherens adhesion, cell-matrix adhesion and morphology. E-cadherin to N-cadherin switch or EMT is also a major pathological process that regulated by Gα12 (Figure 1). Inactivation of Gα12 does not show any phenotype abnormality in mice [63]. Therefore, some small molecules could be developed to specifically inhibit Gα12 activity. It would cause less impact on normal cells but specifically inhibit the activity of Gα12 in cystic renal epithelial cells, which could block the development and expansion of kidney cysts in ADPKD.

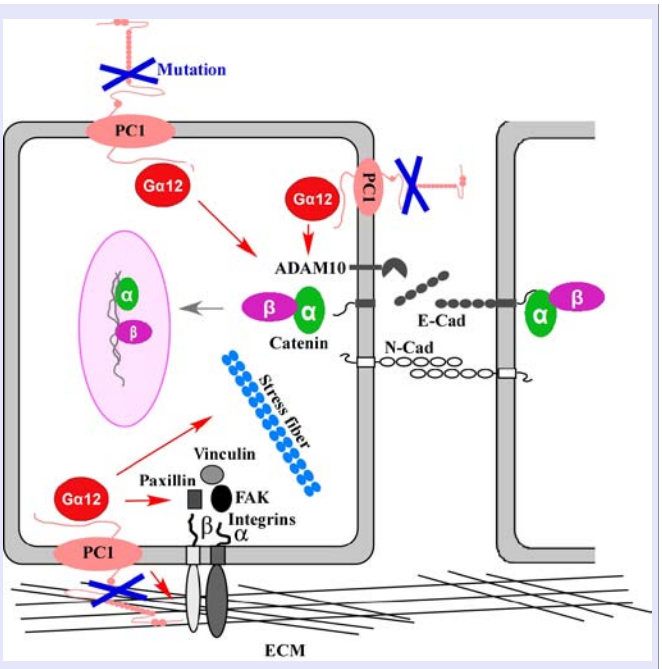

Figure 1 Schematic diagram of the Gα12 and PC1 signaling in renal cystogenesis. PC1 complexes are located in apical, baso-lateral regions of renal epithelial cells. Mutation of PC1 activates Gα12. It increases the activation of ADAM10 that promotes the shedding of E-cadherin, which subsequently releases catenins that translocate into nucleus and trigger certain gene expression. Eventually it changes cell polarity, cell-cell adhesion, and growth behavior. In addition, mutation of PC1 and activation of Gα12 also affect N-cadherin, cell-cell adhesion (integrin-mediated focal adhesion), stress fiber, extracellular matrix (ECM) accumulation, and interstitial fibrosis. All of these favor the development of kidney cysts. Blue cross: mutation or inactivation; Red arrow: activate; grey arrow: translocate.

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