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EDITORIAL

Polycystins and mechanotransduction: From physiology to disease

Christina Piperi, Efthimia K Basdra

Christina Piperi, Efthimia K Basdra, Department of Biological Chemistry - Cellular and Molecular Biomechanics Unit, Medical School, University of Athens Medical School, 11527 Athens, Greece

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Correspondence to: Efthimia K Basdra, Associate Professor, Department of Biological Chemistry - Cellular and Molecular Biomechanics Unit, Medical School, University of Athens Medical School, 75, M. Asias Street, 11527 Athens, Greece. ebasdra@med.uoa.gr
Telephone: +30-210-7462547
Fax: +30-210-7462703

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Abstract

Polycystins are key mechanosensor proteins able to respond to mechanical forces of external or internal origin. They are widely expressed in primary cilium and plasma membrane of several cell types including kidney, vascular endothelial and smooth muscle cells, osteoblasts and cardiac myocytes modulating their physiology. Interaction of polycystins with diverse ion channels, cell-cell and cell-extracellular matrix junctional proteins implicates them in the regulation of cell structure, mechanical force transmission and mechanotransduction. Their intracellular localization in endoplasmic reticulum further regulates subcellular trafficking and calcium homeostasis, finely-tuning overall cellular mechanosensitivity. Aberrant expression or genetic alterations of polycystins lead to severe structural and mechanosensing abnormalities including cyst formation, deregulated flow sensing, aneurysms, defective bone development and cancer progression, highlighting their vital role in human physiology.

Key words: Polycystins; Mechanotransduction; Kidney; Endothelium; Osteoblasts; Cancer

Core tip: Polycystins are key regulators of mechano-sensation in several cell types including kidney, vascular endothelial and smooth muscle cells, osteoblasts and cardiac myocytes. Their expression in primary cilium, plasma membrane and endoplasmic reticulum, along with their ability to interact with diverse ion channels, cell-cell and cell-extracellular matrix junctional proteins renders polycystins as essential regulators of overall cellular mechanoresponse. Abnormal expression or genetic defects of polycystins result in severe structural and mechanosensing faults including cyst formation, deregulated flow sensing, aneurysms, defective bone development and cancer progression, highlighting their crucial role in human physiology.

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INTRODUCTION

Cellular mechanosensitivity plays fundamental role in cell viability and function, tissue development and maintenance of organs. Most cell types are able to respond to mechanical forces which provide them with a means of actively sensing and responding to mechanical properties such as topography and rigidity of the environment. Mechanical forces can be of external (such as acceleration, gravity, touch, stretch, sound) or of internal origin (breathing, fluid flow, blood pressure, osmotic pressure, heart contraction or any membrane deformation) and can vary from modest to high intensity depending on the cell type[1].

Mechanosensitivity constitutes a three-step process. It starts with detection of a mechanical stimulus by a cellular component, followed by mechanotransduction that converts the mechanical signal into a biophysical or biochemical signal, ending with the mechanoresponse during which signal sensation and transduction integrate over space and time[2].

Several mechanosensation models have been proposed based on the nature of the mechanosensor proteins[2-4]. Transmembrane proteins sense mechanical stimuli through changes in tension in their surrounding lipid bilayer ("bilayer tension model"[5]). Proteins involved in cell adhesion and maintenance of cell structure sense mechanical tension through binding with structural components that can transmit force from the intracellular or extracellular side or both ("Tethered protein model"). In this model interaction between the mechanosensor and proteins of the cell-cell junctions, extracellular matrix (ECM), focal adhesion points, microtubules or actin cytoskeleton has been reported. The way a protein responds to the applied force can also differ. A force applied to a mechanosensing protein can unfold it and expose cryptic peptides that can activate intracellular pathways and mechanotransduction[6] ("protein unfolding model"). Mechanical forces either exert a direct effect on the intrinsic activity of the mechanosensor proteins such as ion-channel gating, enzyme activity or ligand-receptor interactions ("mechanosensitive protein activity model"), or an indirect effect by activating a non-mechanosensitive protein leading to mechanotransduction ("adjacent mechanosensitive protein model"). The indirect activation can be through ligand release or through protein-protein interaction. All these models can also work in concert in order to form mechanosensitive complexes.

Mechanosensation is widely distributed in cellular compartments and involves the interaction of several protein complexes including adherent junctions, desmosomes, integrins, focal adhesion points, receptors and actin microtubules. Most of these proteins are connected to signaling pathways that involve cytosolic molecules, calcium signaling or transcription factors[7]. Their expression should match within time and space to the sensory function of the mechanosensor organ, while removal of the protein should annul the sensory response. Mutations that change protein function can modify the mechanosensing ability of the organ or cell. A heterologous expression of the mechanosensor protein in another cell type should lead to a mechanical response.

Interestingly, the protein family of polycystins has been shown to physically interact with most mechanosensing protein complexes mentioned above. Polycystins are implicated in renal flow sensing[8], vascular pressure and flow mechanosensation[9-11], blood-brain barrier mechanical injury[12], nodal flow sensing[13], skeletal development and osteoblast differentiation[14,15] as well as cancer progression[16].

POLYCYSTINS - STRUCTURE AND LOCALIZATION

Polycystins are large integral proteins, broadly expressed in human tissues including kidneys, blood vessels, heart, liver, pancreas, bone and brain. They are found localized in the primary cilium, at the plasma membrane and at endoplasmic reticulum (ER) where they associate and interact with numerous partners[17].

Polycystin 1 (PC1, 460 kDa) consists of 11 transmembrane segments, a short intracellular C-terminal region (200 amino acids) and an extracellular N-terminal part (3000 amino acids) which contains several protein motifs. These include a G protein-coupled receptor proteolytic site, two cysteine-flanked leucine-rich repeats, sixteen Ig-like domains and a C-lectin domain. The terminal intracellular C-region contains a coiled-coil domain (CC) as well as a G protein-binding site (G).

PC1 is found localized at the primary cilium and at the plasma membrane being involved in interactions between proteins and between proteins-carbohydrates. Scientific data support interaction of PC1 with many proteins localized at focal adhesion points, adherens junctions and desmosomes[18].

Polycystin 2 (PC2, TRPP2, 110 kDa) is composed of six transmembrane segments, an intracellular N-terminus which contains a ciliary sorting motif and an intracellular C-terminus with a calcium-binding EF domain, an ER retention domain and a CC domain. PC2 is located in the ER[19] while its translocation to the plasma membrane has been reported to require the presence of PC1[20].

PC2 belongs to the transient receptor potential (TRP) channel family proteins. It has been shown to interact with cytoskeletal proteins as well as other mechanosensitive ion channels in different cells, including potassium-selective stretch-activated potassium channels and non-selective cationic SAC channels.

PC1 and PC2 may interact through their CC domains located in the cytoplasmic C-termini forming an ion channel complex, as well as with many other partners in various subcellular localizations[20,21]. They are considered as important regulators of calcium homeostasis by affecting the resting cytosolic calcium

concentration, decreasing sarcoplasmic reticulum (SR) Ca^{2+}-ATPase (SERCA2a) expression and inhibiting the passive leakage of Ca^{2+} from the ER[22].

Since the original studies that identified polycystins and their gene mutations as a causative link to autosomal dominant polycystic kidney disease (ADPKD), considerable progress has been made in revealing the physiological functions of these proteins in multiple tissues, such as lung, kidney, cardiovascular, brain and bone[14].

POLYCYSTINS - MECHANOTRANSDUCTION IN THE KIDNEY

In the kidney, polycystins are detected at the cilia of renal epithelial cells[23]. PC1 though its extracellular domain is functions as mechanosensor detecting urine flow. Activation of PC1 leads to mechanotransduction by opening the PC2 channel allowing calcium entry and triggering intracellular calcium release in the ER through inositol 1,4,5-trisphosphate (IP3) or ryanodine receptors[8,24]. The mechanical properties of PC1 can be changed by osmolytes such as sorbitol or urea (a major urine component) and modulate mechanosensation[25]. Furthermore, at the primary cilium flow detection by PC1/PC2 complex induces proteolytic cleavage of the intracellular PC1 C-terminus (34 kDa fragment, called CTT), activation of signaling pathways [mammalian target of rapamycin (mTOR), Janus kinase/signal transducers and activators of transcription (JAK/STAT), Wingless-Int (Wnt)] and gene expression changes in order to get a mechanoresponse[26,27]. PC2 does not seem to need the presence of PC1 for its channel activity but it rather forms a heteromeric channel with TRP channel subfamily c member 1 (TRPC1)[27].

Flow sensing by primary cilium has been associated with increased intracellular calcium concentration being lost in PC1 or PC2-deficient cells and it has been proposed to result in cyst formation in polycystic kidneys[28].

Loss-of-function *Pkd1* or *Pkd2* gene mutations encoding PC1 and PC2, are responsible for ADPKD, the most common kidney disease, affecting almost 1 in 1000 individuals[29]. ADPKD clinical phenotype involves cysts presence in the kidney, pancreas, and liver along with severe cardiovascular defects. Arterial hypertension and intracranial aneurysms are often associated with this multisystem disease.

POLYCYSTINS - MECHANOTRANSDUCTION IN VASCULAR TISSUES

PC1 and PC2 expression has been observed in the plasma membrane and primary cilium of endothelial cells, proposed to transmit extracellular shear stress[30]. Shear stress-induced activation of PC2 has been demonstrated to increase the biosynthesis of intracellular NO leading to smooth muscle dilatation and flow-induced vascular relaxation[31].

In agreement, a previous study from our group using partial carotid stenosis to induce low shear stress *in vivo*, has shown upregulation of PC1 and PC2 in endothelium at the low shear stress area[11], implicating both proteins in blood flow alterations sensing. Since low shear stress conditions have been associated with atherosclerotic plaque development, a role of polycystins in atherosclerosis is possible.

Polycystins have been shown to interact with the two major calcium-release channels, IP3 receptors in epithelial cells and ryanodine receptors in cardiomyocytes. PC1 interacts with the IP3 receptors to reduce calcium levels[32]. Similarly, in the heart, PC2 interacts with the ryanodine receptor RyR2 *via* its C-terminus to modulate release of Ca^{2+} from the SR stores[33].

Notably, PC2 can form a channel with TRPC1, being activated in response to mechanical damage of blood-brain barrier endothelial cells by promoting Ca^{2+} influx and formation of actin stress fibers[12].

Finally, in vascular smooth muscle cells PC2 has been implicated in sensing pressure volume and in mesenteric and cerebral arteries in sensing myogenic tone[19,34].

POLYCYSTINS - MECHANOTRANSDUCTION IN OSTEOBLASTIC LINEAGE CELLS

In osteoblasts, the polycystin-primary cilia signaling complex has been attributed a mechanosensory role that regulates skeletogenesis and bone formation. Evaluation of the skeletal phenotype of *Pkd1*-deficient mice revealed PC1 implication in bone development and in the regulation of osteoblast function through intracellular calcium-dependent control of Runx2 expression. Furthermore, abnormal bone development and osteopenia was observed upon loss of *Pkd1* function in mice due to impaired osteoblast differentiation[14].

Another study of a mouse model with midpalatal suture expansion demonstrated that proliferation and differentiation of periosteal osteochondroprogenitor cells that were mechanically stimulated requires *Pkd1*[35]. This is in concert with a recent study from our group, exploring PC1 involvement in mechanical load (stretching)-induced signaling pathways in human pre-osteoblasts. In this study, PC1 was revealed as a major mechanosensor molecule in osteoblasts that modulates their differentiation and gene transcription through the calcineurin/nuclear factor of activated T-cells signaling pathway, thus controlling bone formation[15].

POLYCYSTINS INTERACT WITH CELL ADHESION AND CYTOSKELETAL PROTEINS TO TUNE OVERALL CELLULAR MECHANOSENSITIVITY

Polycystins ability to form multiprotein complexes with components of adherens junctions, focal adhesions, desmosomes and cytoskeleton suggests their critical role in regulating cell-ECM as well as cell-cell interactions.

Strong homophilic interactions between the Ig-like domain of PC1 with other PC1 and Ig domain-containing proteins of neighboring cells have been detected in the Madin-Darby canine kidney cells indicating their role in intercellular adhesion[30]. In cultures of renal epithelial cells, PC1 localizes at lateral cell junctions, involved in cell-cell interactions[30]. In addition, PC1 has been demonstrated to bind to focal adhesion proteins including integrins, pp125 focal adhesion kinase (pp125FAK), vinculin and paxillin which are required for cell adhesion to the ECM[36,37]. Of note, some of these associations have been lost in ADPKD epithelial cells[36].

In aortic smooth muscle cells, PC1 interacts with PC2 at the dense plaques which are involved in the interaction between the cytoskeleton, plasma membrane and ECM[38]. Regarding the components of adherens junctions, PC1 associates with E-cadherin and α-, β- and γ-catenins in a multiprotein complex required for maintenance of tissue structure and function[39,40]. In ADPKD renal epithelial cells, disruption of this multiprotein complex has been observed leading to depletion of PC1 and E-cadherin from the plasma membrane.

In desmosomes, the most abundant cell-cell junctions, PC1 has been found to directly bind though its cytoplasmic tail the CC motif of the intermediate filament proteins cytokeratins 8 and 18, desmin and vimentin[41]. In ADPKD cysts, these desmosomal elements are severely disoriented[42].

Finally, cytoskeletal proteins such as actin-binding proteins, cardiac troponin and tropomysin have been directly associated with PC2 channel activity upon stimulation by osmotic or hydrostatic pressure[43,44]. These numerous partners indicate that polycystins play a central role in the way cells adapt to their mechanical environment.

POLYCYSTINS - IMPLICATION IN CANCER PROGRESSION

All the aforementioned protein interactions that affect cell-cell and cell-ECM communication have been previously associated with cancer. Moreover, mechanical signals have been shown to regulate cancer cell interactions influencing decisive steps of invasion and metastasis. Recently, we have demonstrated the implication of PC1/PC2 in colorectal cancer progression. Overexpression of polycystins was associated with aggressive colorectal cancer phenotype *in vitro*. Clinical analyses revealed a correlation of elevated PC1 expression with poor recurrence-free survival, while aberrant PC2 levels was correlated with poor overall survival[16]. Several studies have also reported a connection between cancer proliferation, migration and metastasis with alterations in ion channels expression, and particularly with changes in TRP channel proteins[45]. More specifically, TRP channel subfamily M member 8 and TRP protein homologue (TRP6) were found highly expressed in prostate cancer where they correlate with histological grade. TRP channel subfamily M member 7 is implicated in proliferation and growth of breast cancer and head and neck tumor cells while TRP channel subfamily V member 4 and TRPC1 were associated with glioma growth[45]. Since some of these channels are known PC2 partners, it is highly likely the implication of polycystins in these malignancies and is currently under investigation.

CONCLUSION

Polycystins are envisioned as polymodal cellular sensors, critical regulators of cell structure integrity, cell communication, force transmission and subcellular trafficking in a broad range of cell types. Aberrant or defective expression of these proteins leads to abnormalities in calcium homeostasis and mechanosensation in major organs contributing to severe pathological conditions including ADPKD and cancer.

Future research should focus in elucidation of the mechanisms involved to integrate the information that arises from polycystin complexes into cellular functions. *In vitro* studies are needed to determine the kind of stimuli that trigger polycystins activation and the way that mechanical stimuli and ligand binding is sensed by PKD complexes. Are polycystins directly activated by mechanical stimuli or indirectly *via* activation of another protein partner? Animal models are required to define the functional consequences of PKD dysfunction in different cell types. How critical are polycystin-induced calcium signaling and enzymatic cascades for cellular growth and differentiation? Is there a specific role for multiple PKD complexes present at different locations in a single cell? How polycystins expression varies in different types of malignancy? Understanding the molecular mechanisms that underpin polycystins functions is urgently needed to identify novel and effective therapeutic schemes for the affected organs in the future.

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