

PROTEIN-PROTEIN INTERACTION BETWEEN TRPP2 CHANNELS AND THE LINKING PROTEINS FOR CA⁺ REGULATION: MOLECULAR, PATCH-CLAMP AND PLANAR LIPID BILAYER ELECTROPHYSIOLOGICAL AND BIOPHYSICAL STUDIES

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ABSTRACT

The polycystic kidney disease (PKD) is considered as the most common human monogenic disorder influencing the kidney, and specially the human ciliopathies. Protein translated from the involved genes are: polycystin1(PC-1), polycystin2 (PC-2), and the fibrocystin found in the specific structures in primary cilium of apical surfaces in renal epithelium for sensing extracellular signals and translating them to intracellular chemical information. Two main cilia related monogenic cystic renal disease types are a): autosomal dominant polycystic PKD (ADPKD) & b): autosomal recessive PKD (ARPKD). The ARPKD is quite a rare and a serious type usually appearing prenatally or in early childhood whereas ADPKD is quite common form that appears mostly in adults. The present article explores the protein-protein interaction between TRPP2 channels and the linking proteins for Ca⁺ regulation employing the molecular, patch-clamp and planar lipid bilayer electrophysiological and biophysical techniques. Hopefully better ideas will emerge in future about how to reverse the cyst formation/ cystic diseases, and the newer and novel therapies are expected to develop in the coming years.

Key-words: Polycystin-2 (PC2), transient receptor potential polycystin-2 (TRPP2) channel, polycystic kidney disease (PKD), autosomal dominant PKD, Ca⁺ regulation

INTRODUCTION

The polycystic kidney disease (PKD) is considered as the most common monogenic disorder influencing the kidney and human ciliopathies (Dalgaard and Nørby, 1989; Hussain, 1990a,b,c; Watson *et al.*, 1990; Shaikewitz, 1993; Torra; 1999; Sutters and Germino, 2003; Yasmeen *et al.*, 2008; Harris and Torres, 2009; Yasmeen *et al.*, 2009; Torra, 2014; Bergmann, 2017; Sudarikova *et al.*, 2021; Boletta and Caplan, 2025; Buqaileh *et al.*, 2025). Several other studies explain the pathophysiological aspects of PKD (Beebe, 1996; Hussain and Hussain, 1998; Augustyniak-Bartosik *et al.*, 2004; Hsu *et al.*, 2007; Kuo and Chapman, 2019; Borghol *et al.*, 2025).

The protein translated from the involved genes are: polycystin1(PC-1), polycystin2 (PC-2), and the fibrocystin found in the specific structures in primary cilium (Boletta and Caplan, 2025) of apical surfaces in renal epithelium for sensing extracellular signals and translating them to intracellular chemical information. There are various unsolved issues associated with polycystic kidney disease (Bergmann *et al.*, 2018). Kidneys with cysts in children and adults lead to end stage kidney disorders. Two main cilia related monogenic cystic renal disease types are a): autosomal dominant PKD (ADPKD) and b): autosomal recessive PKD (ARPKD). The ARPKD is quite a rare and a serious type usually appearing prenatally or in early childhood whereas ADPKD is quite common form that appears mostly in adults.

The main function of the ion channels or transmembrane proteins is transporting ions across the biomembranes (Lal *et al.*, 2018). Functions of ion channels are studied employing patch-clamp, planar lipid bilayer electrophysiology and related techniques (Lal *et al.*, 2018). The 'pkd1' and 'pkd2' genes that encode for (PC1) and (PC2) are mutated in patients with ADPKD, and the C-terminals of 'PC1' and 'PC2' interact through their C terminal, cytosolic regions that regulates the cell proliferation and differentiation (Behn *et al.*, 2010).

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The 'PC2' or a Ca^{2+} permeable non-selective cation channel 'transient receptor potential polycystin2' (TRPP2) is encoded by a gene PKD2 whose mutations lead to PKD (Montalbetti *et al.*, 2007). TRPP2, a protein having six transmembrane domains (Anyatonwu and Ehrlich, 2005) is a part of a flow sensor and is defective in ADPKD whereas TRPP3 that is involved in the regulation of pH sensitive neuronal action potentials in the central canal of spinal canal and sour tasting in taste buds of tongue. It was found that alpha-actinin potentiates the activity of TRPP3 (Li *et al.*, 2007).

ADPKD prevalence in US is 9.3 per 10 000 individuals and constitutes about 5-10% of kidney failure in Europe and US areas (Chebib *et al.*, 2025), 10-15% (Wang *et al.*, 2012), and ~15% in another report (Čelić *et al.*, 2012). The PKD- a ciliopathy is caused mainly by *Pkd1* and *Pkd2* genes mutations, disturbing the sensory organelle primary cilium for cellular signaling, and disrupting renal topology and functions leading to the development of progressive renal failure (Buqaileh *et al.*, 2025). It was suggested that the functions of ciliary receptors/ proteins and their links to PKD, and the therapeutic aspects offer the platform for future research directions and therapeutic strategies for the patients with PKD (Buqaileh *et al.*, 2025). The patients with ADPKD present progressive development of kidney cysts (Chebib *et al.*, 2025).

Protein that is encoded by the PKD2 has the similarity with that of TRP and voltage-dependent cation channels. Hence, mutations in PKD2 gene causing ADPKD in human, and expressed in *Xenopus* oocytes, reconstitution in lipid bilayer was named as PC2. However, to have PC2 representing genetic models for its activities, control, identification as well as cloning of *Drosophila*-PC2 (DmPC2) and its expression in S2 cells of *Drosophila* produced quite a novel PC2 channels (Venglarik *et al.*, 2004).

It was noted that 65 kDa mucolipin1 (ML-1) (also called as TRPML1) protein encoded by gene MCOLN1 and causing autosomal recessive neurogenetic disorder-Mucopolipidosis type IV (MLIV) had similarities of common ancestry sharing homology (sequence homology) and topology with PC2 and TRP channels (Raychowdhury *et al.*, 2004). It was suggested that detection of the regulatory channel-site for an H^+ ion detectable from the cytoplasmic side of channel regulates PC2 (Gonzalez-Perrett *et al.*, 2002). It was revealed that it is PC2-a Ca^{2+} channel protein that mutates in ADPKD and associates with fluid accumulation/development of fluid-filled cysts (González-Perrett *et al.*, 2001). Mammalian tandem affinity procedure for purification and preparation of functional PC2 in yeast cells was developed and PC2 channel activity was detected by patch clamp electrophysiology by reconstituting it in lipid bilayer (Li *et al.*, 2004).

The primary cilium that is a non-motile hair-like microtubule-based organelle lacks the central pair of microtubular structure that is characteristic of the motile cilia that explains the main difference between the primary ciliary membranes that contain just the ciliary proteins, and plasma membrane that contains ion channels. However, later studies confirmed that since primary cilia contain necessary sensory transducer/ receptor characteristics e.g., for responding mechanical stimulation and fluid flow, primary cilium must have ion-channels. The functional aspects of the ion-channel activity associate with sensory properties of primary cilia in renal epithelium and it was proved electrophysiologically by demonstrating that primary cilia in isolated form demonstrate the current records of individual ion-channels. (Raychowdhury *et al.*, 2007).

The PC2 controls by interacting with the microtubular structures of the primary cilia present in the epithelium of kidney that are microtubular structure representing sensory responses/functions (Li *et al.*, 2006; Montalbetti *et al.*, 2007). The PC2 manufactured in syncytiotrophoblast (hST) in the human placenta at term has abundant actin and cytoskeleton structures for controlling the functions of PC2 (Montalbetti *et al.*, 2007).

The present article provides information about the main role of the Ca^{2+} control by calcium dependent calcium channel PC2 in epithelial cell signaling (Kuo *et al.*, 2014). The PC2 is a subtype of the TRP channels and is permeable to Ca^{2+} and other cations, and hence, it is a non-selective cation channel (Velázquez *et al.*, 2023) studied mainly in primary cilium and ADPKD (Cantero and Cantiello, 2011). The PKD comprises mutations in human PC2 (hPC2) where C-terminal tail in the hPC2 has two EF hand domains (helix-loop-helix motifs or domains) and second binds only with Ca^{2+} (Kuo *et al.*, 2014).

Calcium regulation of TRPP2 is important to manage any disordered condition manifesting due to dysfunction of the acinar cells of the lacrimal gland that produces and secretes the tear-fluid. Such dysfunction may lead to disorders associated to the ocular surface conditions, e.g., dry eye syndrome. Ca^{2+} is regulated by cellular mechanisms and acinar secretions are controlled by adrenergic and cholinergic influences stimuli that resultantly regulate the cytosolic Ca^{2+} (Kaja *et al.*, 2011).

Lithium (Li^+) is a naturally occurring powerful, potent and effective pharmaceutical product whose exact mechanism of action at cellular level are not fully known. It influences the electrical properties of PC2 (Cantero and Cantiello, 2011). The lipid peroxidation products increase often in pregnancy due to oxidative stress (OS), lower antioxidants, preeclampsia, gestational diabetes, free radical associated birth disorders, abortions etc. It has been

investigated that quite abundant expression of PC2 by syncytiotrophoblast (hST) occurs that points out towards the impact of PC2 in pregnancy (Montalbetti *et al.*, 2008).

The present article provides information about the PC2 regulation by Ca²⁺. Various reports on protein-protein interaction between TRPP2 channels and the linking proteins for Ca⁺ regulation have been presented where molecular, patch-clamp and planar lipid bilayer electrophysiological, AFM and other biophysical studies have been employed. Further studies would provide the evidence of the impact of protein-protein interaction in renal physiology and renal disorders.

PC2 AND LIPID BILAYER

A study on organic cation permeation in the PC2 channels indicated that the least pore size of the channel as 11 Å was of large size that provides information that in the *in vivo* condition, the PC2 channel is closed for not having leakage of cations through membrane and much leakage of calcium from the stores of endoplasmic reticulum (Anyatonwu and Ehrlich, 2005). It was revealed that clustering of the channels and oscillatory currents were caused by high level of Ca²⁺ transportation/ permeability by PC2 and the presence of phospholipids (Velázquez *et al.*, 2023).

For obtaining simultaneously, the structural and electrical changes of TRPP2 channel to understand the structure-function relationship for the opened and closed states of the functional channels, atomic force microscopy combined with the lipid bilayer setup was used that uncovered an intrinsic mechanosensitivity of PC2 appearing because of the external forces (Lal *et al.*, 2018). The interaction of C-terminal of PC1 and PC2 linked with the lipid bilayer was quantified using quartz crystal microbalance (QCM) that showed C-terminal of PC2 (cPC2) forming trimers in solution and binding to C-terminal of PC1 (cPC1) (Behn *et al.*, 2010).

PROTEIN-PROTEIN INTERACTION

The ‘yeast two-hybrid’ analysis, ‘pull-down’ and ‘dot blot overlay’ assays, co-immunoprecipitation, immunofluorescence and lipid bilayer electrophysiology indicated that the intracellular N- as well as C-termini in PC2 channels interact with the proteins alpha-actinins and those other proteins that bind and bundle in cytoskeleton, and are related to the cell adhesion processes and processes associated with proliferation, migration and other activities for regulating the channel activity (Li *et al.*, 2005). Actin binding proteins in the structural elements of actin cytoskeleton directly interact and influence the activity of PC2 regulated by Ca²⁺ (Cantero and Cantiello, 2015). It was found that the PC2 present in the human syncytiotrophoblast (PC2hst) functionally responded to the intracellular (cis) Ca(2+) but the *in vitro* translated PC2 (PC2(iv)) did not respond (Cantero and Cantiello, 2015). It was further noted that the α -actinin that is considered as an actin-bundling protein showed enhanced activity of PC2iv channel by the presence of cytoplasmic (cis) Ca²⁺ (Cantero and Cantiello, 2015).

Filamin, a protein known for the actin binding domains that it shares with alpha actinin exerted significant inhibitory effect on PC2(iv) function when Ca²⁺ is present but inhibitory effect was absent when cis Ca²⁺ was not present (Cantero and Cantiello, 2015). It was investigated that C-terminal regions in the isoforms of filamin are involved in structural binding and functional activity of PC2 via its N- and C- termini. (Wang *et al.*, 2012). The endogenous TRPP2 channel and filamin were found by reciprocal co-immunoprecipitation experiments as in the same specialized complexes of renal epithelium, whereas planar lipid bilayer electrophysiology showed that filamin A inhibited the TRPP2 channels to much extent, and it was concluded that filamins regulate PC2 channels and make links with actin for precise regulation of PC2 channels (Wang *et al.*, 2012).

Gelsolin influenced PC2(iv) even at much lower concentration of the intracellular Ca⁺ (cis Ca²⁺), but not in the absence of Ca⁺ (Cantero and Cantiello, 2015). However, profilin significantly enhanced the PC2(iv) activity both in the absence or presence of (cis Ca²⁺) (Cantero and Cantiello, 2015).

The influence of lithium on the control of the ciliary length and dysfunctions of lithium were revealed by employing absolute rate theory based ‘energy models’ and ‘Goldman-Hodgkin-Katz equation’ that explained the mechanism of lithium transportation and blocking PC2 that explains to much extent the pharmaceutical and medical significance of Li⁺ for change in electrical properties of PC2 (Cantero and Cantiello, 2011).

Distribution and associated functions of PC2 in mouse retinal ganglion cells using immunohistochemistry employing fluorescence microscopy and planar lipid bilayer electrophysiology revealed that PC2 channels on the basis of pharmacological and biophysical properties are similar to the PC2 for other organisms/tissues and present a common role of Ca²⁺ signaling PC2 channels (Kaja *et al.*, 2012).

The TRPP2 channels were expressed in the lacrimal acinar cells of the adult mouse for studying their functions (Kaja *et al.*, 2011). Employing a variety of techniques including: immunohistochemistry and immunocytochemistry, biophysical measurements, electron microscopy, and lipid bilayer electrophysiology showed the highly expressed

PC2 channels in the endoplasmic reticulum, nucleus & golgi presenting similar electrophysiology/ biophysical properties as obtained for other tissues (Kaja *et al.*, 2011).

For searching a molecular connection for ADPKD & ARPKD, a number of biochemical, molecular, structural biological, electrophysiological and biophysical findings were obtained for exploring the interaction between PC2 and fibrocystin mediated by a motor subunit K1FB3 of kinesin2 (Wu *et al.*, 2006).

PC2 AND SYNCYTIOTROPHBLAST

It was found that reactive oxygen species (ROS) inhibits the PC2 channel activity that allows the calcium transport in term human syncytiotrophoblast (Montalbetti *et al.*, 2008) and the oxidative discomforts in pregnancy cause disordered transfer of cation between mother and fetus. The interaction of microtubular structures with PC2 in human syncytiotrophoblast (hST) of term human placenta has much importance for regulating the ion transport (Montalbetti *et al.*, 2007).

The microtubules were generally not included in apical hST. However, interesting investigations about hST apical structures, microtubular structures and kinesin proteins (KIF3A&KIF3B) were obtained with the cellular and histological techniques (Montalbetti *et al.*, 2007). In vesicles isolated from hST cells, the PC2 and tubulin reveal substantial colocalization (Montalbetti *et al.*, 2007).

Immunofluorescence experiments indicated the PC2 and actin co-localization close to plasma membrane disrupted by cytochalasin D that showed that the physical forces exerted upon the cells control PC2 activity via sensory processes involving actin cytoskeleton (Montalbetti *et al.*, 2005). Influence of colchicine, GTP (guanosine triphosphate), tubulin, and taxol on hST reconstituted bilayers and PC2 functions provide an important connection between PC2 and microtubular functions (Montalbetti *et al.*, 2007).

Dynamical changes in the hST microtubules control the function of PC2 (Montalbetti *et al.*, 2007). Enhanced activity of PC2 in hST showed an evident capability of K1F3A, a kinesin motor protein (Montalbetti *et al.*, 2007). It was investigated that microtubules interacting with PC2 in the hST have important regulatory involvement in human placenta for controlling the ion transport (Montalbetti *et al.*, 2007).

Reconstitution of ion channels of ciliary in comparison with the plasma membranes showed that primary cilia contain a high density clearly found for three channels including PC2 (Raychowdhury *et al.*, 2007). It was revealed by rapidly abolishing microtubular disrupter colchicine and microtubular stabilizer paclitaxel stimulating the PC2 activity that the microtubules present in primary cilia of renal epithelium are controlled by PC2 and the microtubular organization controls PC2 function (Li *et al.*, 2006).

PC2 REGULATION BY Ca²⁺

The PC2 was found highly potential for the control of ryanodine receptor activity and PC2 mutations that may cause disturbance and even loss of the control of ryanodine receptor 2 and disordered Ca²⁺ signaling in the heart occurs (Anyatonwu *et al.*, 2007). The nuclear magnetic resonance (NMR) and bioinformatics revealed that the number as well as the EF hand related domains/ motifs having specific sites of the calcium binding regulate calcium levels for essentially required functions of PC2 channel. (Kuo *et al.*, 2014).

The PC2iv was found not sensitive at all to Ca²⁺ regulation (Cantero and Cantiello, 2013) that clearly indicated that regulatory sites are not intrinsic to TRPP2 channel, and microdomain of Ca²⁺ is found largely via the regulation of PC2 activity in hST (Cantero and Cantiello, 2013). Interatomic distance (D(max)) measurement by NMR and small angle x-ray scattering (SAXS) led to suggest that conformational alterations caused by calcium in the C-terminal tail of PC2 are essential for channel's opening and closing, and the regulation of PC2 and Ca²⁺ dependent TRP channels are in general similar conformational/ oligomerization alterations in the domain in cytoplasmic tail of PC2 that propagate to channel pore region (Ćelić *et al.*, 2012).

CONCLUSIONS

The polycystin complexes are crucial for the development and functions of kidney and they have the features of both ion channels and of receptors. The PC2 is encoded by the gene PKD2 and has a major role in PKDs. Mutations occurring in PKD2 lead to cyst formation and disordered signaling and homeostasis. Extensive research involving rigorous and wide scope methodologies appeared especially in the last two decades for understanding the cystic diseases. However, we have to admit that despite enormous research effort, the mechanisms whereby the polycystins work in normal functions as well as in cyst formation and various disordered processes are unknown to a great extent. However, since the cyst formation is a dysregulated repair process, one thing seems evident that polycystins are involved in controlling the repair processes. Hopefully better ideas will emerge in future about how to reverse the cyst formation/ cystic diseases, and the newer and novel therapies are expected to develop in near future.

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