The role of transient receptor potential polycystin channels in bone diseases

Maria A. Katsianou, Foteini G. Skondra, Antonios N. Gargalionis, Christina Piperi, Efthimia K. Basdra

Cellular and Molecular Biomechanics Unit, Department of Biological Chemistry, Medical School, National and Kapodistrian University of Athens, Athens, Greece

Contributions: (I) Conception and design: AN Gargalionis, C Piperi, EK Basdra; (II) Administrative support: EK Basdra; (III) Provision of study materials or patients: All authors; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Efthimia K. Basdra. Cellular and Molecular Biomechanics Unit, Department of Biological Chemistry, Medical School, National and Kapodistrian University of Athens, 11527 Athens, Greece. Email: tegk.84@gmail.com.

Abstract: Transient receptor potential (TRP) channels are cation channels which act as molecular sensors that enable cells to detect and respond to a plethora of mechanical and environmental cues. TRPs are involved in various physiological processes, such as mechanosensation, non-inception and thermosensation, while mutations in genes encoding them can lead to pathological conditions, called "channelopathies". The subfamily of transient receptor potential polycystins (TRPPs), Polycystin 1 (PC1, TRPP1) and Polycystin 2 (PC2, TRPP2), act as mechanoreceptors, sensing external mechanical forces, including strain, stretch and fluid shear stress, triggering a cascade of signaling pathways involved in osteoblastogenesis and ultimately bone formation. Both *in vitro* studies and research on animal models have already identified their implications in bone homeostasis. However, uncertainty veiling the role of polycystins (PCs) in bone disease urges studies to elucidate further their role in this field. Mutations in TRPPs have been related to autosomal polycystic kidney disease (ADKPD) and research groups try to identify their role beyond their well-established contribution in kidney disease. Such an elucidation would be beneficial for identifying signaling pathways where polycystins are involved in bone diseases related to exertion of mechanical forces such as osteoporosis, osteopenia and craniosynostosis. A better understanding of the implications of TRPPs in bone diseases would possibly lay the cornerstone for effective therapeutic schemes.

Keywords: Bone diseases; ion channels; mechanotransduction; polycystin; transient receptor potential polycystin cation channels (TRPP cation channels)

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Introduction

The balanced and well-controlled transport of ions via channels is highly significant for various physiological cellular and tissue processes. Such processes involve the decision of either cell proliferation or apoptosis at a cellular level, as well as gene transcription, muscle contraction and transmitter release (1). Recent research findings have indicated a new family of druggable channels, which are called transient-receptor potential channels-TRPs (2). Several inherited diseases in humans (known as "channelopathies") are caused by mutations in genes encoding TRPs and can lead to pathological impairment of many tissues and systems (3).

The TRP ("transient receptor potential") superfamily comprises more than 30 cation channels that can be further divided into six main subfamilies in humans based on their amino-acid homology. The TRP channels are mostly permeable for Ca^{2+} and, some also for Mg^{2+}, while they provide not only entry pathways for Ca^{2+}, but also pathways

for its release from intracellular organs, modulating the balance between the intracellular and extracellular levels of Ca^{2+}. All TRPs seem to have six transmembrane domains, which assemble as homo-or-hetero-tetramers within the channel (1). A wide range of both intracellular or extracellular factors, such as chemical and osmotic stress, can act as stimuli for the activation of TRPs (4). On the contrary, many TRPs resident in the plasma membrane remain constantly open and their levels can be regulated by intracellular insertion, when necessary (5,6).

Current scientific data has related TRPs to the development and progression of pathological conditions in humans, either directly or indirectly. Cardiovascular diseases, kidney and endocrine disorders, as well as cancer have been correlated with calcium homeostasis in general and more specifically with TRP channels (7). Nevertheless, although the expression of TRPs in the skeletal homeostasis along with the importance of calcium homeostasis in bone tissue are known and well-established, there is a lack of evidence regarding possible implications of TRP channels in bone pathobiology.

The present review targets to summarize the most recent evidence regarding transient receptor potential polycystins (TRPPs) and the interactions among the members of the TRPP subfamily, focusing on their role in the development and progress of bone diseases. More emphasis will be put on data indicating that TRPP1 and TRPP2 regulate the pathobiological framework of bone diseases.

TRPs: an overview

Consisting of cation channels, permeable for both monovalent and bivalent cations, TRPs are important mediators of sensory signals. TRPs contribute to changes and balance of the concentration of free cytosolic Ca^{2+} (7). Being present in the plasma membrane, they act as Ca^{2+} entry pathways or as driving force for its transport, while they participate in release pathways of Ca^{2+} from cell organelles, when located intracellularly (1). Also, TRPs' expression profile differs highly among its members. Some TRPs are tissue specific, while others are globally expressed (8).

TRPs are present in excitable and non-excitable cells, where they exert their functions (9). Their family consists of more than 30 cation channels, which are further subcategorized into six subfamilies for mammals, the Canonical (TRPC), the Vanilloid (TRPV), the Melastatin (TRPM), the Polycystin (TRPP), the Mucolipin (TRPML) and the Ankyrin (TRPA) (10-12). Two of the above-mentioned subfamilies, more specifically TRPP and TRPML, were named after the discovery and description of the gene mutations that provoked the corresponding diseases (2). The initial discovery of TRPs was in a blind strain of *Drosophila*, which presented changes in the inception of intense light, when a gene of TRP was mutated (13). The first mammalian TRP subfamily discovered that had high homology with that observed and analyzed in Drosophila was named "Canonical" (14,15). It must be stated that TRPs share less homology as family, when compared with any other channel family. Three TRP subfamilies, the TRPVs, TRPA and TRPPA, are closely related to that firstly described in Drosophila, while the subgroups of TRPPs and TRPML are more distantly related (13,16). Contrary to these, NOMPC, a TRP subgroup not expressed in mammals, but only in yeast and worms, is the least related to the subfamily of Canonical TRPs (17).

TRP channel research has revealed the diverse roles of TRPs in both physiological and pathological processes. Being mediators of sensory signals, they can take part in health and disease. Mutations in genes encoding TRPs lead to the emergence of TRP channelopathies. The stimuli that can activate TRPs are either extracellular or intracellular (3). They can sense chemical, osmotic and mechanical stress, as well as oxidation at an extracellular level (4). They also contribute to thermosensation in the relevant cell types (18) and the taste perception (19). Despite TRPs' activation by various extracellular messengers, only a few endogenous ligands for TRPs are known (20,21). PIP2, DAG, ATP and calmodulin have been described as endogenous ligands of TRP channels, while a small number of intracellular proteins were proved able to interact with them. An important function of TRPs is their capacity of sensing the abundance of intracellular Ca^{2+} stores, and trigger stimulation of signaling transduction pathways for the restoration of Ca^{2+} balance. Direct phosphorylation in serine/threonine sites has been mentioned as means of TRP stimulation. Nevertheless, the specific mechanism has not been elucidated yet (1,6,22).

TRP channels consist of six transmembrane spanning domains, which form a pore loop between transmembrane section 5 and 6 (4,10,11). The vast majority of them is permeable for Ca^{2+}, but the permeability ratio Pca^{2+}/Pna^{+} differs greatly among the various subfamilies. Both the -COOH and -NH_2 termini are located

intracellularly. A functionable TRP channel seems to arise from the homotetramerization or, less frequently, the heterotetramerization of the basic structure (3).

TRP channel regulation is very complicated. Some of them appear to be constantly in open state, and a stimulus may induce their closure. Others seem to become activated when receiving a signal that the intracellular Ca^{2+} levels have been significantly reduced. The latter issue remains still controversial and needs further examination (4,23).

TRPCs, the first TRP channel subfamily studied, are present in almost all cell types. Each given cell type seems to express more than one TRPC channel (1,7). They are activated by receptors that, when stimulated, activate PLC-β or PLC-γ, and they contain structurally a TRP-box in their -COOH terminal tail (4,12). TRPVS are characterized by the presence of 3–5 ankyrin repeats in their -NH_2 terminus. On the contrary, TRPMs do not contain ankyrin repeats and the permeability ratio Ca^{2+}/Mg^{2+} varies greatly among the members of this subgroup. They are widely known as "channenzymes" as they contain entire functional enzymes in their -COOH terminus (7). TRPMLs are widely expressed and share low homology with TRPCs (1). Lysosomal storage mucolipidosis type IV arises when the TRPML gene is mutated (24,25). TRPPs are structurally divided into two distinct subgroups- TRPP1 (PKD1, PC1)-like channels and TRPP2 (PKD2, PC2)-like channels. They are located both in motile and non-motile cilia. Mutations in genes encoding TRPP1 and TRPP2 are responsible for autosomal dominant polycystic kidney disease (26). Lastly, TRPA subfamily consists of only one member, which participates in the mammalian auditory response (27). Its properties are Ca^{2+} and voltage-dependent (28).

Mutations that reduce, or even diminish the function of TRP channels are the cause of a wide range of pathological conditions (7,9). It must be underlined that only few defects in TRP genes have been reported as the direct cause of channelopathies (7). The first and best described channelopathies have already been mentioned: ADPKD and lysosomal storage mucolipidosis. Apart from these, cardiovascular disorders, diabetes mellitus, or even cancer have been related to TRP channels. To extend our point of view, TRPA1 and TRPV1 serve as sensors of toxic chemicals for the airways and are associated with respiratory disorders. Along with these, TRP channels may be critical players in the patho-biological mechanisms involved in the development of skin disorders (3,9).

Bone mechanosensing

Various living cells are mechanically induced, sensing external mechanical cues and translating them into an intracellular biochemical response. This process is called "mechanotransduction" and is crucial for the survival of many tissues, including the skeletal (29). Bone tissue consists of four major cell types, the osteoblasts, the osteocytes, the osteoclasts and the osteoprogenitors, which can sense fluid shear stress, pressure and strain to an extend which varies among each given cell type (30). Mechanoreceptors present in the plasma membrane of bone cells are activated by external mechanical stimuli and trigger signaling pathways intracellularly. Recent advances in the field of bone mechanotransduction have indicated a plethora of both mechanoreceptors and intracellular signaling mediators (30,31).

Any protein complex can be defined as "mechanosensor or mechanoreceptor", a molecule or even a biological structure, able to detect alteration in the external force (32). Integrins are major mechanosensory molecules in bone cells. They locate in the plasma membrane, where they form a structural lineage between extracellular matrix and cell membrane (33). The integrin complex consists of two subunits, a and β. When stimulated, a conformational change in β subunit leads to the activation of the signaling cascade (34).

Another family of integral membrane proteins, the cadherins, has also been proposed to serve as "launching platforms" for β-catenin, which is an important intracellular mediator in bone mechanosensing (35). Along with cadherins, cell-cell connections via the cytoskeleton and ephrins seem to participate in the perception of mechanical stimuli from the noisy environment (30). Ion channels, as well as connexins, which constitute hexameric membrane complexes forming pores in the membrane, enabling proper transmission of signaling pathways among cells within the bony area (30). Ion channels involved in the mechanosensitive pathways may be TRPs, as well as gadolinium-sensitive stretch-activated cation channels (36) and multimeric voltage sensitive calcium channels (VSCC) (37,38).

It must be pointed that the primary cilia, which is a structure present in nearly every cell type (39), is a classic mechanosensory organ in bone cells. The bending malformations that they present as a consequence of the exertion of external force cause the triggering of an array

of intracellular signaling effects that regulate cell fate and differentiation (30).

As far as signal transduction pathways are concerned, plenty of cascades and key signaling molecules that orchestrate mechanotransduction in bone tissue have been studied. The mitogen-activated protein (MAP) kinases (MAPKs) are often triggered by activated membrane mechanosensors and regulate the expression pattern of many osteoblastic genes (40,41). A thoroughly-studied transcription factor whose expression is targeted by the cascade of MAPKs is Runx-2 (42,43). It is notable that the above-mentioned cascade often affects and stimulates nitric oxide and prostaglandin signaling (44). Additionally, Ca^{2+} signaling and the well-described Wnt/β-catenin pathway have been identified as major coordinators of the biological response following mechanical stimulation in bone cells (31). Nevertheless, a detailed description of the signal transduction pathways in the complicated field of bone mechanobiology is out of the aims of the present review.

TRPPs: the polycystins family

Polycystin 1

Polycystins (PCs) are part of the larger family of TRP channels and constitute a protein family with mechanosensory properties, involved in mechanotransduction and possibly in bone mechanosensing. PCs are located in the cilia, in the plasma membrane and the endoplasmic reticulum (ER), triggering signaling transduction (*Figure 1*) (26). Being expressed in various tissues such as kidneys, blood vessels, pancreas, liver and various cell types, their presence is reported in various processes, including renal flow sensing, arterial pressure and flow mechanosensation, brain trauma, skeletogenesis, and osteoblast differentiation. PCs are regarded as crucial mechanosensory candidates, as their deregulation is connected with severe structural deficiencies such as cysts, aneurysms, colorectal cancer, atherosclerosis, cranial defects and osteoporosis (45-48).

ADKPD has been attributed to *Pkd1*; therefore its relevance to kidney development and renal pathology has been extensively studied. *Pkd1* gene encodes Polycystin 1 (PC1, TRPP1, 3072 aa), first identified by positional cloning as a gene mutated in 85% of patients. It is an 11-segment integral glycoprotein, which comprises a long extracellular N-terminal region and an integral short cytoplasmic C-terminal region of 200 amino acids (*Figure 1*). PC1 forms interactions through protein motifs localized on its N-terminus. These motifs are: flanked leucine-rich repeats (LRRs), Ig-like domains (ILDs or PKD repeats), a G-protein-coupled receptor proteolytic site (GPS), and a C-lectin-like domain (CLD). It has been proposed that it mediates mechanosensation, as observed in studies focusing on urine flow in the kidney (49-51). Studies have further illustrated its role in cell signaling and cell elasticity due to the extensive capacity of its Ig domains (52,53). *In vivo* it is rapidly cleaved and remains tethered to the C-terminal domain, forming a high-affinity ligand (54). Immunohistochemistry experiments have shown that PC1 is intensely expressed in fetal tissues, in contradiction with adult tissues (55-57); thus highlighting its developmental regulation. In ADKPD cells PC1 localizes largely to the cell cytoplasm, whereas in normal cells mainly localizes in the plasma membrane and the cilia (52,55,58).

Polycystin 2

Polycystin 2 (PC2, TRPP2, 110 kDa) is a six-segment integral membrane protein, forming a calcium-permeable channel (59). It was first discovered and studied in ADPKD, where the PC2-gene product mutated was observed (59). It comprises 968 amino acids and consists of six transmembrane segments and an intracellular N-terminus. In most PC2-like proteins, there is a large extracellular loop between the first and the second transmembrane part (*Figure 1*) (60,61). It consists of intracellular N- and C-termini. The C-terminus contains motifs such as, a calcium-binding EF-hand domain (EF), an ER retention domain, and a coiled-coil helix (CC), important for channel formation and hetero-oligomerization (53,62,63). The ciliary sorting motif (CSM) located in the N-terminus enables oligomerization and primary cilia localization (64,65). PC2 is mainly located in the ER but it is also present in plasma membrane and the cilia (58,61,66). PC2 is regulated by various stimuli such as cations, pH, voltage and phosphorylation (61,67-69). Immunostaining has further shown that PC2 levels are increased in the plasma membrane, after calcium release from ER stores (70).

PC2 is located mostly in ER, while under PC1 presence is often translocated to the plasma membrane (60). It also localizes in both mobile and static cilia (71). Evidence from literature has depicted that PC2 is expressed in many human tissues, including blood cells, kidney, liver, brain and bone (26,72).

PC2 besides PC1 interacts with cytoskeletal proteins as

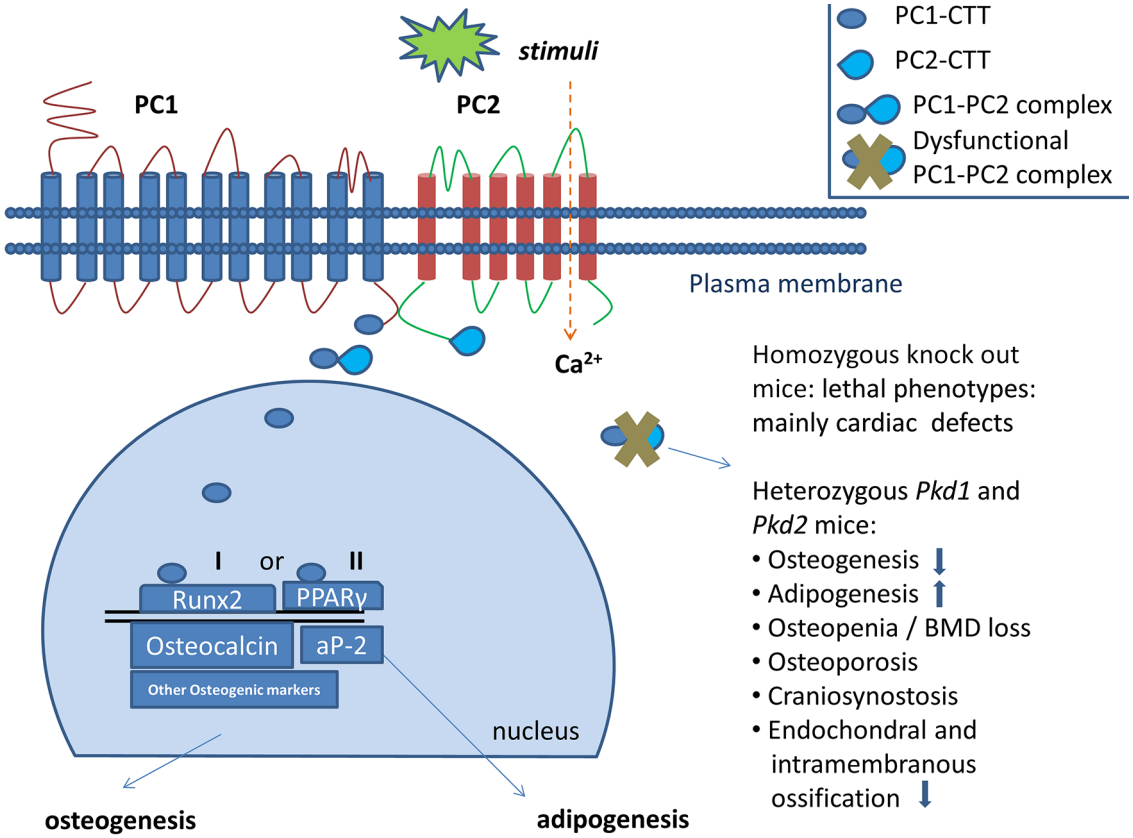

Figure 1 Polycystins 1 and 2, their structure and relation to bone disease. Together they form a complex which is either active or deactivated when Pkd1 or Pkd2 are inhibited. Form I: the PC1/PC2 complex triggers signaling pathways. PC1 CTT translocates to the nucleus where it can bind to Runx2 or other osteogenic markers and enhance the transcription of osteogenic genes. Form II: when PC1 is inhibited, this can lead to either osteogenesis or adipogenesis, through the activation of PPARγ. Deactivated Complex Form can lead to various bone disease manifestations. aP-2, Activating Protein 2; CTT, C-terminal tail; Oc, Osteocalcin; PPARγ, peroxisome proliferator-activated receptor γ; PC1/PC2 complex, Polycystin 1-Polycystin 2 complex; RUNX2, runt-related transcription factor 2.

well as other mechanosensitive ion channels in different cells, including potassium-selective stretch-activated potassium channels and non-selective cationic SAC channels (73-76). It has been further reported that PC2 binds to cytoskeleton proteins, such as Hax-1, tropomyosin 1, troponin 1, actinins, actin-binding and actin-bundling proteins, and filamins (73-76), highlighting PC2's presence in skeletogenesis and calcium homeostasis. When PC2 is knocked down with the use of siRNAs, it can mediate cell-to-cell adhesions partially through E-cadherin (60).

PC1 coordinates the translocation of PC2 from the ER to the nucleus (60). The coiled-coil domain present in PC2 is crucial for its interaction with PC1 and the formation of the polycystic complex (60,77). PC1 shares a homologous sequence to that of PC2, through binding of their C-terminal coiled-coil domains. Together they form a complex which is located in the cilia where its ion channel function facilitates their trafficking (78).

Further studies have indicated the formation of a PC2 homotrimer through a coiled-coil domain in the C terminus, interacting with a single PC1 to form a cell surface PC2/PC1 complex (79). PC2 trimer's capacity is crucial as it may connect with other channel-forming subunits, such as TRPC1 and TRPV4, thus forming versatile cation channels (79).

Polycystins 1 and 2 interactions

PC1 is involved in protein-protein interactions, highlighting its extracellular presence (80,81), as it spans the

cellular membrane and acts as a cell membrane receptor for extracellular ligands while it couples stimuli to intracellular pathways (*Figure 1*) (26). The intracellular C-terminal has been implicated in various signaling pathways such as JAK-STAT, the mammalian target of rapamycin (mTOR), the Wnt, the activator protein 1 (AP-1), and the calcineurin-Nuclear factor of activated T-cells (NFAT) pathway (26,82). Specific sequences attribute properties to C-terminal, among those its coiled-coil sequence, that binds specifically to the C-terminus of PC2 (53), and a heterotrimeric G-protein activation sequence which activates heterotrimeric Gi/Go (83). Notably, when PC2 couples with PC1 to Gi/Go proteins the complex is inhibited (84). The cleaved C-terminal domain of PC1 translocates to the nucleus (85).

PCs are crucial functional molecules, as mutations in *Pkd2* and *Pkd1* are the main causes for ADPKD, one of the most common inherited human diseases (61,86). Mutations in *Pkd2* and *Pkd1* genes cause similar pathologies. Thus, a disruption of the PC1/PC2 complex might be the leading cause of these manifestations.

Mechanical forces regulate TRPPs function. In a recent study, where short-term mechanical stretching was applied on pre-osteoblastic cells derived from human periodontal ligament tissue (hPDL), PC1 was found to orchestrate osteoblastic gene transcription and bone cell differentiation through the calcineurin/NFAT signaling pathway (87). Studies on Wnt signaling, proved that mechanotransduction via PC1 involves proteolytic cleavage of its cytoplasmic tail (CT) and interaction with intracellular pathways and transcription factors to regulate cell function (88). Furthermore, in stretched human osteoblastic cells, the interaction of PC1-CT with JAK2/STAT3 signaling axis, leads to transcriptional induction of *Runx2* gene, a critical regulator of osteoblastic differentiation (*Figure 1*) (89). Such mechanical studies, implicate PCs in osteoblastic differentiation and ultimate bone formation (90). PC1 has been involved in mechanical strain signal transduction, controlling osteogenesis. PC1 deficiency causes lack of the cells' ability to sense external mechanical stimuli. PC1 deficiency caused impaired osteoblastogenesis and proliferation through the enhancement of intracellular calcium and downstream Akt/β-catenin signaling pathway (*Figure 1*) (90).

In endothelial cells, it has been shown that PC1/PC2 is a flow-tensing protein complex, which responds to shear stress, and induces cell proliferation changes, thus leading to atherosclerosis, a symptom of ADKPD (46).

Polycystins and bone disease

PC1 and bone disease

Bone is a mechanosensitive organ, and its cilia are crucial for absorbing mechanical stimuli, required for bone formation and resorption (91). Bone is regulated by a complicated skeletal network. As a result, how osteocytes and other cells of bone lineage sense mechanical cues, is still ambiguous. Nonetheless, many mediators of mechanical forces have been proposed, including primary cilia and the polycystins. Their function may be activated by the external microenvironment, by forces such as flow, stretch, deformation, cell-cell interactions. According to several studies, selective or whole abscission of polycystin genes in osteoblasts and osteocytes either *in vitro* or *in vivo* results in bone loss depicted in forms of Bone Mass Density (BMD) loss, osteopenia, osteoporosis, craniosynostosis or in general inhibition of calcium signaling and homeostasis, thus disturbed bone formation and resorption balance (*Figure 1*) (92-95).

More specifically, polycystins have been implicated in bone formation, osteoblastogenesis and adipogenesis in mouse models (96). Mutations in *Pkd1* and *Pkd2* are bound to the majority of ADPKD cases which are characterized by cyst formation in the kidney, liver, and pancreas and are associated with cardiovascular abnormalities such as hypertension, mitral valve prolapse, and intracranial aneurysms. These mutations can be alleged for bone malformations during skeletogenesis or at a mesenchymal level, to cranial suture development (97,98). Homozygous *Pkd1* embryos display lethal phenotypes at embryonic days 13.5–14.5, related to cardiovascular defects including cardiac defects such as double outflow right ventricle, disorganized myocardium (*Figure 1*) (95). Similar defects of disorganized organs were observed in *Pkd2* knockout mice, where the left axis determination was inhibited (*Figure 1*) (99). Under the absence of PKD1 and PKD2, skeletal development is severely compromised, thus it is suggested that PC1 and PC2 are both involved *in vivo* in tubule morphology and skeletal function (97). Null *Pkd1* homozygous mice developed aberrant phenotype, further implicating PC1 in epithelium and chondrocyte development (100).

PC1 and PC2 form an intricate compound which localizes to primary cilia in osteoblasts and osteocytes acting as a mechanosensor. Selective deletion of *Pkd1* in both osteoblasts and osteocytes results in bone loss, which is attributed to both diminished osteoblast bone formation

and increased bone marrow adipogenesis. *Pkd1*-deficient mice share age-related bone loss symptoms, a phenotype related to osteopenia (*Figure 1*) (94,101). Thus, elucidating the role of polycystins in bone will enable the prognosis and treatment of osteoporosis (102).

Runx2 is regulated by PC1 in bone mass (*Figure 1*) (92,93). *Runx2* and *Pkd1* het mice both have cumulative effects on bone mass reduction. PC1 by coupling to PC2 calcium channel mediates Runx2 activity and subsequently regulates calcium signaling pathways. It is suggested that Runx2 reduction in *Pkd2* deficient mice is related to intracellular calcium signaling, stating that PC1 and PC2 signaling can be uncoupled in bone. It has been shown that cilia along with PC1 are regulating osteoblast and osteocyte differentiation (92,93). Such a suggestion is possible considering that the cilia sense extracellular chemical stimuli into cellular responses, signaling cascades. Bone cells, such as osteoblasts and osteocytes sense such cues, and bone homeostasis depends on their proper response.

In another mouse model, homozygous *Pkd*1m1*Bei* developed impaired endochondral and intramembranous bone formation. However, heterozygous *Pkd*1m1*Bei* mutant mice due to osteoblast malfunction developed osteopenia (93). In both heterozygous and homozygous *Pkd*1m1*Bei* mice, difference in Runx2 and bone related genes' expression levels was further observed (93). PC1 is an osteoblast regulator, possibly by regulating through PC2 the Runx2-II expression. Ablation of *Pkd1* caused defective chondrogenesis, impaired osteoblast formation and osteopenia. All effects were related to decreased intracellular calcium levels, further correlating PCs with bone formation and calcium homeostasis (92).

When *Pkd1* was inactivated in postnatal mature osteoblasts compared with control mice, it resulted in a gene dose-dependent reduction in bone mineral density, trabecular bone volume, and cortical thickness (94). In addition, mineralization rates and genes' expression, including Runx2-II, osteocalcin, osteopontin, and bone sialoprotein, osteoblast related, were respectively reduced. Adipogenesis was also evident in bone marrow and in osteoblasts, indicating the malfunction of bone formation (101,103). Parallel studies have further confirmed that conditional deletion of *Pkd1* in osteoblasts enhances defective postnatal bone formation and osteopenia. *Pkd1* is also expressed in undifferentiated mesenchyme the precursors of the osteoblast lineage (103).

Osteopenia was further observed in studies where heterozygous *Pkd1*- and *Kif3a*-deficient mice were crossed, achieving a targeted deletion of *Pkd1* (104). Mutants were characterized by diminished BMD, trabecular bone volume and cortical thickness, the symptoms of osteopenia. These manifestations are in conjunction with studies which observed decreased levels of Runx2 expression but increased PPARγ expression, highlighting the increased adipogenesis (96). In addition, the lack of *Pkd1* is related to dysfunctional osteoblastic differentiation, accompanied by adipogenesis in both primary osteoblasts and/or bone marrow stromal cell cultures. These changes were also associated with osteoblast genes and transcription factors, such as Runx2 and PPARγ, whose levels were decreased and enhanced respectively. Moreover, hedgehog signaling was evidenced to be impaired manifesting decreased Gli2 expression in bone and osteoblast cultures (104).

Mutations in *Pkd1* may result in craniofacial abnormalities. In a subsequent study, mice with conditionally deficient PC1 were subjected to midpalatal suture expansion. *Pkd1* was conditionally removed in mice with floxed alleles of *Pkd1* and were crossed with Dermo-1-Cre, Wnt1-Cre, and Osx-Cre delete strains. The presphenoid and sphenooccipital synchondroses at the cranial base of mutant animals closed prematurely (105). As mechanical stress is to formulate postnatal skeletal growth, it was revealed that bone formation due to expansion was reduced. However, it was proven that PC1 is a critical candidate in osteochondroprogenitor cells' response to mechanical stress. Notably, *Pkd1* absence caused alterations in chondrocyte arrangement in nasal cartilage (105).

PC1's role as a mechanosensor has been demonstrated in subsequent studies of signaling pathways (103). With lentivirus-mediated shRNA technology, *Pkd1* was stably knocked down in human osteoblastic MG-63 cell line, resulting in cell proliferation, impaired osteoblastic differentiation and low levels of osteoblast-related genes *Runx2* and *Osterix* compared to control shRNA MG-63 cells. In addition, knockdown of *Pkd1* mRNA enhanced adipogenesis in stable PC1 shRNA MG-63 cells. Elevated lipid accumulation and increased expression of adipocyte-related markers such as PPARγ and aP2 was observed. These findings suggest that downregulation of PC1 in human MG-63 cells resulted in defective osteoblast function. PC1 was reported to act as a regulator of the intracellular calcium-cAMP/PKA signaling pathway, a critical pathway in bone formation (103). Inactivated cAMP leads to bone diseases, with significant defects in intramembranous

ossification and resulting in osteochondrodysplasia (103).

PC2 and bone disease

Similarly, Pkd2 homozygous mice share a lethal phenotype in utero at embryonic day 13.5, presenting symptoms such as acute edema, haemorrage, polyhydramnion and left-right deficiencies. In contrast, heterozygous mice develop normally. In contradiction to the respective *Pkd2* heterozygous humans, who ultimately develop ADKPD, *Pkd2* het mice develop mild, cystic disease (106). Evidence, however, provide input into the lethality of the *Pkd2* homozygous mice. Deletion either permanent or temporary of *Pkd2* in mice has triggered several PC2 events. *Pkd1* and *Pkd2* null embryos have been characterized by aberrant lymphatic vessel formation, which is related to abnormal cell migration and decreased vessel capacity. Notably, removal of *Pkd2* in endothelial cells of the fetus was associated with the complexity of the placental development (107). Therefore, het mice share defective lymphatic and placental vasculature, which possibly contributes to aberrant defects related to embryonic lethality (108).

In addition, conditional deletion of *Pkd2* in neural-crest originated cells, using Wnt-Cre mice suggested a role for PC2 in craniofacial development. It is known that the skull is an intricate organ, which consists of bones and tissues that undergo processes of bone development and growth, mainly affected by mechanical stimuli and forces (109). PC2 is mainly localized in the primary cilia, acts as a mechanoreceptor which can trigger multiple biological processes including Ca^{2+} influx, chemical activity and signalling pathways.

The cranium constantly receives mechanical forces and is known to develop and grow through intricate signaling pathways. In a study by Khonsari *et al.*, the role of *Pkd2* was investigated in mice with conditional deletion of *Pkd2* in neural crest-derived cells, using Wnt1Cre mice. *Pkd2* mutants manifested mechanical trauma such as fractured molar roots, distorted incisors, alveolar bone loss and compressed temporomandibular joints, in addition to abnormal skull shapes (109). Significantly, this study stated that mutants showed no indication of any of these phenotypes at embryonic stages when heads perceive no significant mechanical stress in utero. Therefore, *Pkd2* is likely to play a critical role in craniofacial growth as a mechanoreceptor gene. Thus, *Pkd2* mutations are possibly linked to anomalies in cranial development in ADKPD patients (98,109). PKD2 has also been implicated in cranial suture development. More specifically, in biomechanical studies where mice were subjected to midpalatal suture expansion, cartilage formation was observed (98,109).

Further research using siRNA mediated knock-down of *Pkd2* in osteoblasts has proposed that PC2 loss is correlated to impaired osteoblast differentiation *in vitro*. Loss of PC2 can lead to osteopenia and decreased bone marrow fat. Data from a genome-wide association (GWAS) meta-analysis also highlighted the role of PC2 in bone loss as a *Pkd2* SNP ss12511728 has been associated with femoral neck BMD (110).

More specifically, in two human BMD GWAS meta-analyses, SNPs in *Bicc1* and *Pkd2* were identified to be associated with BMD. Bicc1 is a stimulator of osteoblastogenesis and BMD, by regulating *Pkd2* transcript levels. PC2 overexpression rescued Bicc1 deficiency-dependent osteoblast defects in *Bicc1* and *Pkd2* null mice (110).

There are notable differences between the phenotypes of conditional *Pkd1* and deficient *Pkd2* mice, suggesting that PC1 and PC2 function independently, as well as that the dose of either PC1 or PC2 affects the mechanical strain sensed (111). To this point, PC1 deficiency in osteoblasts results in aberrant effects compared to respective PC2 deficiency in osteoblasts. PC1 deficiency can result in a decrease in Runx2 levels and an increase in adipocytes molecule PPARγ, whereas PKD2 deficiency results in Runx2 and PPARγ reduction (101,112). Selective deletion of *Pkd1* in the osteoblast lineage regulates osteoblastogenesis and adipogenesis (96). *Pkd2* was conditionally inactivated in mature osteoblasts by crossing Osteocalcin (*Oc*)-Cre;*Pkd2*+/null mice with floxed *Pkd2* (*Pkd2*flox/flox) mice.

In *Oc*-Cre;*Pkd2*flox/null (*Pkd2Oc*-cKO) mice, due to *Pkd2* deficiency Runx2 expression in bone was dwindled. Therefore, decreased BMD, trabecular bone volume, and mineral apposition rate were observed highlighting the absence of the biomechanical properties of bone. PC2 deficiency resulted in diminished Runx2 expression in bone and impaired osteoblastic differentiation *ex vivo*. Loss of *Pkd2* also resulted in diminished peroxisome proliferator-activated receptor γ (PPARγ) expression and reduced bone marrow fat *in vivo* while it reduced adipogenesis in osteoblast culture *ex vivo* (112).

Therapeutic schemes

Recently, studies have implicated TAZ (transcriptional

co-activator with PDZ-binding motif, or WWTR1), in osteoblastogenesis and adipogenesis. It responds to the extracellular matrix microenvironment by co-activating Runx2 and co-repressing PPARγ activities (96). Its identification will further facilitate the understanding and manipulation of pathways related to bone disease. Moreover, adipose-derived stem cells (ASC) which are multipotent stem cells located at the cilia can be used as osteogenic tissue replacements (113). Thus, the elucidation of the pathways related to TRPPs and the cilia is demanding.

As far as therapy is concerned it is possible that drugs for ADKPD treatment could also apply to bone disease. However, as TRPPs role in bone disease is not yet fully elucidated, it is imperative to search for specific ligands that induce PC1 or PC2 malfunctioning associated with bone loss. A possible therapeutic scheme would include, a triptolide, a diterpenoid epoxide, which is an agonist for PC2 (113).

In addition, mechanical forces such as fluid flow, hydrostatic pressure, pulsed ultra sound and atomic force can influence bone formation. Different types of exercise, such as jogging have also been suggested for bone loss rescue (114). Specifically for spaceflight bone loss, advanced resistive exercise could act as a deterrent (115,116). Interestingly low-intensity pulsed ultrasound (LIPUS) could accelerate the healing of fractures (117). Lastly, low BMD can be rescued with whole body vibration (WBV) (118). Elucidation of the specific role of polycystins and cilia could give answers to various riddles.

Conclusions

In conclusion, this review has highlighted the critical role of PCs in bone formation. However, the lack of understanding of their specific function, poses a definite limit. Unveiling their involvement in bone signaling pathways, could possibly permit the identification of molecules, targeting bone disorders. We suggest that malfunctions of the *PKD* genes can lead to impaired skeletal development. Ongoing research should focus on mechanical forces and on how these influence PCs role in bone mechanosensing pathways. Such unraveling could permit identification of small molecules to target specific components of these pathways (*Figure 1*), contributing to the treatment of bone disorders.

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Footnote

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