The versatile nature of the calcium-permeable cation channel TRPP2

Aurélie Giamarchi[1], Françoise Padilla[1], Bertrand Coste[1], Matthieu Raoux[1], Marcel Crest[1], Eric Honoré[2] & Patrick Delmas[1+]

[1]Laboratoire de Neurophysiologie Cellulaire, CNRS, Marseille, France, and [2]Institut de Pharmacologie Moléculaire et Cellulaire, CNRS, Valbonne, France

TRPP2 is a member of the transient receptor potential (TRP) super-family of cation channels, which is mutated in autosomal domi-nant polycystic kidney disease (ADPKD). TRPP2 is thought to function with polycystin 1—a large integral protein—as part of a multiprotein complex involved in transducing Ca^{2+}-dependent information. TRPP2 has been implicated in various biological functions including cell proliferation, sperm fertilization, mating behaviour, mechanosensation and asymmetric gene expression. Although its function as a Ca^{2+}-permeable cation channel is well established, its precise role in the plasma membrane, the endo-plasmic reticulum and the cilium is controversial. Recent studies suggest that TRPP2 function is highly dependent on the subcellular compartment of expression, and is regulated by many interactions with adaptor proteins. This review summarizes the most pertinent evidence about the properties of TRPP2 channels, focusing on the compartment-specific functions of mammalian TRPP2.

Introduction

Transient receptor potential (TRP) channels belong to a super-family of multifunctional cation channels that are present in virtually all mammalian cell types and which are mutated in auto-somal dominant polycystic kidney disease (ADPKD). The TRP superfamily (Fig 1) includes 56 related six-transmembrane domain channels, which are classified into seven families: TRPC (Canonical), TRPV (Vanilloid), TRPM (Melastatin), TRPN (Nompc, from no mechanoreceptor potential-c), TRPA (Ankyrin-like with transmembrane domain 1), TRPML (Mucolipin) and TRPP (Polycystin; for reviews see Clapham et al, 2005; Delmas, 2004a, 2005; Montell, 2005; Nilius & Voets, 2005).

[1]Laboratoire de Neurophysiologie Cellulaire, CNRS, UMR 6150, Faculté de Médecine, IFR Jean Roche, Boulevard Pierre Dramard, 13916 Marseille Cedex 20, France
[2]Institut de Pharmacologie Moléculaire et Cellulaire, CNRS, 660, Route des Lucioles, Sophia Antipolis, 06560 Valbonne, France
[+]Corresponding author. Tel: +00 33 4 91 69 89 70; Fax: 00 33 4 91 69 89 77;
E-mail: delmas.p@jean-roche.univ-mrs.fr

The polycystin family is divided structurally and functionally into two subfamilies, the polycystin 1 (PKD1)-like and polycystin 2 (PKD2)-like proteins, both of which have a modest degree of sequence similarity between subfamilies (Delmas, 2004a, 2005; Igarashi & Somlo, 2002; Nauli & Zhou, 2004). In humans, the PKD2-like subgroup contains three homologous proteins—PKD2, PKD2L1 and PKD2L2—which are now referred to as TRPP2, TRPP3 and TRPP5. The PKD1-like subgroup contains five homolo-gous proteins, all with an 11-transmembrane topology, and—by virtue of their structure—are not considered as members of the TRP superfamily (Fig 1).

TRPP2 has been shown to assemble with PKD1 to form a receptor–ion channel complex (Delmas et al, 2004a; Hanaoka et al, 2000). Both proteins localize to primary cilia of renal epi-thelial cells, where they are implicated in mechanosensitive trans-duction signals (Pazour et al, 2002; Yoder et al, 2002; Nauli et al, 2003). TRPP2 has been also documented at two other subcellular locations—the plasma membrane (PM) and the endoplasmic reticulum (ER)—but it is still disputed whether TRPP2 functions as an intracellular or a plasmalemmal channel. The finding that TRPP2 is retained in the ER of most cell systems has supported the view that TRPP2 might function as a reticular Ca^{2+}-release chan-nel (Koulen et al, 2002). Conversely, TRPP2 has been shown to reside and act at the PM, notably in Madine–Darby canine kidney (MDCK) cells derived from cortical collecting ducts (Luo et al, 2003; Scheffers et al, 2002). These apparently incongruent views might be reconciled by the recent demonstration that subcellular transport and localization of TRPP2 are controlled by many inter-actions with adaptor proteins and enzymes (Hidaka et al, 2004; Köttgen et al, 2005a; Köttgen & Walz, 2005; Streets et al, 2006; Geng et al, 2006). Such varied transport behaviour provides a mechanism for the dynamic regulation of TRPP2 channel density at the ER, PM and cilial localizations, and for different subcellular TRPP2 signalling functions. Thus, the knowledge of the compartment-specific regulations of TRPP2 is of crucial importance for the understanding of its roles in health and disease.

Subcellular localization and transport of TRPP2

A long-standing debate has surrounded the subcellular locali-zation of TRPP2. In most cell-based systems, TRPP2 concentrates
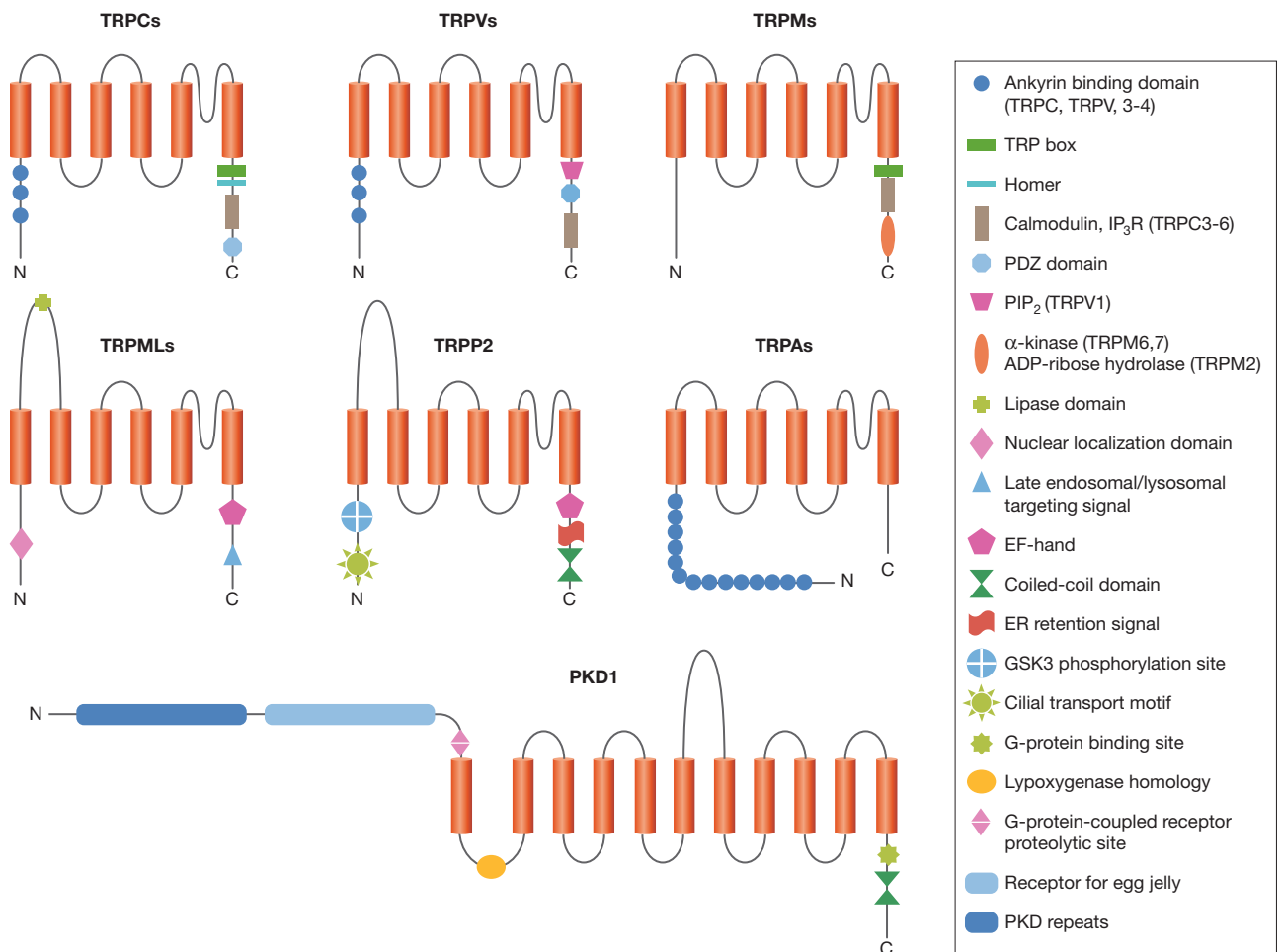
Fig 1 | Structural elements of the mammalian transient receptor potential cation channels and polycystin 1. ER, endoplasmic reticulum; GSK3, glycogen synthase kinase 3; PKD, polycystin; TRP, transient receptor potential family (TRPA, TRPC, TRPM, TRPML, TRPP, TRPV).

in intracellular compartments, most notably in the ER (Cai *et al*, 1999). TRPP2 encompasses an ER-retention signal within its carboxyl terminus (Fig 2), which seems to prevent transport to the cell surface when expressed alone (Cai *et al*, 1999). Deletion mutants for this ER-retention signal translocate to the cell surface and can be detected by immunological and electrophysiological methods (Chen *et al*, 2001). Opposing these findings are reports that TRPP2 is present at the PM of MDCK cells (Scheffers *et al*, 2002) or after treatment with chemical chaperones/proteasome inhibitors (Gonzalez-Perrett *et al*, 2001; Luo *et al*, 2003; Vassilev *et al*, 2001). TRPP2 has been also localized to basolateral PMs, lamellipodia, primary cilia and mitotic spindles (Cai *et al*, 1999; Foggensteiner *et al*, 2000; Nauli *et al*, 2003; Newby *et al*, 2002; Rundle *et al*, 2004; Yoder *et al*, 2002).

Recent data have begun to clarify the location of TRPP2. First, Köttgen *et al* (2005a) reported that TRPP2 transport between the ER, Golgi and PM compartments might be directed by the phosphofurin acidic cluster proteins PACS1 and PACS2—two sorting proteins that bind to an acidic cluster in the C-terminal domain of TRPP2 (Fig 2). Binding of these adaptor proteins to TRPP2 is promoted by casein kinase 2 (CK2)-dependent phosphorylation of

Ser 812. Mutation of Ser 812 to alanine or destruction of the acidic cluster abrogates the interaction between TRPP2 and the PACS proteins, and increases whole-cell TRPP2 currents. Thus, mechanisms that regulate the interaction of PACS proteins with TRPP2 are likely to have a key role in TRPP2 transport. Importantly, TRPP3 and TRPP5 lack the PACS-binding acidic cluster (Fig 2B), suggesting that their transport is regulated in a different way to that of TRPP2. This might explain why TRPP3 is targeted at the cell surface, whereas TRPP2 is retained in the ER. Second, a recently discovered protein called PIGEA14 (polycystin-2 interactor, Golgi- and ER-associated protein) has been shown to interact with the C-terminus of TRPP2. Co-expression of both proteins in HeLa cells and in pig kidney LLC-PK1 cells causes a redistribution of TRPP2 as well as PIGEA14 from the ER to a putative trans-Golgi compartment (Hidaka *et al*, 2004), indicating that transport of TRPP2 is regulated at the ER and the trans-Golgi network. Finally, the TRPP2 amino-terminus contains signal domains that are required for PM and cilial localizations. PM, but not cilial, localization of TRPP2 is regulated by glycogen synthase kinase 3 phosphorylation of Ser 76 (Streets *et al*, 2006), whereas another N-terminal motif ($R_6V_7xP_8$) is necessary for localization in cilia (Fig 1; Geng *et al*, 2006). The study by Geng

A

C-ter DFSTFQECIFTQFRIILGDINFAEIEEANRVLGPIYFTTFVFFMFFILLNMFLAI

684
INDTYSEVKSDLAQQKAEMELSDLIRKGYHKALVKLKLKKNTVDDISESLRQGGGKLNFDELRQDLKGKGHTDA

754   782 787   **Acidic cluster**
                                                      812   820
EIEAIFTKYDQDGDQELTEHEHQQMRDDLEKEREDLDLDHSSLPRPMSSRSFPRSLDD**S**EEDDDEDSGHSSRRR
         EF-hand   **ER-localization domain**

832   895
GSIS**SGVSYEEFQVLVRRVDRMEHSIGSIVSKIDAVIVKLEIMERAKLKRREVLGRLLDGVAEDERLG**RDSEIH
                    TRPP2–PKD1 interacting domain

                                     968
REQMERLVREELERWESDDAASQISHGLGTPVGLNGQPRPRSSRPSSSQSTEMEGAGGNGSSNVHV

B

Human-PKD2L1	538	PAYFVTYVFFVFFVLLNMFLAIINDTYSEVKEELAG-QKDELQLSDLLKQGYNKILLRLR
Human-PKD2L2	468	PIYFITFIFFVFFVLLNMFLAIINDTYSEVKADYSIGRRPDFELGKMIKQSYKNVLEKFR
Human-PKD2	658	PIYF TFVFFMFFILLNMFLAIINDTYSEVKSDLAQ-QKAEMELSDLIRKGYHKALVKLK

Human-PKD2L1	597	LRKERVSDVQKVLQGGEQEIQFEDFTNTLRELGHAEHEITELTATFTKFDRDGNRILDEK
Human-PKD2L2	528	LKKAQKDEDKKTKGSG------DLAEQARREGFDENEIQNAEQVKKWKERLEKKYYSME
Human-PKD2	717	LKKNTVDDISESLRQGGGK---LNFDELRQDLKGKGHTDAEIEAIFTKYDQDGDQELTEH
		EF-hand

Human-PKD2L1	657	EQEKMRQDLEEERVALNTEIEKLGRSIVSSPQGKSGPEAARAG---------------GW
Human-PKD2L2	581	IQDDYQPVTQEEFRDGTTTKYKMRFSLSA-----------------------------
Human-PKD2	774	EHQQMRDDLEKEREDLDLDHSSLPRPMSSRSFPRSLDDSEEDDDEDSGHSSRRRGSISSG
		ER-localization domain

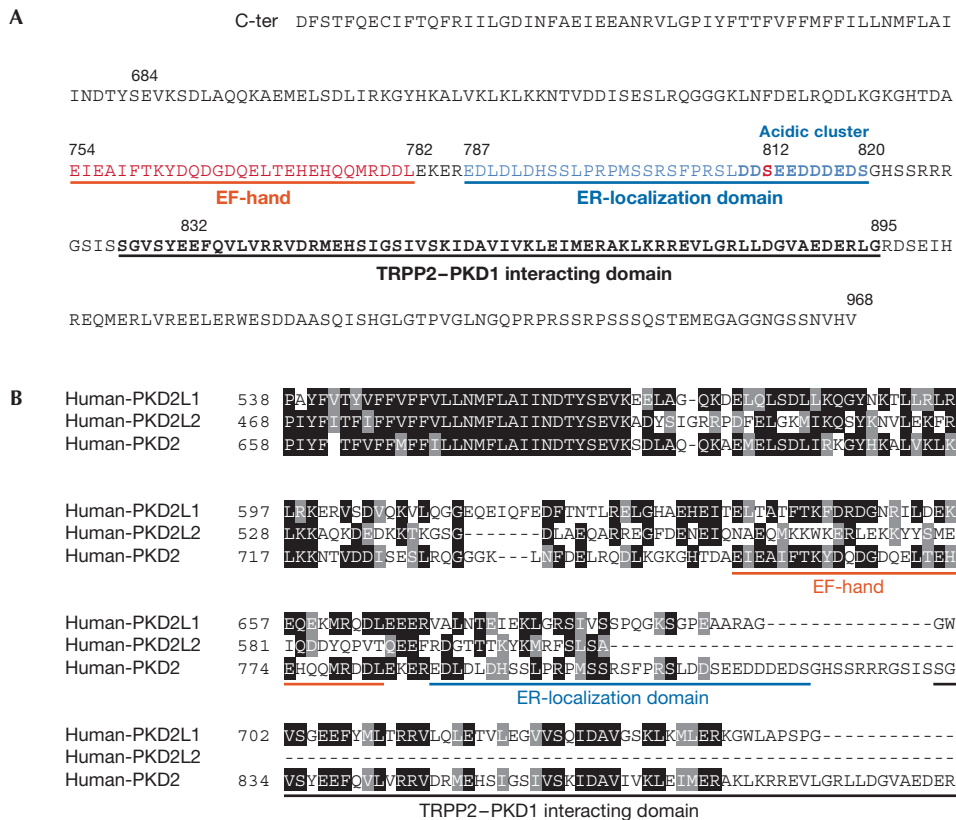|		
Human-PKD2L1	702	VSGEEFYMLTRRVLQLETVLEGVVSQIDAVGSKLKMLERKGWLAPSPG------------
Human-PKD2L2		--
Human-PKD2	834	VSYEEFQVLVRRVDRMEHSIGSIVSKIDAVIVKLEIMERAKLKRREVLGRLLDGVAEDER

TRPP2–PKD1 interacting domain

Fig 2 | Regulatory carboxy-terminal domains of transient receptor potential polycystin proteins. (**A**) Sequence of human TRPP2 C-terminus. (**B**) Sequence alignment of the variable C-termini of human PKD2L1 (TRPP3), PKD2L2 (TRPP5) and PKD2 (TRPP2). Identical and similar residues are highlighted in black and grey, respectively. TRPP, transient receptor potential polycystin.

et al (2006) also provides evidence that TRPP2 transport to cilia is independent of PKD1 because TRPP2 mutants lacking the PKD1 interaction region still transport to cilia.

TRPP2 as an intracellular Ca^{2+}-permeable cation channel

TRPP2 might act as a Ca^{2+}-release channel in ER membranes, which amplifies Ca^{2+} transients initiated by inositol-1,4,5-trisphosphate (Ins(1,4,5)P$_3$)-generating PM receptors (Koulen *et al*, 2002). This led to the suggestion that TRPP2 is a novel type of intracellular receptor that might be involved in mediating Ca^{2+}-induced Ca^{2+} release (Fig 3). TRPP2 seems to be directly activated by Ca^{2+} and displays a bell-shaped dependence on cytoplasmic Ca^{2+} (Koulen *et al*, 2002). Although it is not yet clear whether the Ca^{2+}-binding EF-hand of TRPP2 is involved in Ca^{2+}-dependent modulation of TRPP2, it is worth noting that pathogenic TRPP2 mutants with a premature termination of the peptide chain in their C-tail lost their ability to detect Ca^{2+}. However, TRPP3 artificial truncation mutants lacking the EF-hand show Ca^{2+}-activated channel activities, suggesting that, at least for TRPP3, the EF-hand and other parts of the C-tail are not key determinants of the Ca^{2+}-dependent activation (Li *et al*, 2002).

Phosphorylation of Ser 812 by a putative CK2 results in a significant increase in the sensitivity of the TRPP2 channel to Ca^{2+} stimulation (Cai *et al*, 2004). The S812A substitution shifts the Ca^{2+} dependence such that TRPP2-S812A has a maximum open probability at tenfold higher Ca^{2+} concentrations (~3 µM [Ca^{2+}]) than phosphorylated TRPP2. Reticular TRPP2 is therefore likely to have enhanced Ca^{2+} sensitivity, as CK2 is opportunely associated with the ER and most TRPP2 channels are phosphorylated *in vivo* (Cai *et al*, 2004).

In line with a role for ER-localized TRPP2 in regulating intra-cellular Ca^{2+}, TRPP2$^{+/-}$ vascular smooth muscle cells have altered intracellular Ca^{2+} homeostasis (Qian *et al*, 2003). Moreover, TRPP2 has been recently shown to interact functionally and physically with Ins(1,4,5)P$_3$R in an oocyte expression system (Fig 3; Li Y *et al*, 2005). The physiological relevance of these results remains to be clarified.

TRPP2 as a cell surface Ca^{2+}-permeable cation channel

A key issue surrounding TRPP2 is the extent to which channel activity depends on the presence of PKD1. Hanaoka *et al* (2000) provided evidence that PKD1 and TRPP2 interact to form heteromeric complexes *in vitro* (Newby *et al*, 2002; Qian *et al*, 1997; Tsiokas *et al*, 1997, 1999). Co-expression of PKD1 and TRPP2 in Chinese hamster ovary cells, as well as in neurons, promotes the translocation of TRPP2 to the PM and generates a non-selective cation channel the selectivity of which is identical to that of homomeric TRPP2 (Delmas *et al*, 2004b; Hanaoka *et al*, 2000). Channel activity is not observed when the C-terminal interaction between PKD1 and TRPP2 is inhibited, indicating that co-assembly of PKD1 and TRPP2 is required for the proper targeting of TRPP2 to the PM. In this model, TRPP2 acts as the ion-translocating component because
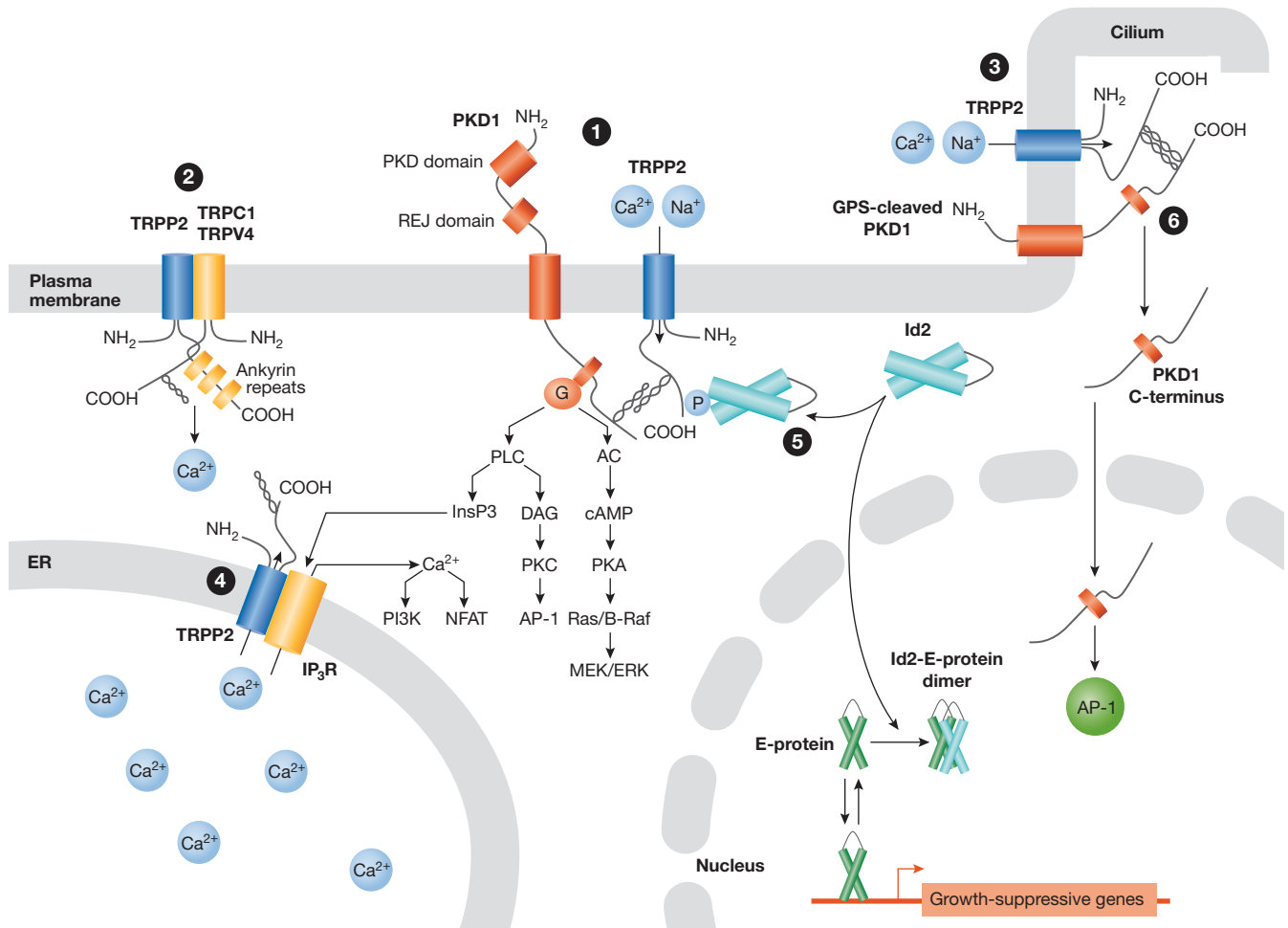
Fig 3 | Compartment-specific functions of transient receptor potential polycystin 2. The various models for the localization-dependent functions of TRPP2 are shown. TRPP2 mediates Ca^{2+} influx at the plasma membrane (PM) and ciliary membrane (cilium), where it functions in a protein complex with polycystin 1 (PKD1) (1, 3) and possibly with other members of the TRP channel superfamily (TRPC1, TRPV4) (2). Ca^{2+} influx induced by shear flow in renal epithelial cells is triggered by bending of the luminal cilium and seemingly requires the presence of PKD1–TRPP2 complexes in the cilium (3). Mechanical stress results in activation of PKD1–TRPP2 complexes to allow Ca^{2+} influx either in the shaft or in the base of the cilium. TRPP2 acts as a Ca^{2+}-release channel in the endoplasmic reticulum (ER), where it might interact with, and regulate, inositol-1,4,5-trisphosphate receptors (Ins(1,4,5)P_3Rs) (4). Serine-phosphorylated TRPP2 sequesters Id2 in the cytoplasm and prevents it from entering the nucleus (5). PKD1 can undergo a proteolytic cleavage that releases its carboxy-terminal tail, which translocates to the nucleus and activates the transcription factor AP1 (6). Note that it is hypothesized that PKD1 targeted to the primary cilium is also cleaved at its GPCR proteolytic site (GPS). ERK, extracellular signal-regulated kinase; GPCR, G-protein coupled receptor; Id2, inhibitor of DNA binding 2; MEK, mitogen-activated protein kinase/ERK kinase; NFAT, nuclear factor of activated T-cells; PI3K, phosphatidyl-inositol 3-kinase; PKA, cAMP-dependent protein kinase; PKC, protein kinase C; REJ, receptor for egg jelly; TRPP2, transient receptor potential polycystin 2.

PKD1 alone cannot form an ion channel (Delmas *et al*, 2002; Hanaoka *et al*, 2000). In the complex, PKD1 seems to regulate TRPP2 channel activity (Delmas *et al*, 2004a; Xu *et al*, 2003). Conversely, TRPP2 binding to PKD1 reduces the ability of PKD1 to constitutively activate G-proteins possibly by competitive interaction (Delmas *et al*, 2002, 2004a). These data support the view that in addition to its ion-channel function, TRPP2 also regulates the downstream effects of PKD1 on its target effectors. Therefore the balance between TRPP2 and PKD1 expression, which is disrupted in ADPKD, might have a crucial role in normal PKD1–TRPP2 signalling. Functional regulation of PKD1 by TRPP2 has been further substantiated in the case of PKD1-mediated nuclear factor of activated T cells (NFAT) activation (Puri *et al*, 2004), the nuclear translocation of the PKD1 C-terminal domain (Chauvet *et al*, 2004) and Janus kinase (JAK)/signal transducers and activators of transcription (STAT) signalling (Fig 3; Bhunia *et al*, 2002).

The TRPP2–PKD1 complex regulates signalling by preventing the pro-proliferative helix–loop–helix protein Id2 from entering the nucleus (Fig 3; Li X *et al*, 2005). Id2 is known to associate with E-proteins and blocks their ability to turn on growth-suppressive genes. It is normally prevented from translocating to the nucleus through its association with the serine-phosphorylated C-terminal domain of TRPP2, which is promoted by PKD1. These data predict that loss-of-function mutations in either TRPP2 or

PKD1, or disruption of their functional interaction, will cause Id2 to enter the nucleus and turn off growth-suppressive genes. Such a mechanism might be involved in the pathogenesis of ADPKD.

Activation of the PKD1–TRPP2 multiprotein complex

The idea that PKD1 and TRPP2 are interacting partners within a signalling pathway first arose from the observation that mutations in PKD1 or TRPP2 produce virtually identical clinical presentations. Other early evidence came from studies of *Caenorhabditis elegans* orthologues of ADPKD genes—*lov-1* (location of vulva, a PKD1 orthologue) and *pkd-2*—which might be associated subunits of a sensory pathway necessary for normal mating behaviour (Barr *et al*, 2001; Barr & Sternberg, 1999). Reconstituted PKD1–TRPP2 complexes can be activated by applying antibodies directed against the extracellular receptor for egg jelly (REJ) domain of PKD1 (Delmas *et al*, 2004a). This leads to the concordant activation of TRPP2 and heterotrimeric G-proteins. Thus, PKD1 and TRPP2 can form functionally associated subunits of a receptor–ion channel complex in which PKD1 acts as a 'receptor' that regulates TRPP2 activity and G-protein signalling. This mechanism might mimic a yet-to-be-determined extracellular signal that activates the polycystin complex.

This mechanism has fascinating parallels with the acrosome reaction in sea-urchin spermatozoa (Mengerink *et al*, 2000). The acrosome reaction requires activation of REJ1/REJ3—two PKD1 orthologues harbouring REJ modules—and which bind components of the egg jelly (Hirohashi & Vacquier, 2002). As for their mammalian counterparts, antibodies directed against the REJ domain of sea-urchin REJs induce the acrosome reaction by opening Ca^{2+}-permeable channels (Moy *et al*, 1996). Recently, sea-urchin REJ3 has been shown to bind physically to the sea-urchin sperm orthologue of TRPP2 in the acrosome PM (Neill *et al*, 2004), raising the possibility that TRPP2 might be involved in the Ca^{2+}-regulated acrosome reaction in sea urchins. Collectively, these findings add further weight to the primary importance of the REJ domain in activation of the PKD1–TRPP2 signalling complex.

TRPP2 might be involved in mechanosensitive functions

Recent studies have provided evidence that PKD1 and TRPP2 localize together in primary cilia of renal epithelial cells where they might function in transducing sensory information, such as shear fluid stress (McGrath *et al*, 2003; Nauli *et al*, 2003; Pazour *et al*, 2002). The primary cilium is proposed to act as a flow sensor because it was shown to be essential for the ability of MDCK cells to detect laminar fluid flow (Praetorius & Spring, 2001, 2003). Fluid shear-force bending of the cilium causes Ca^{2+} influx through mechanically sensitive channels. In this model, the PKD1–TRPP2 complex can be envisaged as a mechanosensor, which is used to transduce stimulus energy into a change in membrane permeability. However, the demonstration that the PKD1–TRPP2 complex is mechanosensitive still awaits direct experimental evidence.

A recent study provided the first evidence for the presence of single cation channel currents from isolated primary cilia of LLC-PK1 cells (Raychowdhury *et al*, 2005), although their molecular identity and mechanosensitivity remains to be established. In these cells, the epidermal growth factor receptor modulates TRPP2 and localizes with TRPP2 in the primary cilium (Ma *et al*, 2005), suggesting that TRPP2 might be involved in both mechanical and chemical transduction processes.

TRPP2 has been also shown to have a central role in the establishment of the left–right asymmetry of visceral organs (McGrath *et al*, 2003). TRPP2 is expressed in both motile and immotile monocilia of embryonic nodal cells. However, a perinodal Ca^{2+} signal is absent in *Trpp2⁻/⁻* mice embryos, suggesting that TRPP2 functions as a mechanotransducer in immotile monocilia, transducing leftward nodal flow into an increase in Ca^{2+}. This function is consistent with the observation that targeted disruption in TRPP2 causes *situs inversus*, in addition to the hallmark cardiac and kidney defects (Pennekamp *et al*, 2002). It is interesting in this regard that the lack of laterality defects in PKD1-knockout embryos correlates with the absence of PKD1 in cilia (Karcher *et al*, 2005), favouring the view that TRPP2 might be involved in mechanosensation in the absence of PKD1. A similar mechanosensitive role for TRPP orthologues has been proposed in axonemal-based sperm flagella of *Drosophila melanogaster* (Gao *et al*, 2003; Watnick *et al*, 2003).

Interaction with other putative mechanosensitive channels

The recent identification of TRP channels as core components of mechanoreceptors in *C. elegans*, *D. melanogaster* and vertebrates might offer clues to the conservative mechanoreceptive structural elements of mechanotransducers (O'Neil & Heller, 2005; Pedersen *et al*, 2005). In the fruit fly, *D. melanogaster*, mechanoelectrical responses in bristle sensory neurons involve—among others—the Nompc channel, a member of the TRPN family. The nematode *C. elegans* can sense touch through the activation of the OSM-9 channel, a distant member of the TRPV family. Importantly, all these TRP channels have intracellular N-terminal tails harbouring several ankyrin repeats, which might anchor the channels to the cytoskeleton. Ankyrin repeats contain antiparallel α-helices that can stack to form a superhelix with spring-like behaviour (Lee *et al*, 2006). Atomic force microscopy measurements have revealed that tandem ankyrin repeats display linear elasticity and behave as a fully reversible nanospring, reinforcing the idea that ankyrin motifs might be key to mechanotransduction.

In vertebrates, TRPV2 and TRPV4 have been implicated in mechanosensation because they can sense membrane stretch (Muraki *et al*, 2003) and hypo-osmotic stress (Alessandri-Haber *et al*, 2003), respectively. Here again, it is worth noting that TRPV4 requires the N-terminal domain with the three ankyrin repeats to sense physical challenges (Liedtke *et al*, 2000).

Neither PKD1 nor TRPP2 have ankyrin repeats, raising the question as to whether these two proteins are putative mechanotransducers. On this issue, the extracellular domain of PKD1 has been recently shown to display a dynamic extensibility whereby its length might be regulated through unfolding/refolding of its immunoglobulin-like domains (Qian *et al*, 2005). This would provide the structural support for a tethered mechanism that might be required for mechanical gating. Although these mechanical properties of PKD1 are important in the context of mechanosensation, they seem more appropriate to providing structural support in cell–cell and/or cell–matrix interactions at basolateral membranes than in mechanotransduction in the solitary cilium.

It is therefore reasonable to consider an alternative model in which mechanical force is transmitted indirectly to the protein complex or through an auxiliary subunit. For example, TRPP2 might assemble with other TRP channels to form a mechanosensitive channel. A tantalizing link points to TRPV4 as it is expressed in renal epithelial cells, particularly in the distal nephron and collecting ducts, which are flow-sensitive segments (Tian *et al*, 2004). In this regard, preliminary evidence by Gerd Walz's group indicate

that TRPV4 and TRPP2 interact and co-localize in the primary cilium (Köttgen *et al*, 2005b). Recently, TRPC1 was also found to be a component of the vertebrate mechanosensitive cation channel (Maroto *et al*, 2005). Interestingly, TRPC1 is known to interact with TRPP2 in expression systems (Tsiokas *et al*, 1999) and might form functional heteromers with TRPP2 (Delmas, 2004b), suggesting that TRPC1 might contribute to the mechanosensory TRPP2 apparatus.

Concluding remarks

In the past few years, considerable progress has been achieved in evaluating the distribution and functional characteristics of TRPP proteins. Most notably, TRPP2 channels have been shown to transport to different subcellular compartments and, as such, display specific subcellular functions. In renal primary cilia TRPP2 interacts with PKD1, a process that might be essential for the regulation of mechanosensation and the cell cycle. However, the available information does not support the candidacy of the PKD1–TRPP2 complex as the core component of the mechanosensitive apparatus of the primary cilium. In the ER, TRPP2 acts as an intracellular Ca^{2+} release channel. It will be important to identify ligands for PKD1 that affect the function of the PKD1–TRPP2 complex and to identify the factors interacting with TRPP2 that determine its compartment-specific functions. These studies will contribute not only to a better understanding of TRPP physiological functions but also to the development of new strategies for targeted therapeutic intervention in ADPKD.

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From left to right: Aurélie Giamarchi, Françoise Padilla, Bertrand Coste, Matthieu Raoux, Marcel Crest, Eric Honoré & Patrick Delmas