The TRPV4 Channel

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Contents

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B. Nilius and V. Flockerzi (eds.), *Mammalian Transient Receptor Potential (TRP) Cation Channels*, Handbook of Experimental Pharmacology 222,
DOI 10.1007/978-3-642-54215-2_12,

Abstract

The widely distributed TRPV4 cationic channel participates in the transduction of both physical (osmotic, mechanical, and heat) and chemical (endogenous, plant-derived, and synthetic ligands) stimuli. In this chapter we will review TRPV4 expression, biophysics, structure, regulation, and interacting partners as well as physiological and pathological insights obtained in TRPV4 animal models and human genetic studies.

Keywords

TRPV4 • genetics • knock-out • pathophysiology • biophysics

1 Gene

The TRPV4 channel was first described in 2000 (Liedtke et al. 2000; Strotmann et al. 2000; Wissenbach et al. 2000) and received several different names before the current nomenclature was accepted: OTRPC4 (osmosensitive transient receptor potential channel), VR-OAC (vanilloid receptor-related osmotically activated channel), VRL-2 (vanilloid receptor-like), and TRP-12. The human TRPV4 gene is found in chromosome 12q23-q24.1 and presents 15 exons. Five splice variants (TRPV4-A-E) have been identified. Variants B, C, and E involve deletions in the N-terminal ankyrin repeat domains (ANK) that result in protein retention in the endoplasmic reticulum, defective oligomerization, and lack of channel activity (Arniges et al. 2006; Vazquez and Valverde 2006).

Compared to the vast knowledge obtained about TRPV4 channel regulation, little is known about the control of TRPV4 transcription. Progesterone receptor mediates repression of TRPV4 transcription in epithelial and vascular smooth muscle cells (Jung et al. 2009). Downregulation of TRPV4 expression by microRNA 203 in condylar cartilage of the temporomandibular joint (Hu et al. 2012) and by probiotic bacteria strains in the colon (Distrutti et al. 2013) has also been reported. Inflammatory signals such as interleukin 1β and interleukin 17 increase

TRPV4 mRNA levels in dorsal root ganglia (DRG) neurons (Segond von Banchet et al. 2013), and nerve growth factor (NGF) increases TRPV4 expression in the urothelium (Girard et al. 2013). Hypoxia/ischemia increases TRPV4 expression and function in astrocytes (Butenko et al. 2012) and in pulmonary arterial smooth muscle cells of mice exposed to chronic hypoxia-induced pulmonary hypertension (Xia et al. 2013).

2 Expression

TRPV4 is broadly expressed in heart, arteries, lung, skin, bone, brain, urinary bladder, kidney, intestine, liver, pancreas, and female reproductive tract [for a review see Everaerts et al. (2010a)]. TRPV4 is commonly found in the epithelial cells of the cornea (Mergler et al. 2010; Pan et al. 2008), bronchi (Fernandez-Fernandez et al. 2002, 2008; Li et al. 2011), trachea (Arniges et al. 2004; Lorenzo et al. 2008), intestine (d'Aldebert et al. 2011), urothelium (Everaerts et al. 2010b), larynx (Hamamoto et al. 2008), oviduct (Andrade et al. 2005), bile duct (Gradilone et al. 2007), epidermis (Sokabe et al. 2010), mammary gland (Jung et al. 2009), and endolymphatic sac (Kumagami et al. 2009). TRPV4 is also found in the endothelium (Watanabe et al. 2002b), smooth (Earley et al. 2005; Jia et al. 2004) and skeletal muscle (Kruger et al. 2008), sensorial and brain neurons (Alessandri-Haber et al. 2003; Li et al. 2013; Shibasaki et al. 2007), glia (Benfenati et al. 2007; Konno et al. 2012), immune cells (Kim et al. 2010), osteoclasts (Masuyama et al. 2008), osteoblasts and chondrocytes (Muramatsu et al. 2007), and pancreatic islets (Casas et al. 2008).

3 Protein

The TRPV4 protein consists of 871 amino acids (aa) with 6 transmembrane (TM) domains presenting both N- and C-terminal cytoplasmic tails (Fig. 1). The pore of the channel (aa 663–686) is found in the loop between TM5 and TM6. The 12 central amino acids of the pore are identical to those of TRPV1 and 2, the closest relatives of TRPV4 (Voets et al. 2002). Two key amino acids have been shown to regulate TRPV4 permeability: D672 and D682. Neutralization of both D672 and D682 greatly reduces permeability for calcium and rectification and increases monovalent permeation, suggesting that these two negatively charged residues are important for binding calcium ions inside the pore (Voets et al. 2002). D682 also participates in ruthenium red block. M680 residue strongly affects Ca^{2+} permeation; K675 does not contribute significantly to the properties of the pore. Glycosylation of N651 is involved in the trafficking of TRPV4 (Xu et al. 2006). Mutation of E797 renders the channel constitutively opened (Watanabe et al. 2003a).

The long N-terminal tail (aa 1–465) accounts for more than 50 % of total TRPV4 length and contains 6 ANK (Phelps et al. 2010) that participate in channel oligomerization (Arniges et al. 2006). The N-terminal tail plays a prominent role in channel regulation, having a phosphoinositide-binding site (PIBS, aa 121–125)

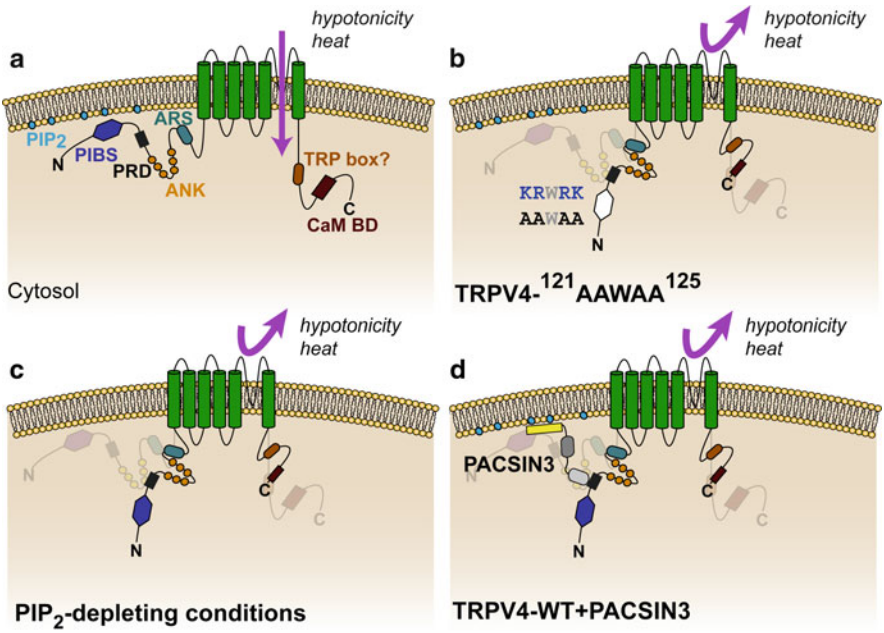

Fig. 1 Domain structure and PIP_2-dependent functional rearrangement of TRPV4. (**a**) Cartoon of a single TRPV4 protein in its expanded conformation due to interaction of the N-tail with PIP_2. Phosphoinositide-binding site (PIBS), proline-rich domain (PRD), ankyrin domains (ANK), arachidonate-like recognition sequence (ARS), the six transmembrane domains, a questioned TRP box, and the CaM-binding domain (CaM-BD). Intracellular tail rearranges into a more compacted form upon neutralization of positive charges in the PIBS (**b**), depleting PIP_2 from the plasma membrane (**c**), or coexpression of TRPV4 with PACSIN3 (**d**). The expanded conformation is required for TRPV4 response to hypotonic and heat stimuli

required for channel activation by physiological stimuli, hypotonicity and heat (Garcia-Elias et al. 2013); a proline-rich domain (PRD) (aa 132–144) used for binding of and regulation by kinase C and casein kinase substrate in neurons 3 (PACSIN3) (Cuajungco et al. 2006), and an arachidonate-like recognition sequence (ARS-L) (aa 402–408) (Nilius et al. 2003). In addition, complete deletion of PRD (Garcia-Elias et al. 2008), aa 1–130 or 100–130, renders the channel insensitive to all stimuli, including the synthetic activator 4α-phorbol 12,13 didecanoate (4α-PDD), suggesting an important role of the N-tail in the gating of TRPV4 (Fig. 2). The C-terminal tail presents a calmodulin-binding domain (CaM-BD) (812–831 aa) (Strotmann et al. 2003), an oligomerization domain (Becker et al. 2008), and a PDZ-like domain (Garcia-Elias et al. 2008; van de Graaf et al. 2006). The existence of a TRP box in the C-terminal tail has been proposed for TRPV1 (Garcia-Sanz et al. 2007) although its existence in TRPV4 has not been thoroughly studied. Heteromerization of TRPV4 with other TRP channels is discussed in Sect. 4.4.

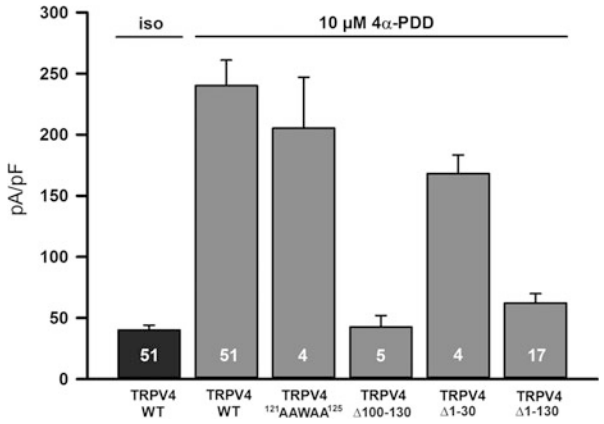

Fig. 2 Response to 4α-PDD of N-terminal truncations and mutations of TRPV4. Mean current responses to 4α-PDD (10 μM) stimulation in cells transfected with TRPV4-WT, TRPV4-^{121}AAWAA^{125}, TRPV4-Δ1-30, TRPV4-Δ1-130, and TRPV4-Δ100-130. The number of cells recorded is shown for each condition. *Iso* isotonic

4 Interacting and Regulatory Proteins

A detailed database of TRPV4 channel protein–protein interactions (Chun et al. 2014; Shin et al. 2012b) is available at http://trpchannel.org/summaries/TRPV4.

4.1 Proteins Modifying TRPV4 Location on the Plasma Membrane

In addition to being triggered by activating stimuli, TRPV4 channel activity in the plasma membrane is affected at several different levels: targeting of the channel protein to its final destination, posttranslational modification, and lysosomal degradation.

TRPV4 location on the plasma membrane and channel response to hypotonicity and warm temperature is regulated by PACSIN3 (Cuajungco et al. 2006; D'hoedt et al. 2008). PACSIN3 belongs to a family of three proteins with the Bin-amphiphysin-Rvs (BAR) domain required to penetrate and remodel the plasma membrane and to participate in endocytic processes, neurotransmission, and cell morphology and motility (Plomann et al. 2009). All members of the PACSIN family bind to the PRD of TRPV4 through their SRC homology 3 (SH3) domain; however, only PACSIN3 appears to regulate TRPV4.

A few more proteins affect the presence of TRPV4 at the plasma membrane. OS-9, a ubiquitous protein found in the cytoplasmic site of the endoplasmic reticulum (ER), plays a role in selecting substrates for degradation. It interacts

with TRPV4 monomers (aa 438–468 at the N-tail) retaining the monomers in the ER and reducing the amount of channel in the membrane, thereby protecting TRPV4 from polyubiquitination and premature proteasomal degradation (Wang et al. 2007). The ubiquitin ligase AIP4 binds TRPV4 (presumably to its N-tail) and promotes its endocytosis (Wegierski et al. 2006). Intimately linked to TRPV4 ubiquitination in vascular smooth muscle is the complex formed by the G protein-coupled angiotensin receptor, β-arrestin and TRPV4 (Shukla et al. 2010). In the absence of angiotensin, β-arrestin (an adaptor between AIP4 and TRPV4) does not bind TRPV4 and no AIP4-dependent internalization occurs. Another protein binding to and modulating TRPV4 presence and function at the plasma membrane is caveolin-1 (Saliez et al. 2008). TRPV4 location to lipid rafts containing caveolin-1 favors nitric oxide (NO) and endothelium-derived hyperpolarizing factor-dependent vasodilatation. Annexin 2A, a calcium-dependent membrane-binding protein that is linked to vesicular trafficking and endosome formation, also binds TRPV4 in dorsal root ganglia (Huai et al. 2012), although the functional relevance of this interaction is presently unknown.

4.2 Signaling Molecules

Early studies on TRPV4 reported its activation and/or modulation by phorbol esters and protein kinase C (PKC) (Watanabe et al. 2002a; Xu et al. 2003a) as well as by activators of protein kinase A (PKA) (Alessandri-Haber et al. 2006). Subsequent studies (Fan et al. 2009) identified the residues involved in PKA (S824)- and PKC (S162, T175, and S189)-mediated modulation of TRPV4 and the role of the A Kinase Anchoring Protein (AKAP79) in the optimization of TRPV4 phosphorylation by PKA and PKC.

TRPV4 regulation by tyrosine kinases is controversial. The proposed role of Y253 in the hypotonicity-mediated activation of TRPV4 (Xu et al. 2003b) was not observed by others (Vriens et al. 2004). Y110 has been shown to participate in the sensitization of TRPV4 response to heat and hypotonicity but not to 4α-PDD (Wegierski et al. 2009). However, preincubation with the tyrosine kinase inhibitors PP1 (Vriens et al. 2004) or PP2 (Fig. 3) does not affect TRPV4-WT activation by hypotonicity.

The "with no lysine" (WNK) kinases WNK1 and WNK4 downregulate TRPV4 membrane location; hypertension-causing WNK mutants are not able to exert this effect. Experiments deleting the TRPV4 N-tail suggested the participation of this region in TRPV4 interaction with WNK kinases, without providing evidence for a direct interaction between WNK proteins and TRPV4 (Fu et al. 2006).

Calmodulin (CaM) binding to TRPV4 has been identified within the second ANK domain (a binding site shared with ATP) (Phelps et al. 2010) and at the C-tail (aa 812–831) (Strotmann et al. 2003), a site also used for binding to the inositol 1,4,5-trisphosphate (IP3) receptor (IP_3R) (Fernandes et al. 2008; Garcia-Elias et al. 2008) and phosphorylation by the serum glucocorticoid-induced protein kinase-1 (SGK-1) (Shin et al. 2012a). However, the reported effects of CaM on

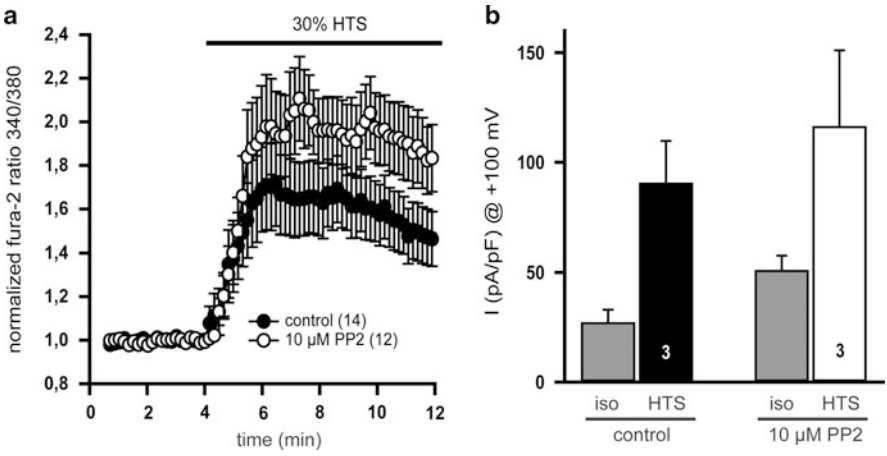

Fig. 3 Tyrosine phosphorylation and TRPV4 activation. Calcium signals (**a**) and whole-cell currents (**b**) obtained in HeLa cells transfected with TRPV4-WT and exposed to vehicle (control) or the tyrosine kinase inhibitor PP2 (10 μM). *Iso* isotonic, *HTS* 30 % hypotonic solution

TRPV4 activity range from a positive modulation (Strotmann et al. 2003) to an inhibitory effect (Phelps et al. 2010). The other molecules interacting with these sites, ATP and IP_3R, are positive modulators of TRPV4 channel activity.

4.3 Cytoskeletal Proteins

The first reported link between TRPV4 and the cytoskeleton came with the observation that microtubule-associated protein 7 (MAP7), which also interacts with actin microfilaments, enhances TRPV4 presence at the plasma membrane and, thereby, increases TRPV4 activity (Suzuki et al. 2003a). The binding of MAP7 to TRPV4 was proposed to be at the channel C-tail.

TRPV4 interacts directly with actin and tubulin (Becker et al. 2009; Goswami et al. 2010). The interaction between TRPV4 and F-actin is essential to support channel activation following cell swelling (Becker et al. 2009), and tubulin competes with actin for binding to the TRPV4 C-tail. The interplay between these three molecules exerts a two-way modulation of cytoskeletal dynamics and TRPV4 activity (Fiorio et al. 2012; Goswami et al. 2010) that may contribute to the mechanical allodynia reported in mice models of neuropathic pain (Huai et al. 2012; Wei et al. 2013). Key molecules that connect the actin cytoskeleton with structures that maintain the barrier function in epithelia also interact with TRPV4. Both β-catenin and E-cadherin, the major components of the tight junctions in keratinocytes, interact with the proximal TRPV4 N-tail to maintain the integrity of the skin barrier (Sokabe et al. 2010). Another study showed coimmunoprecipitation of TRPV4 with α-catenin in urothelial cells but not with

β-catenin (Janssen et al. 2011). TRPV4 also interacts with and is regulated by non-muscle myosin IIa (Masuyama et al. 2012).

TRPV4 coimmunoprecipitates with α2 integrin and Lyn kinase in rat dorsal root ganglion (DRG) neurons (Alessandri-Haber et al. 2008) and participates in mechanical activation of β1 integrin (Thodeti et al. 2009). Moreover, mechanical forces applied to β1 integrin activate TRPV4 at focal adhesions (Matthews et al. 2010), another illustration of the cross talk between TRPV4 and cytoskeletal structures involved in mechanotransduction.

4.4 Channel Proteins

Heteromeric channels are formed by TRPV4 interacting with TRPP2 (Kottgen et al. 2008), aquaporin 4 (Benfenati et al. 2011), aquaporin 2 (Galizia et al. 2012), TRPC1 (Ma et al. 2010), or calcium-activated potassium channel ($K_{Ca}2.3$ cells) (Ma et al. 2013). IP_3R3 interacts with and modulates TRPV4 response, particularly under conditions of low-level stimulation (Fernandes et al. 2008; Garcia-Elias et al. 2008).

5 TRPV4 Biophysics and Activation

5.1 Basic Biophysical Properties

TRPV4 is a nonselective cationic channel with higher permeability to Ca^{2+} and Mg^{2+} than to Na^+ cations, which generates an influx of Ca^{2+} following its activation under normal physiological conditions (Voets et al. 2002). Although TRPV4 also permeates monovalent cations in the absence of divalent ions, it discriminates very poorly between them. The sequence of permeation is $K^+ > Cs^+ > Rb^+ > Na^+ > Li^+$ (Nilius et al. 2001).

Single-channel conductance of TRPV4 is larger at positive (80–100 pS) than at negative potentials (30–60 pS), and the current–voltage relationship of TRPV4 whole-cell currents presents outward rectification (with a slight inward rectification at very negative voltages). This process depends on extracellular Ca^{2+} ions that at the same time permeate and block TRPV4 (Everaerts et al. 2010a; Nilius et al. 2004; Voets et al. 2002; Watanabe et al. 2002a).

5.2 Activation by Osmotic and Mechanical Stimuli

TRPV4 responds to osmotic changes in the cell environment by increasing or decreasing its activity in hypotonic and hypertonic solutions, respectively (Liedtke et al. 2000; Strotmann et al. 2000; Wissenbach et al. 2000), thereby contributing to cellular (Arniges et al. 2004; Fernandez-Fernandez et al. 2008) and systemic volume homeostasis (Liedtke and Friedman 2003; Mizuno et al. 2003). TRPV4

also responds to mechanical stimuli such as shear stress (Gao et al. 2003; Kohler et al. 2006) or high viscous loading (Andrade et al. 2005). Its osmotic (Vriens et al. 2004) and mechanical (Andrade et al. 2005; Fernandes et al. 2008) sensitivity depends on phospholipase A_2 activation and the subsequent production of the arachidonic acid (AA) metabolites, epoxyeicosatrienoic acids (EET), by the cytochrome P450. A recent report has also claimed a direct and potent activation of TRPV4 by AA (Zheng et al. 2013). To date, however, it is not known how EETs mediate channel opening. In any case, whether it binds TRPV4 or is related to changes in the lipid environment, EET-mediated activation of TRPV4 requires the binding of PIP_2 to a PIBS at the N-tail (Garcia-Elias et al. 2013). Alternatively, EET-independent mechanisms have also been reported: TRPV4 is activated by membrane stretch in excised patches from oocytes (Loukin et al. 2010), in apparent contradiction with early reports (Strotmann et al. 2000), and responds to hypotonic stimuli in yeast, which do not contain AA (Loukin et al. 2009).

5.3 Activation by Temperature

Moderate heat (24–38 °C) activates TRPV4 (Q_{10} between 10 and 20) in heterologous expression systems and native tissues (Garcia-Elias et al. 2013; Guler et al. 2002; Watanabe et al. 2002b), although other studies claimed no role of TRPV4 in mouse thermosensation (Huang et al. 2011). Early reports (Guler et al. 2002; Watanabe et al. 2002b) showed no channel response to heat in excised patches, but it has recently been demonstrated that the reported lack of activation is fully recovered in the presence of PIP_2, which suggests that TRPV4 is a bona fide thermosensitive channel (Garcia-Elias et al. 2013). Mutation of the PIBS (Garcia-Elias et al. 2013) or Y556 (Vriens et al. 2004, 2007) impairs TRPV4 activation by heat.

5.4 Activation by Chemicals

The non-PKC-activating, synthetic phorbol ester 4α-PDD (EC_{50} ~ 400 nM) (Watanabe et al. 2002a) is widely used as a TRPV4 activator. 4α-PDD binds to a pocket formed between TM 3 and TM4. Mutations of Y556, L584, W586, and M587 affect 4α-PDD-mediated responses (Klausen et al. 2009; Vriens et al. 2007). Another potent channel activator is GSK1016790A (EC_{50} ~ 10 nM) (Dunn et al. 2013; Thorneloe et al. 2008). However, it has been recently reported no activation of TRPV4 by GSK1016790A and TRPV4-independent, 4-α-PDD-mediated Ca^{2+} responses in DRG neurons (Alexander et al. 2013).

TRPV4 is activated by bisandrographolide A (BBA, EC_{50} ~ 800 nM) extracted from *Andrographis paniculata*, a plant commonly used in Chinese traditional medicine, and mutation of L584 and W586, but not of Y556, prevents TRPV4 activation by BBA (Smith et al. 2006; Vriens et al. 2007). Apigenin, a plant-derived flavone, activates TRPV4 (EC_{50} ~ 10 μM) in heterologous systems as well as in

cultured mesenteric artery endothelial cells (Ma et al. 2012). Plant cannabinoids also activate TRPV4 (EC_{50} ~ 1–6 μM) (De et al. 2012).

Two endogenous activators of TRPV4 have been identified. The endocannabinoid anandamide produces a robust TRPV4 activation via its metabolite AA and the formation of 5,6-EET (Watanabe et al. 2003b), and dimethylallyl pyrophosphate (DMAPP), a metabolite of the mevalonate pathway, activates TRPV4 (EC_{50} ~ 5 μM) in heterologous expression systems, cultured sensory neurons, and keratinocytes (Bang et al. 2012b).

5.5 Regulation by Calcium

Calcium-dependent regulation of TRPV4 is complex. Extracellular Ca^{2+} is responsible for the rectification of the whole-cell TRPV4 currents and intracellular Ca^{2+}, depending on its concentration, inhibits or potentiates TRPV4 channel activity. Intracellular Ca^{2+}-dependent inactivation (IC_{50} ~ 400 nM) mediates the transient response of TRPV4 to many stimuli (Watanabe et al. 2002a, 2003a). Although the exact mechanisms of Ca^{2+}-dependent inactivation are not fully characterized, F707 in TM 6 is involved in the extracellular Ca^{2+}-dependent inactivation (Watanabe et al. 2003a). Positive modulation of TRPV4 by Ca^{2+} via a CaM-dependent mechanism has also been proposed (Strotmann et al. 2003).

5.6 Modulation by PIP_2 and the Phospholipase C (PLC)-IP_3R Pathway

Modulation of TRPV4 by the purinergic receptor (P2Y2)-PLC-IP_3R pathway was first described in ciliated epithelial cells and heterologous expression systems (Fernandes et al. 2008; Garcia-Elias et al. 2008; Lorenzo et al. 2008) and later in kidney cells (Mamenko et al. 2011) and astrocytes (Dunn et al. 2013). TRPV4 and many other TRP channels are regulated by PIP_2. The interaction of the N-tail PIBS with plasma membrane PIP_2 favors an expanded conformation of the intracellular tails as well as channel activation by hypotonicity and heat (Garcia-Elias et al. 2013). Conditions such as mutations in the PIBS, coexpression with PACSIN3, or reduced PIP_2 levels interfere the interaction of TRPV4 with PIP_2 and promote a compacted tail conformation and prevent channel activation. Following the activation of P2Y2 receptor, the sensitization of TRPV4 activity to low mechanical/osmotic stimulation may be counteracted by depletion of PIP_2 due to PLC activation. The meaning of this dual and antagonistic TRPV4 regulation by the PIP_2-PLC-IP_3R pathway remains unclear at present.

5.7 TRPV4 Antagonists

Three blockers have been classically used for inhibition of TRP channels, although none of them are specific: ruthenium red, gadolinium, and lanthanum (Nilius et al. 2004). Citral, a bioactive component of lemongrass commonly used as a taste enhancer and insect repellent, is a transient TRPV4 antagonist (Stotz et al. 2008). HC-067047 (IC_{50} ~ 50–120 nM) has been shown to be a potent and reversible TRPV4 inhibitor that improved bladder function in animal models of cystitis but inhibited TRPM8 at higher concentrations (Everaerts et al. 2010b). GSK2193874 (IC_{50} ~ 2–100 nM) has been identified as a TRPV4 inhibitor with therapeutic potential against pulmonary edema (Thorneloe et al. 2012).

Butamben (n-butyl-p-aminobenzoic acid), a local anesthetic for topical use known to affect voltage-gated channels, blocks TRPV4 (IC_{50} ~ 20 μM) and TRPA1 (IC_{50} ~ 70 μM) (Bang et al. 2012a). RN-1747 and RN-1734 have both agonist (EC_{50} = 700 nM) and antagonist activity (IC_{50} ~ 2–6 μM), respectively (Vincent et al. 2009). Both compounds affect TRPV1, TRPV3, and TRPM8 channels at higher concentrations (Vincent et al. 2009).

6 Physiological Functions of TRPV4

6.1 Osmoregulation and Mechanotransduction

When exposed to hypotonic solutions, cells rapidly swell. The regulatory response to this increase in cell volume is called regulatory volume decrease (RVD), which is normally associated with changes in intracellular Ca^{2+} concentrations, particularly in epithelial cells, and typically activates K^+ and Cl^- channels, permitting the passive loss of inorganic ions and osmotically obliged water [(Arniges et al. 2004) and references within]. TRPV4 provides the Ca^{2+} signal required to activate Ca^{2+}-dependent potassium channels and the subsequent RVD in epithelial cells (Arniges et al. 2004; Fernandez-Fernandez et al. 2002). TRPV4 also acts in astrocyte RVD (Benfenati et al. 2011) and participates in the maintenance of systemic osmoregulation (Liedtke and Friedman 2003; Mizuno et al. 2003). TRPV4 is expressed in primary osmosensory neurons in the brains' organum vasculosum (Liedtke et al. 2000) and kidney epithelium (Berrout et al. 2012; Tian et al. 2004), although the exact mechanism by which TRPV4 participates in systemic osmoregulation is not yet known.

Mechanical and osmotic activation of TRPV4 triggers ATP release from many different epithelial cells (Gevaert et al. 2007; Seminario-Vidal et al. 2011; Ueda et al. 2011) and increases ciliary beat frequency (CBF) in ciliated epithelia (Andrade et al. 2005). ATP-induced increase in Ca^{2+} and CBF acceleration are also favored by TRPV4 (Lorenzo et al. 2008), which may generate a positive feedback mechanism between ATP- and TRPV4-mediated responses.

TRPV4 channels activated by AA, EET, and shear stress are coupled to the calcium-dependent potassium channels in the endothelium (Bagher et al. 2012;

Kohler et al. 2006; Sonkusare et al. 2012; Vriens et al. 2005) and in vascular smooth muscle (Earley et al. 2005), thereby favoring vasodilation. TRPV4 is essential to endothelial reorientation in response to mechanical forces, which is required to shape vascular growth and development (Thodeti et al. 2009). Excessive activation of TRPV4 also bears harmful vasculature consequences due to increased endothelial permeability and circulatory collapse (Thorneloe et al. 2012; Willette et al. 2008). For a recent review on TRPV4 and the control of vascular tone, see Filosa et al. (2013).

TRPV4 is highly expressed in the kidneys, particularly in the apical water-impermeant regions of the nephron (Delany et al. 2001; Strotmann et al. 2000), although discrepancies exist on its polarized membrane location (Berrout et al. 2012; Tian et al. 2004). It also has functions in the sensing of flow and osmolality (Wu et al. 2007), RVD (Galizia et al. 2012), ATP release (Silva and Garvin 2008), and, more importantly, in flow-dependent salt reabsorption and potassium secretion (Taniguchi et al. 2006). A heteromeric TRPV4-TRPP2 channel in the primary cilium of collecting duct cells is required for the calcium cascade involved in flow sensing (Du et al. 2012; Kottgen et al. 2008).

TRPV4 is also highly expressed in the bladder urothelium where it participates in the sensing of intravesical mechanical pressure (bladder filling) and ATP release (Birder et al. 2007; Everaerts et al. 2010b; Gevaert et al. 2007). TRPV4-KO mice manifest an incontinent phenotype with a lower frequency of voiding contractions (Gevaert et al. 2007).

6.2 Thermoregulation

TRPV4 activates at normal body temperatures (see Sect. 5.3), thereby participating in cell functions ranging from regulating neuronal excitability (Shibasaki et al. 2007) and possibly thermogenesis (Guler et al. 2002) to maintaining epithelial barrier function (Sokabe and Tominaga 2010) and vasodilation (Earley et al. 2005; Watanabe et al. 2002b). However, direct evidence of TRPV4-mediated vasodilation in response to heat is lacking. Peripheral temperature sensing at the level of keratinocytes, corneal epithelium, and sensory neurons has been also associated with TRPV4 (Chung et al. 2003; Lee et al. 2005; Mergler et al. 2010) but challenged by other studies (Huang et al. 2011).

6.3 Nociception and Neuroinflammation

TRPV4 is expressed in peripheral nociceptive neurons and has been involved in hyperalgesia. Hypotonic stimuli trigger pain-related behavior by activating TRPV4 channels in dorsal root ganglion neurons (Alessandri-Haber et al. 2003), and TRPV4-KO mice have a lower sensitivity to harmful pressure on the tail (Suzuki et al. 2003b). TRPV4 is sensitized by PKC, PKA, and Src phosphorylation (Alessandri-Haber et al. 2008); proteases (Grant et al. 2007); and serotonin,

histamine, and neurogenic inflammation (Cenac et al. 2010; Vergnolle et al. 2010). This can lead to hypersensitivity.

6.4 TRPV4 in the Central Nervous System

In the brain, TRPV4 expression and function has been seen in both neurons and glial cells. Activation of microglia by lipopolysaccharide (LPS) is suppressed following activation of TRPV4 (Konno et al. 2012). TRPV4-mediated Ca^{2+} entry into astrocytic end feet leads to parenchymal arteriole dilation (Dunn et al. 2013) and in hippocampal CA1 pyramidal neurons potentiates NMDA response and the excitotoxicity associated with cerebral ischemia (Li et al. 2013). Together with TRPV1, TRPV4 is involved in the glucocorticoid-mediated regulation of feeding-related neuroendocrine cells (Boychuk et al. 2013).

6.5 TRPV4 in Cell Migration and Motility

In recent years, somewhat contradictory reports on the role of TRPV4 in cell migration have appeared. TRPV4 activation reduces migration of neuroendocrine cells (Zaninetti et al. 2011) but mediates migration of pulmonary artery smooth muscle (Martin et al. 2012) and AA-induced migration of endothelial cells (Fiorio et al. 2012). At present no clear explanation exists for these apparent discrepancies.

7 Lessons from Knockout Mice

Many different studies have made use of TRPV4 knockout models ($Trpv4^{-/-}$). In this section we focus on studies offering novel insights into the physiological role of TRPV4 that have not been introduced in other sections or reporting results that conflict with previous cell-based experiments. Two different $Trpv4^{-/-}$ mice models have been generated through neo-replacement of exon 4 (Mizuno et al. 2003) and lox-cre-mediated excision of exon 12 (Liedtke and Friedman 2003), a fact to be considered in view of contradictory information when comparing functional responses between the two $Trpv4^{-/-}$ models.

7.1 Thermosensation

Initial studies with $Trpv4^{-/-}$ mice revealed the contribution of TRPV4 in detecting warm temperatures (Lee et al. 2005; Todaka et al. 2004) and chemically induced hyperalgesia (Todaka et al. 2004). However, more recent studies from the same laboratories showed no thermal response differences between $Trpv4^{+/+}$ and $Trpv4^{-/-}$ mice (Huang et al. 2011).

7.2 Systemic Osmoregulation

In vivo analysis of *Trpv4*$^{-/-}$ mice has produced conflicting results, showing increased (Liedtke and Friedman 2003) or unaffected serum osmolarity (Mizuno et al. 2003). In other reports, *Trpv4*$^{-/-}$ mice have no defect in the response to tonicity or mechanical stimulation by the primary osmosensory neurons in the organum vasculosum lamina terminalis (Ciura et al. 2011) but defective responses in peripheral osmosensory neurons (Lechner et al. 2011).

7.3 Epithelia

Mechanically induced ATP release and bladder function are strongly impaired in *Trpv4*$^{-/-}$ mice (Gevaert et al. 2007). Moreover, the development of cystitis-induced bladder dysfunction is lessened in *Trpv4*$^{-/-}$ mice (Everaerts et al. 2010b). TRPV4 activity and ATP release from esophageal keratinocytes are also reduced in *Trpv4*$^{-/-}$ mice (Mihara et al. 2011). In *Trpv4*$^{-/-}$ mice, the response to different TRPV4-activating stimuli in tracheal ciliated cells displays a reduced Ca^{2+} entry and CBF (Lorenzo et al. 2008). Activation of TRPV4 disrupts the alveolar barrier and activates macrophages, both leading to acute lung injury (Alvarez et al. 2006; Hamanaka et al. 2010).

7.4 Osteoarticular and Muscular Systems

Bone resorption defects due to disrupted osteoclast function have been reported for *Trpv4*$^{-/-}$ mice (Masuyama et al. 2008; Mizoguchi et al. 2008). Normal cartilage physiology also depends greatly on TRPV4 function. Chondrocyte differentiation requires TRPV4 (Muramatsu et al. 2007) and responses to hypotonic and 4α-PDD are reduced in *Trpv4*$^{-/-}$ mice (Clark et al. 2010).

7.5 Metabolism

Knockout of *Trvp4* induces compensatory increases in TRPC3 and TRPC6, elevation of calcineurin activity affecting energy metabolism in skeletal muscle, and protection from diet-induced obesity in mice (Kusudo et al. 2012). *Trpv4*$^{-/-}$ mice have elevated thermogenesis and protection from diet-induced obesity, adipose inflammation, and insulin resistance, highlighting the role of TRPV4 in metabolic disorders (Ye et al. 2012).

7.6 Vascular Function

The development of pulmonary hypertension, right heart hypertrophy, and vascular remodeling was significantly delayed and suppressed in hypoxic *Trpv4*$^{-/-}$ mice, suggesting that TRPV4 serves as a signal pathway crucial for the development of hypoxia-induced pulmonary hypertension (Yang et al. 2012). TRPV4 plays also a role in blood pressure control. Although portal osmolality decreases after water ingestion in both wild-type and *Trpv4*$^{-/-}$ mice, only the wild-type animals show a pressure response (McHugh et al. 2010).

8 TRPV4 in Hereditary and Acquired Diseases

The participation of TRPV4 in disease has been documented at different levels ranging from disease-causing mutations (Fig. 4) and single nucleotide polymorphisms (SNP) to abnormal responses to pathological stimuli. Further research is required to address the intriguing questions that remain.

8.1 Causal Mutations

A puzzling question about the pathophysiological consequences of TRPV4 dysfunction is why the clinically relevant TRPV4 mutations mainly affect osteoarticular and peripheral nervous systems despite wide tissue distribution of TRPV4. Also surprising is the very mild phenotype of *Trpv4*$^{-/-}$ mice under normal conditions. Together, these observations may indicate that the cellular environment is essential to determining TRPV4 function and regulation. Cells from different tissues most likely present different protein networks that modulate the final outcome of TRPV4 functions.

8.1.1 Osteoarticular Disorders

The first disease-causing TRPV4 mutations were identified in patients with autosomal dominant brachyolmia (ADB), a rather mild type of skeletal dysplasia (Rock et al. 2008). TRPV4-R616Q and TRPV4-V620I were identified as causal gain-of-function mutants, and 33 other TRPV4 mutations have been linked to different skeletal dysplasias. Due to space restrictions, we cannot cite all original studies on TRPV4-causing mutations and, instead, refer the reader to excellent reviews (Dai et al. 2010; Nilius and Voets 2013). All these skeletal dysplasias form part of a heterogeneous group of bone disorders ranging from mild to lethal. Patients may present abnormalities in vertebrae and tubular bones as well as cartilage, resulting in severe scoliosis, short trunk, and extremities and craniofacial defects. Although phenotypes may differ widely, they all share defects in bone ossification. Furthermore, the same mutation may be found in patients presenting widely different phenotypes.

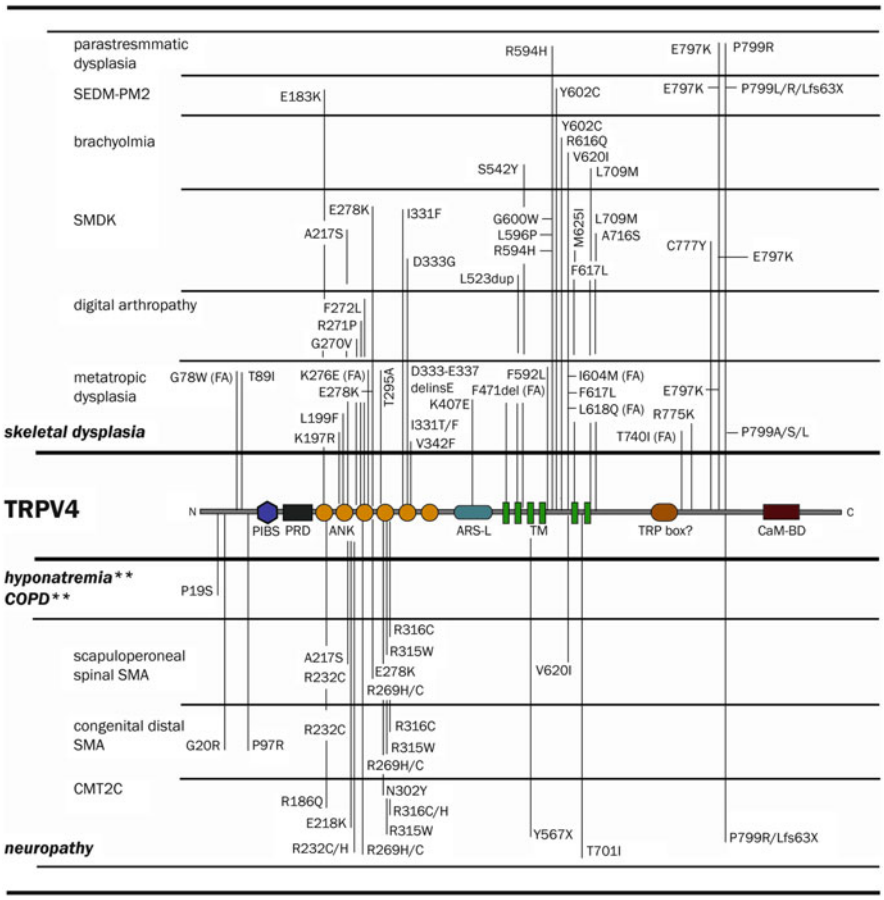

Fig. 4 TRPV4 mutations related to human diseases. TRPV4 mutations and SNPs associated to different skeletal dysplasias, neuropathies, hyponatremia, and COPD are shown. Each mutation is positioned over the schematic representation of the channel. **TRPV4-P19S SNP, although not causal, has been associated with hyponatremia and COPD. *PRD* proline-rich domain, *ANK* ankyrin repeats, *ARS-L* arachidonate recognition sequence like, *TM* transmembrane segments, *CaM-BD* calmodulin-binding domain, *CMT2C* hereditary motor and sensory neuropathy 2C (Charcot-Marie-Tooth 2C disease), *SMA* spinal muscular atrophy, *COPD* chronic obstructive pulmonary disease, *SMDK* spondylometaphyseal dysplasia Kozlowski type, *SEDM-PM2* spondyloepimetaphyseal dysplasia Maroteaux pseudo-Morquio type 2. Adapted from Dai et al. (2010)

Three TRPV4 mutations have been found in familial digital arthropathy-brachydactyly (FDAB), an inherited arthropathy in hands and feet with a related severe osteoarthritis (OA) (Lamande et al. 2011). These three mutations presented increased baseline but decreased stimuli-dependent channel activity. The mechanism by which these mutations lead to OA is not known. Previous studies in animal models had shown that TRPV4 was responsible for the hypotonic responses seen in articular chondrocytes and that TRPV4 KO mice had an age- and sex-dependent

progression to OA (Clark et al. 2010). Still unanswered is the question of how TRPV4 mutations lead to osteoarticular pathology: Is the cause of the disease related to changes in TRPV4 channel activity and/or TRPV4 interaction with other proteins?

8.1.2 Neuropathies

TRPV4-linked neuropathies were first described in 2010 (Auer-Grumbach et al. 2010; Deng et al. 2010; Landoure et al. 2010). Although very heterogeneous, all of the disorders lead to a degeneration of peripheral nerves. They may occur alone or with sensory-associated phenotypes such as vocal cord paresis (Chen et al. 2010) or hearing defects (Zimon et al. 2010). Wide variability in phenotype or in age at onset is observed, even between families that share the same causal mutation. Genetic and environmental factors are likely responsible for such variation, but further studies should clarify this point. As seen with the skeletal disorders, most of the neuropathy-related TRPV4 mutations generate gain of function, and the same mutation can produce different phenotypes (Nilius and Voets 2013). Single-channel analysis of skeletal (Loukin et al. 2011) and neuronal (Fecto et al. 2011) disease-causing mutations revealed increased basal open probability of mutant channels.

8.1.3 Mixed Skeletal and Neuromuscular Disorders

A few TRPV4 mutations have been associated with both skeletal and neuromuscular disorders. Patients with motor neuropathies have a short trunk (Chen et al. 2010; Cho et al. 2012), although patients with the mild forms of skeletal dysplasias rarely have any neuropathy except in metatropic dysplasia with fetal akinesia (Unger et al. 2011).

8.2 Single Nucleotide Polymorphisms and Abnormal TRPV4 Responses Associated with Disease

The rs3742030 polymorphism (P19S) generates a TRPV4 channel with reduced response to mild hypotonic shocks and is associated with higher risk of hyponatremia (Tian et al. 2009) and chronic obstructive pulmonary disease and forced expiratory volume in 1 s (FEV_1) (Zhu et al. 2009) but not with cough in asthmatic children (Cantero-Recasens et al. 2010) or healthy/asthmatic adults (Smit et al. 2012). Dysregulation of TRPV4 has been described in cystic fibrosis epithelium (Arniges et al. 2004). TRPV4 mRNA and protein are increased in sinus mucosal biopsies from chronic rhinosinusitis patients (Bhargave et al. 2008). TRPV4 participates in the inflammatory signaling pathways leading to neurogenic inflammation and pancreatitis (Ceppa et al. 2010; Zhang et al. 2013), intestinal chronic inflammation (d'Aldebert et al. 2011; Fichna et al. 2012), and mastication-associated pain at the temporomandibular joint (Chen et al. 2013).

Acknowledgments Work at the authors' laboratory is supported by the Spanish Ministry of Economy and Competitiveness (SAF2012-38140, SAF2010-16725), Fondo de Investigación Sanitaria (Red de Investigación Cardiovascular RD12/0042/0014), Fondos Europeos de Desarrollo Regional (FEDER), and Generalitat de Catalunya (SGR05-266). M.A.V. is the recipient of an ICREA Academia Award.

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