Published in final edited form as:

Adv Exp Med Biol. 2011 ; 704: 323–339. doi:10.1007/978-94-007-0265-3_18.

***C. elegans* TRP channels**

Rui Xiao and X.Z. Shawn Xu

Life Sciences Institute and Department of Molecular & Integrative Physiology, University of Michigan, 210 Washtenaw Avenue, Ann Arbor, Michigan 48109, USA

Abstract

TRP (*transient receptor potential*) channels represent a superfamily of cation channels found in all eukaryotes. The *C. elegans* genome encodes seventeen TRP channels covering all of the seven TRP subfamilies. Genetic analyses in *C. elegans* have implicated TRP channels in a wide spectrum of behavioral and physiological processes, ranging from sensory transduction (e.g. chemosensation, touch sensation, proprioception and osmosensation) to fertilization, drug dependence, organelle biogenesis, apoptosis, gene expression, and neurotransmitter/hormone release. Many *C. elegans* TRP channels share similar activation and regulatory mechanisms with their vertebrate counterparts. Studies in *C. elegans* have also revealed some previously unrecognized functions and regulatory mechanisms of TRP channels. *C. elegans* represents an excellent genetic model organism for the study of function and regulation of TRP channels *in vivo*.

Keywords

TRP; *C. elegans*; channel; behavior; neuron; chemosensation; mechanosensation; osmosensation; proprioception; nicotine

Introduction

The first TRP (*transient receptor potential*) channel was cloned in *Drosophila* from a mutant strain with a transient instead of sustained light-evoked photoreceptor potential (1;2). An expanding number of TRP channels have been identified in various organisms, including *C. elegans*. Currently, the vertebrate TRP channel superfamily comprises seven subfamilies: TRPC (TRP-Canonical), TRPV (TRP-Vanilloid), TRPM (TRP-Melastatin), TRPN (TRP-NompC), TRPA (TRP-Ankyrin), TRPP (TRP-Polycystin), and TRPML (TRP-Mucolipin) (3). The *C. elegans* genome encodes 17 TRP members that cover all of the seven TRP subfamilies. A dendrogram displaying their relationship is shown in figure 1A. *C. elegans* TRP channels are also believed to be composed of four subunits similar to their vertebrate homologues (4;5). Each subunit contains six putative transmembrane segments (S1-S6) with the pore loop buried between S5 and S6 (figure 1B).

C. elegans is a powerful model organism, featuring tractable genetics and a short generation period (~3 days). The anatomy of *C. elegans* has been well characterized and reviewed by White *et al.* (figure 1C and D) (6). The body of *C. elegans* is composed of two concentric tubes separated by a pseudocoelom (figure 1D). The outer tube comprises cuticle, hypodermis, body wall muscle, nervous system, and excretory system, and the inner tube consists of pharynx, intestine and gonad (figure 1D) (6). Among the 959 somatic cells in adult hermaphrodite worms, 302 are neurons (7; 8). These neurons are further classified into

118 subtypes and communicate via ~6000 chemical synapses and ~900 gap junctions (8). Despite its simple nervous system, *C. elegans* exhibits complex behaviors, including locomotion, mating, feeding, defecation and drug dependent behaviors, as well as learning and memory. In addition, worms are capable of detecting and reacting to a wide range of sensory cues and display a variety of sensory behaviors such as chemosensation, osmosensation, touch sensation, proprioception, and photosensation (9–11). Importantly, many *C. elegans* TRP channels are enriched in the nervous system and play important roles in behavioral control (12; 13).

Several *C. elegans* TRP channels were cloned by classic forward genetic screens, including *osm-9*, *gon-2* and *cup-5*. In addition, *C. elegans* is one of the first organisms with its whole genome sequenced (14;15). This has greatly facilitated the identification of other *trp* genes in *C. elegans*. Mutants have been isolated for every *C. elegans trp* gene. Many *C. elegans* TRPs exhibit high sequence homology and functional similarity to their vertebrate counterparts, and characterization of these *C. elegans* TRP channels has provided novel insights into the function and regulation of TRP channels in vertebrates, including humans. Here, we review the physiological functions of each worm TRP channel and also discuss their activation and regulatory mechanisms.

Functions of TRP Channels in *C. elegans*

TRPC subfamily

The *C. elegans* TRPC subfamily includes three members: TRP-1, TRP-2 and TRP-3. These channels were cloned based on their high sequence homology to *Drosophila* TRP (16–19). TRP-1 and TRP-2 are expressed in motor neurons, interneurons, a few sensory neurons and muscles (18;20). Mutant worms lacking functional *trp-1* or *trp-2* are superficially wild type, but exhibit an interesting phenotype in nicotine-dependent behavior (20). Similar to established rodent models, wild type worms display acute response, tolerance, withdrawal, as well as sensitization to nicotine treatment (20;21). These behavioral responses are nearly absent in *trp-1* and *trp-2* null worms (20). Importantly, ectopic expression of human TRPC3 can rescue this phenotype in *C. elegans*, suggesting a conserved role for TRPC channels in nicotine dependence (20;22;23). TRP-3, another *C. elegans* TRPC channel, is enriched in sperm (19;24). Consistent with this expression pattern, *trp-3* mutants are sterile due to a specific defect in sperm, i.e. mutant sperm cannot fuse with the egg (19). All mammalian TRPCs are expressed in sperm, and mouse TRPC2 has been reported to be involved in triggering the acrosome reaction in sperm (25). It is not known whether other mammalian TRPCs function in fertilization.

TRPV subfamily

The TRPV channel OSM-9 is the first characterized TRP channel in *C. elegans*. It was cloned from mutant strains with behavioral phenotypes in mechanosensation (nose touch response), osmosensation and chemosensation (18;26). OSM-9 is primarily expressed in sensory neurons such as AWA, ASH, ADL, AFD, AWC, OLQ, PHA, PHB, etc (18). Subsequent homology analysis has identified four additional *osm-9*/capsaicin receptor related genes, *ocr-1-4* (27). OCR channels are typically co-expressed with OSM-9, but not *vice versa* (27;28). In wild type worms, the chemosensory neurons AWA and AWC mediate chemotaxis to attractive odorants, while the polymodal neuron ASH is important in avoidance response to repellent odorants, high osmotic stress and nose touch (29). AWA- and ASH-mediated sensory behaviors are severely impaired in *osm-9* and *ocr-2* mutant worms, revealing a critical role for these two TRPV channels in chemosensation, osmosensation, and mechanosensation (18;27). Interestingly, ectopic expression of rat TRPV4 in ASH neurons functionally rescued the avoidance response to nose touch and high

osmolarity, but not repellent chemicals, suggesting an evolutionarily conserved role for TRPV channels in osmosensation and mechanosensation (30). Several mammalian TRP channels also function as polymodal sensors in sensory physiology, especially TRPV1, TRPM8 and TRPA1 (31–34). In this respect, *C. elegans* TRPV channels are functionally conserved as polymodal sensory detectors. In ASH and ADL neurons, OSM-9 and OCR-2 are required for sensing food shortage and population density increase (35). In harsh environments, OSM-9 and OCR-2 are believed to directly or indirectly detect noxious chemicals in ASH and ADL neurons where they regulate social feeding behavior (35). In the serotonergic neuron ADF, OSM-9 and OCR-2 act upstream of the serotonin synthesis gene tryptophan hydroxylase (*tph-1*), as mutations in *osm-9* or *ocr-2* dramatically downregulate *tph-1* expression (36). OCR channels can also function independently of OSM-9. In a subset of uterus-associated endocrine cells, OCR-1, -2 and -4 channels may form functional heteromeric channels without an involvement of OSM-9 (28). These three TRPV channels function in uv1 endocrine cells to promote release of tyramine and other neurotransmitters to repress premature egg laying (28). In a small set of sensory neurons, particularly ADL, OCR-2 regulates neuropeptide release (37).

TRPM subfamily

GON-2, the first TRPM channel cloned in *C. elegans*, is highly expressed in the gonad and intestine (38;39). GON-2 is required for normal gonadogenesis (38). In addition, the *C. elegans* genome encodes three other TRPM channels: GTL-1, GTL-2 and CED-11. GTL-1 is co-expressed with GON-2 in the intestine, whereas GTL-2 is mainly expressed in excretory cells (39). GON-2 and GTL-1 are essential for maintaining electrolyte homeostasis (39–41). Consistently, mammalian TRPM6 and TRPM7 have also been reported to be important for Mg^{2+} homeostasis (42–46). In intestine cells, GON-2 carries a Mg^{2+} -regulated outward rectifying current, and GTL-1 regulates the Mg^{2+} sensitivity of GON-2 (39). GON-2 and GTL-1 may mediate the entry of some trace metals such as Ni^{2+} and Mg^{2+} , as a *gon-2;gtl-1* double mutant exhibits a significant decrease in Mg^{2+} and Ni^{2+} absorption (39). In addition, GON-2 and GTL-1 are important for maintaining defecation rhythms in *C. elegans*. *C. elegans* defecation behavior is characterized by rhythmic cycles of posterior body wall muscle contraction (pBoc) followed by relaxation, anterior body wall muscles contraction (aBoc) and finally expulsion (Exp) (47;48). This defecation cycle occurs every 45 seconds with little variation (47). Ca^{2+} oscillation in intestine cells is tightly coupled to defecation rhythms, and IP_3 receptor (IP_3R) is essential for this rhythmic activity (49). Interestingly, mutant alleles of *gon-2* and *gtl-1* display abnormal defecation rhythms (39–41). It has been proposed that these two worm TRPM channels regulate defecation rhythms through modulating IP_3Rs (40).

TRPA subfamily

Two TRPA channels (TRPA-1 and TRPA-2) are present in *C. elegans*, but only TRPA-1 has been characterized. TRPA-1 is widely expressed in multiple tissues, including many sensory neurons (e.g. ASH, AWA, AWB, ASI, ASK, PHA, PHB, PVD, PDE, IL1, and OLQ), muscle cells, excretory system, rectal gland cells, and epithelial cells (50). In OLQ and IL1, but not ASH, TRPA-1 regulates mechanosensitive behaviors such as foraging behavior and nose-touch behavior (50). However, it is unclear whether TRPA-1 functions as a mechanotransduction channel or indirectly modulate the signal of the transduction channel in these neurons.

TRPN subfamily

TRP-4 is the sole TRPN channel in *C. elegans*. TRP-4 is expressed in the DVA and DVC neurons, as well as the dopamine neurons CEP, ADE, and PDE (10;51). TRP-4 functions in mechanosensation. Specifically, it controls the body posture of the worm during locomotion

through regulating the activity of the stretch-sensitive proprioceptive neuron DVA (10). Ca^{2+} imaging shows that body stretch can elicit TRP-4-dependent calcium transients in DVA (10). TRP-4 is also required for the function of dopamine neurons that detect mechanical attributes from the bacteria lawn on which worms feed and navigate (10;52).

TRPP subfamily

PKD-2 is the worm homologue of mammalian PKD2/TRPP2 (53). PKD-2 is co-localized with LOV-1/PKD1 in the male specific head neuron CEM, hook neuron HOB, and sensory ray neurons (53). PKD-2 is required for male mating behavior. Specifically, *pkd-2* mutant male cannot efficiently locate the vulva of its mate during mating (53). It has been proposed that PDK-2 may function as a mechanosensor and/or chemosensor in male-specific sensory neurons (53).

TRPML subfamily

CUP-5, the sole TRPML channel in *C. elegans*, was identified in genetic screens for mutant worms defective in endocytosis and apoptosis (54;55). It displays a high homology to human TRPML1 (mucolipin), mutations of which cause type IV mucopolipidosis (56;57). CUP-5 is expressed in many cell types, including coelomocytes, sensory neurons, pharynx, reproductive system, and muscle (54). Similar to mammalian TRPML1, CUP-5 is important for lysosome biogenesis and function (54;58). *cup-5* mutant worms accumulate large vacuoles composed of hybrids of late endosomes and lysosomes (54;58). The apoptosis phenotype observed in both *cup-5* mutant worms and a *Drosophila* model of type IV mucopolipidosis may also result from lysosomal malfunction (55;59).

In summary, TRP channels play diverse functions in *C. elegans*, such as sensory transduction, drug dependence, intracellular ion homeostasis, organelle biogenesis, cell fusion, apoptosis, gene expression, neurotransmitter/hormone release, etc. Given that many *C. elegans* TRP channels share similarities with their vertebrate counterparts at both the sequence and function levels, TRP channels appear to represent an ancient, functionally conserved superfamily of cation channels.

Activation of TRP Channels in *C. elegans*

1) Receptor-operated activation

Many *Drosophila* and mammalian TRP channels, particularly TRPCs, are coupled to phospholipase C (PLC) that acts downstream of GPCRs (G protein-coupled receptors) or RTKs (receptor tyrosine kinases) (3;60). Although PLC has a critical role in TRPC channel activation, the precise mechanism by which stimulation of PLC leads to the opening of TRPCs remains controversial. PLC hydrolyzes PIP_2 to produce IP_3 and DAG. All these three signaling molecules have been reported to activate TRP channels (61–63). Protons, a third product of PIP_2 hydrolysis, have also been shown to activate *Drosophila* TRPC channels (64). This model proposes that protons in conjunction with the reduction of PIP_2 level account for the full activation of *Drosophila* TRPC channels *in vivo*. However, it remains to be determined whether this model can be applied to TRPCs in other organisms.

C. elegans TRPC channels also form receptor-operated channels *in vitro*. When expressed in HEK293 cells, TRP-2 and TRP-3 promote receptor-operated Ca^{2+} entry that depends on the Gq-PLC β pathway. Specifically, carbachol stimulation of endogenous muscarinic receptors induces a robust TRP-2-mediated Ca^{2+} entry following a transient release of Ca^{2+} from intracellular Ca^{2+} stores (20). Similar results were obtained using histamine to stimulate HEK293 cells co-expressing the histamine receptor H1R (19). Moreover, TRP-2 appears to

be permeable to both Ba^{2+} and Si^{2+} in heterologous cells, a feature shared by its mammalian counterparts (20;65).

Similar to mammalian TRPA1, *C. elegans* TRPA-1 can also be activated by stimulating Gq/11-coupled receptors. When the bradykinin 2 receptor (B2R) was co-expressed with TRPA-1 in CHO cells, bradykinin evoked a TRPA-1-dependent current that was partially blocked by Gd^{3+} , a mouse TRPA1 inhibitor (50).

In AWA and ASH neurons, the TRPV channels OSM-9 and OCR-2 are probably activated independently of PLC and Gq. Instead, the Gi-like proteins ODR-3 and GPA-3 appear to reside downstream of GPCRs and upstream of OSM-9 and OCR-2 (66). The current model is that through an unknown mechanism, Gi-like signaling promotes the synthesis of long chain polyunsaturated fatty acids (PUFAs), which may directly or indirectly activate TRPV channels in AWA and ASH (66).

2) Mechanical activation

Many mammalian TRP channels have been proposed to be mechanosensitive channels, including TRPC1, TRPC3, TRPC6, TRPV1, TRPV2, TRPV4, TRPM4, TRPM7, TRPA1, and TRPP2 (67;68). In addition, TRPY1 in yeast and TRPN channels in *Drosophila* and zebra fish have also been suggested to be mechanosensitive (51;69;70). However, it remains enigmatic and also controversial whether these TRP channels are directly or indirectly activated by mechanical forces (67;68).

The cellular basis of mechanosensitivity in *C. elegans* gentle touch receptor neurons has been well characterized. In adult hermaphrodites, five non-ciliated PLML/R, ALML/R and AVM neurons are responsible for sensing gentle body touch (71–73). Three pairs of ciliated sensory neurons are responsible for detecting nose touch: ASH, FLP and OLQ (74). The proprioceptive neuron DVA senses body stretch. Additionally, the dopamine neurons ADE, PDE and CEP detect the mechanical attributes from bacterial lawn (75). Lastly, six IL1 cells are suggested to be mechanosensitive and involved in spontaneous foraging behaviors(76).

TRP channels are broadly involved in mechano- and osmo-sensation in *C. elegans*. In fact, OSM-9 is the first TRP family channel shown to function in mechanosensation and osmosensation (18). Mutant worms lacking *osm-9* or *ocr-2* are insensitive to high osmotic stress and nose touch (18;27). However, it is unclear whether OSM-9 and OCR-2 are directly gated by forces or act downstream of an unknown transduction channel to amplify and/or modulate its signal. The fact that OSM-9 and OCR-2-dependent nose touch and osmotic responses in ASH neurons require G-protein signaling seems to support the latter possibility. *C. elegans* PKD-2 has also been implicated in mechanosensation in male mating behavior (53). However, its role in mechanosensation could be indirect, as recent work shows that mammalian TRPP2 regulates mechanosensation not by acting as a mechanotransduction channel but rather by modulating the activity of another mechanically-gated channel of unknown molecular identity (77;78).

TRPA-1 has also been proposed to be a mechanosensitive channel. *trpa-1* mutant worms exhibit a behavioral defect in OLQ-mediated nose touch response (50). A Ca^{2+} imaging assay detected a reduction in the amplitude of Ca^{2+} transients in OLQ in response to the second, but not the initial, nose touch stimulus, suggesting that TRPA-1 may not be the primary mechanotransduction channel in OLQ but instead function downstream of this channel to amplify/modulate its activity. However, when expressed in CHO cells, mechanical stimulation can evoke a robust TRPA-1-dependent current, suggesting that TRPA-1 is mechanosensitive in heterologous cells (50).

TRP-4/TRPN1 has also been suggested to be a mechanosensitive channel based on its essential role for proprioception in DVA (10). TRP-4 may also act as a mechanosensitive channel in dopamine neurons (10;52). However, no patch-clamp recording has been performed on TRP-4-expressing neurons. In *Drosophila* and zebrafish, direct patch-clamp recording of TRPN1/NOMPC-expressing sensory neurons has not been reported either. Therefore, it remains an open question whether TRPN channels are mechanically-gated.

3) Other activation modes

Several mammalian TRP channels are sensitive to environmental and internal temperatures ranging from ~15 °C to >40 °C (32;79). These temperature-sensing TRP channels are called thermo-TRPs (80). However, no TRP channel in *C. elegans* has been reported to be temperature-sensitive. In addition, many agonists from plants directly activate some mammalian TRP channels (see below), and these TRPs can thus be considered ligand-gated channels. However, most such ligands have not been tested on *C. elegans* TRPs.

Similar to TRPM6 and TRPM7, the *C. elegans* TRPM channels GON-2 and GTL-1 appear to be constitutively active (39;40). For these constitutively active channels, regulation of their surface expression essentially functions as a gating mechanism. Surface insertion of TRPM6 is upregulated by epidermal growth factor (EGF), a mutation of which causes TRPM6-dependent recessive hypomagnesemia (81;82). A similar mechanism may regulate GON-2 and GTL-1 in *C. elegans*.

Mammalian TRPA1 is directly activated by intracellular Ca^{2+} through a EF-hand Ca^{2+} -binding motif in its N-terminus (83;84). As this domain is conserved in *C. elegans* TRPA-1, TRPA-1 may also be directly gated by intracellular Ca^{2+} . If this is the case, TRPA-1 could function as an amplifier for other Ca^{2+} permeable sensory channels in *C. elegans*.

Regulation of TRP Channels in *C. elegans*

As TRP channels are conserved between *C. elegans* and mammals, many of them share similar regulatory mechanisms. Additionally, genetic screens have identified some novel regulators for *C. elegans* TRP channels. Homologues of these regulators may potentially regulate mammalian TRP channels.

TRPC subfamily

Similar to *Drosophila* and mammalian TRPC channels, *C. elegans* TRPCs are coupled to the Gq-PLC β pathway, and thus could be regulated by PIP₂, IP₃, and/or DAG. Based on sequence alignment, all three *C. elegans* TRPCs contain a calmodulin (CaM)/IP₃R-binding (CIRB) motif in their C-terminus, a feature shared by all mammalian and *Drosophila* TRPC channels (85;86). In addition, the CIRB motif in TRPC6 has been shown to bind several phosphoinositides (PIs) (87). It has been proposed that CaM competes with IP₃R or/and PIs for binding to CIRB. CaM negatively regulates TRPC activity, whereas IP₃R and PIs promote channel activity (61;87). It is not known whether worm TRPCs are also regulated by CaM, PIs and/or IP₃R.

TRPV subfamily

A number of natural compounds isolated from plants are agonists for several mammalian TRPV channels, such as capsaicin (TRPV1), cannabinol (TRPV2), camphor (TRPV3 and TRPV1), carvacrol, thymol and eugenol (TRPV3), and bisandrographolide (TRPV4) (88–92). However, most of these agonists have not been tested on *C. elegans* TRPV channels. One regulatory mechanism for worm TRPV channels is channel heteromerization. Genetic and cell biological studies show that distinct *C. elegans* TRPV channels may form

heteromeric channels in different cell types. For example, in AWA and ASH neurons, OSM-9 and OCR-2 are co-localized and depend on each other for their ciliary localization (27). Functionally, OSM-9 and OCR-2 both are required for chemosensation, mechanosensation and osmosensation in these neurons (27). As many cells co-express multiple TRPV channels, the activity of these TRPV channels may be regulated by the formation of distinct heteromers. This type of regulation has also been demonstrated for many mammalian and *Drosophila* TRP channels (93–97).

A conserved acidic residue (Asp or Glu) is present in the putative pore region of all mammalian TRPV channels (98–101). It is important for ion selectivity and also mediates channel inhibition by extracellular divalent cations (98;101). This acidic residue is conserved in the *C. elegans* TRPV channels OSM-9 (Asp545) and OCR-1 (Glu684). Thus, extracellular divalent cations, particularly Ca^{2+} , may directly regulate these two worm TRPVs. Given that many worm TRPV channels are highly enriched in the cilia that are directly exposed to the outside environment rich in divalent cations, these ions may represent a distinct type of sensory input directly or indirectly impinging on TRPV channels. Indeed, some heavy metals have been reported to induce avoidance behavior in worms, some of which are mediated by TRPV-expressing sensory neurons and require the TRPV channel OSM-9 (102;103). In addition, *C. elegans* TRPVs appear to act downstream of G proteins. Some G protein signaling regulators can directly or indirectly modulate TRPV channel activity, including GRK-2 (G protein-coupled receptor kinase-2) and RGS-3 (regulator of G protein signaling) (104;105). It is not known whether these G protein signaling modulators also regulate TRP channel activity in mammals.

TRPM subfamily

The worm TRPM channels GON-2 and GTL-1 are highly expressed in the intestine where they play an essential role in intracellular Ca^{2+} signaling and maintaining Mg^{2+} homeostasis (39;40). Whole-cell recordings of cultured embryonic intestinal cells show that GON-2 and GTL-1 are more permeable to Ca^{2+} and Mg^{2+} than to Na^{+} , and both divalent cations negatively regulate GON-2 and GTL-1 (40). This inhibitory effect by divalent cations is also observed in their mammalian homologues TRPM6 and TRPM7 (106;107). Divalent cations bind two Glu residues (Glu1047 and Glu1052 of mouse TRPM7; Glu1030 and Asp1035 of mouse TRPM6) in the putative pore region of TRPM7 and TRPM6 (107). Since the putative pore region, including these two residues, are very well conserved in *C. elegans* GON-2, GTL-1 and GTL-2, these worm TRPM channels may be inhibited by Ca^{2+} and Mg^{2+} in a similar manner. In a genetic screen for GON-2 suppressors, Kemp *et al.* has identified *gem-1* (*gon-2* extragenic modifier), a homolog of the SLC16 family monocarboxylate transporter, and *gem-4*, a copine family Ca^{2+} -dependent phosphatidylserine binding protein (108;109). It will be interesting to examine whether TRPM6 and TRPM7 are regulated by the mammalian homologues of GEM-1 and GEM-4.

TRPA subfamily

Mammalian TRPA1 is a polymodal sensor for a wide range of endogenous and environmental chemicals, noxious cold, and probably noxious mechanical forces (32;34;110). Consistent with its diverse functions, TRPA1 expression and activity are under complex regulation (32;110;111). However, many established agonists and blockers of mammalian TRPA1 channel are ineffective on *C. elegans* TRPA-1 (50). This may result from the lack of the conserved cysteines in its N terminus, through which multiple structurally unrelated compounds covalently activate mammalian TRPA1 (112;113).

TRPN subfamily

TRPN channels are found in invertebrates and lower vertebrates (13). In *C. elegans*, TRP-4 is expressed in mechanosensory neurons, including the stretch-sensitive proprioceptive neuron DVA and dopamine neurons (10;51). As TRP-4 has not been well characterized at the genetic level, genetic regulators of TRP-4 remain elusive.

TRPP subfamily

The *C. elegans* TRPP channel PKD-2 is co-localized with LOV-1, the *C. elegans* homolog of mammalian PKD1 (53). Genetic studies show that PKD-2 and LOV-1 act in the same signaling pathway (114). Accumulating evidence supports that mammalian TRPP2 and PKD1 form a complex through physical interaction (78;115–119). Importantly, the coiled-coil domain in the C terminus of TRPP2, which mediates channel dimerization, is well conserved in *C. elegans* PKD-2, implying that PKD-2 may bind LOV-1 through this region (118;119). In addition, LOV-1 may promote the surface expression of PKD-2 by binding to the coiled-coil domain of PKD-2, a phenomenon observed in mammalian TRPP2 and PKD1 (117;118;120). PKD-2 is highly expressed in the cell body and ciliary endings of male specific sensory neurons (53). In fact, many other *C. elegans* TRP channels are also enriched in the cilia of various sensory neurons. A common mechanism may underlie the ciliary targeting of *C. elegans* TRP channels. Using PKD-2 as a model, multiple molecules regulating its ciliary localization have been identified in *C. elegans*, such as KLP-6/kinesin-3, UNC-101/AP-1, KIN-3/casein kinase II (CK2), and CIL-1 (121–123). It will be interesting to test whether the mammalian homologues of these molecules play a similar role in ion channel trafficking.

TRPML subfamily

The *C. elegans* TRPML channel CUP-5 is required for normal endosomal and lysosomal biogenesis in worms (58). CUP-5 activity may be regulated by PPK-3 (phosphatidylinositol phosphate kinase 3) (124). PPK-3 phosphorylates phosphatidylinositol 3-monophosphate (PtdIns(3)P) to produce phosphatidylinositol-3,5-bisphosphate [PtdIns(3,5)P₂]. *ppk-3* mutant worms display a similar phenotype to that of *cup-5* mutants (124). Genetic evidence reveals that *ppk-3* and *cup-5* function in the same pathway (124). This suggests that PtdIns(3,5)P₂ may regulate and/or gate CUP5. It will be interesting to directly test this mechanism on mammalian TRPMLs.

Perspectives

Benefiting from its simple and well characterized anatomy, facile genetics, and short generation period, *C. elegans* provides a convenient model to investigate the *in vivo* function and regulation of TRP channels at the whole organism level. All TRP channels in *C. elegans* have mutant strains available. Many *C. elegans* TRP channels are well correlated with their vertebrate homologues in both physiological functions and regulatory mechanisms. Insights learned from *C. elegans* TRPs could be very informative for their vertebrate counterparts. For instance, the surprising role of TRP channels in nicotine dependence was initially discovered in *C. elegans*. Interestingly, recent genome-wide association studies have implicated multiple TRPCs (TRPC4, 5 and 7) and TRPV1 in nicotine dependence and other types of drugs of abuse, suggesting that TRP channels may be broadly involved in drug dependence (20;22;125). Ciliary targeting and function of TRPP2 channels were first revealed in *C. elegans* and subsequently confirmed in mammals. A functional role for TRP channels in mechanosensation and osmosensation was also first unveiled in *C. elegans* (OSM-9) and later found to be case in mammals.

Previously, electrophysiological recordings of *C. elegans* neurons were rather limited due to technical difficulties. As a result, we know very little about the biophysical properties of *C. elegans* TRP channels. Recently, conventional whole-cell recording has been successfully applied to *C. elegans* neurons to study glutamate receptors, ENaC/degenerin channels and CNG channels *in vivo* (11;126–128). Similar techniques can be utilized to characterize TRP channels *in vivo*. As most, if not all, worm neurons are nearly isopotential and voltage attenuation (space clamp) is not a concern (129), one can reliably record sensory channel activity by patching the soma of the sensory neuron, even though sensory channels are localized at the sensory endings distant from the soma. This permits in-depth characterization of the biophysical properties of sensory TRP channels *in vivo* at the whole animal level. It would be difficult to perform such experiments on mammalian DRG neurons where many sensory TRP channels are expressed. *C. elegans* thus has the potential to resolve some of the controversies surrounding the role of TRP channels in sensory transduction. For example, it is possible to address in *C. elegans* whether those “mechanosensitive” TRP channels are directly gated by mechanical forces or merely act as a downstream amplifier/modulator of another mechanically-gated transduction channel of unknown molecular identity.

Although many TRP channels in *C. elegans* have been characterized *in vivo*, some have not. These include *gtl-2*, *ced-11*, *trpa-2*, *ocr-3*, and *ocr-4*. Using a multidisciplinary approach combining molecular genetics, cell biology, electrophysiology, functional imaging and behavioral assays, future studies will help us gain a thorough understanding of the function and regulation of TRP channels in *C. elegans*, which may provide novel insights into their vertebrate counterparts.

Note added in proof

Using *C. elegans* as a model, we have recently reported TRP-4 as the first TRP family protein that acts as a pore-forming subunit of a mechanosensitive channels *in vivo* [131]. Thus, TRP proteins can function as mechanosensitive channels.

Acknowledgments

We are grateful to members of the Xu lab, particularly Beverly Piggott, for insightful discussion and comments. Work in the lab is supported by a Pew Scholar Award and grants from the NIH (X.Z.S.X.).

References

1. Cosens DJ, Manning A. Abnormal electroretinogram from a *Drosophila* mutant. *Nature* 1969;224:285–287. [PubMed: 5344615]
2. Montell C, Rubin GM. Molecular characterization of the *Drosophila* *trp* locus: a putative integral membrane protein required for phototransduction. *Neuron* 1989;2:1313–1323. [PubMed: 2516726]
3. Venkatachalam K, Montell C. TRP channels. *Annu Rev Biochem* 2007;76:387–417. [PubMed: 17579562]
4. Tsuruda PR, Julius D, Minor DL Jr. Coiled coils direct assembly of a cold-activated TRP channel. *Neuron* 2006;51:201–212. [PubMed: 16846855]
5. Moiseenkova-Bell VY, Stanciu LA, Serysheva, Tobe BJ, Wensel TG. Structure of TRPV1 channel revealed by electron cryomicroscopy. *Proc Natl Acad Sci U S A* 2008;105:7451–7455. [PubMed: 18490661]
6. Wood, WB. Cold Spring Harbor monograph series 17. Cold Spring Harbor, N.Y.: Cold Spring Harbor Laboratory; 1988. The Nematode *Caenorhabditis elegans*; p. xiiip. 667
7. Sulston JE, Horvitz HR. Post-embryonic cell lineages of the nematode, *Caenorhabditis elegans*. *Dev Biol* 1977;56:110–156. [PubMed: 838129]

8. White JGSE, Thomson JN, Brenner S. The structure of the nervous system of the nematode *C. elegans*. *Philos Trans R Soc Lond B Biol Sci* 1986;314:1–340.
9. Hart, AC. WormBook. The *C. elegans* Research Community. WormBook; 2006. Behavior.
10. Li W, Feng Z, Sternberg PW, Xu XZ. A *C. elegans* stretch receptor neuron revealed by a mechanosensitive TRP channel homologue. *Nature* 2006;440:684–687. [PubMed: 16572173]
11. Ward A, Liu J, Feng Z, Xu XZ. Light-sensitive neurons and channels mediate phototaxis in *C. elegans*. *Nat Neurosci* 2008;11:916–922. [PubMed: 18604203]
12. Kahn-Kirby AH, Bargmann CI. TRP channels in *C. elegans*. *Annu Rev Physiol* 2006;68:719–736. [PubMed: 16460289]
13. Xiao R, Xu XZ. Function and regulation of TRP family channels in *C. elegans*. *Pflugers Arch* 2009;458:851–860. [PubMed: 19421772]
14. Sulston J, Du Z, Thomas K, Wilson R, Hillier L, Staden R, Halloran N, Green P, Thierry-Mieg J, Qiu L, et al. The *C. elegans* genome sequencing project: a beginning. *Nature* 1992;356:37–41. [PubMed: 1538779]
15. Hodgkin J, Plasterk RH, Waterston RH. The nematode *Caenorhabditis elegans* and its genome. *Science* 1995;270:410–414. [PubMed: 7569995]
16. Wes PD, Chevesich J, Jeromin A, Rosenberg C, Stetten G, Montell C. TRPC1, a human homolog of a *Drosophila* store-operated channel. *Proc Natl Acad Sci U S A* 1995;92:9652–9656. [PubMed: 7568191]
17. Zhu X, Chu PB, Peyton M, Birnbaumer L. Molecular cloning of a widely expressed human homologue for the *Drosophila* *trp* gene. *FEBS Lett* 1995;373:193–198. [PubMed: 7589464]
18. Colbert HA, Smith TL, Bargmann CI. OSM-9, a novel protein with structural similarity to channels, is required for olfaction, mechanosensation, and olfactory adaptation in *Caenorhabditis elegans*. *J Neurosci* 1997;17:8259–8269. [PubMed: 9334401]
19. Xu XZ, Sternberg PW. A *C. elegans* sperm TRP protein required for sperm-egg interactions during fertilization. *Cell* 2003;114:285–297. [PubMed: 12914694]
20. Feng Z, Li W, Ward A, Piggott BJ, Larkspur ER, Sternberg PW, Xu XZ. A *C. elegans* model of nicotine-dependent behavior: regulation by TRP-family channels. *Cell* 2006;127:621–633. [PubMed: 17081982]
21. Dvoskin LP, Crooks PA, Teng L, Green TA, Bardo MT. Acute and chronic effects of nornicotine on locomotor activity in rats: altered response to nicotine. *Psychopharmacology (Berl)* 1999;145:442–451. [PubMed: 10460322]
22. Caporaso N, Gu F, Chatterjee N, Sheng-Chih J, Yu K, Yeager M, Chen C, Jacobs K, Wheeler W, Landi MT, Ziegler RG, Hunter DJ, Chanock S, Hankinson S, Kraft P, Bergen AW. Genome-wide and candidate gene association study of cigarette smoking behaviors. *PLoS One* 2009;4:e4653. [PubMed: 19247474]
23. Drgon T, Montoya I, Johnson C, Liu QR, Walther D, Hamer D, Uhl GR. Genome-wide association for nicotine dependence and smoking cessation success in NIH research volunteers. *Mol Med* 2009;15:21–27. [PubMed: 19009022]
24. Reinke V, Smith HE, Nance J, Wang J, Van Doren C, Begley R, Jones SJ, Davis EB, Scherer S, Ward S, Kim SK. A global profile of germline gene expression in *C. elegans*. *Mol Cell* 2000;6:605–616. [PubMed: 11030340]
25. Jungnickel MK, Marrero H, Birnbaumer L, Lemos JR, Florman HM. Trp2 regulates entry of Ca²⁺ into mouse sperm triggered by egg ZP3. *Nat Cell Biol* 2001;3:499–502. [PubMed: 11331878]
26. Colbert HA, Bargmann CI. Odorant-specific adaptation pathways generate olfactory plasticity in *C. elegans*. *Neuron* 1995;14:803–812. [PubMed: 7718242]
27. Tobin D, Madsen D, Kahn-Kirby A, Peckol E, Moulder G, Barstead R, Maricq A, Bargmann C. Combinatorial expression of TRPV channel proteins defines their sensory functions and subcellular localization in *C. elegans* neurons. *Neuron* 2002;35:307–318. [PubMed: 12160748]
28. Jose AM, Bany IA, Chase DL, Koelle MR. A specific subset of transient receptor potential vanilloid-type channel subunits in *Caenorhabditis elegans* endocrine cells function as mixed heteromers to promote neurotransmitter release. *Genetics* 2007;175:93–105. [PubMed: 17057248]
29. Bargmann CI. Chemosensation in *C. elegans*. *WormBook* 2006:1–29. [PubMed: 18050433]

30. Liedtke W, Tobin DM, Bargmann CI, Friedman JM. Mammalian TRPV4 (VR-OAC) directs behavioral responses to osmotic and mechanical stimuli in *Caenorhabditis elegans*. *Proc Natl Acad Sci U S A* 2003;100 (Suppl 2):14531–14536. [PubMed: 14581619]
31. Clapham DE. TRP channels as cellular sensors. *Nature* 2003;426:517–524. [PubMed: 14654832]
32. Dhaka A, Viswanath V, Patapoutian A. Trp ion channels and temperature sensation. *Annu Rev Neurosci* 2006;29:135–161. [PubMed: 16776582]
33. Talavera K, Nilius B, Voets T. Neuronal TRP channels: thermometers, pathfinders and lifesavers. *Trends Neurosci* 2008;31:287–295. [PubMed: 18471901]
34. Basbaum AI, Bautista DM, Scherrer G, Julius D. Cellular and molecular mechanisms of pain. *Cell* 2009;139:267–284. [PubMed: 19837031]
35. de Bono M, Tobin DM, Davis MW, Avery L, Bargmann CI. Social feeding in *Caenorhabditis elegans* is induced by neurons that detect aversive stimuli. *Nature* 2002;419:899–903. [PubMed: 12410303]
36. Zhang S, Sokolchik I, Blanco G, Sze JY. *Caenorhabditis elegans* TRPV ion channel regulates 5HT biosynthesis in chemosensory neurons. *Development* 2004;131:1629–1638. [PubMed: 14998926]
37. Lee BH, Ashrafi K. A TRPV channel modulates *C. elegans* neurosecretion, larval starvation survival, and adult lifespan. *PLoS Genet* 2008;4:e1000213. [PubMed: 18846209]
38. Sun AY, Lambie EJ. *gon-2*, a gene required for gonadogenesis in *Caenorhabditis elegans*. *Genetics* 1997;147:1077–1089. [PubMed: 9383054]
39. Teramoto T, Lambie EJ, Iwasaki K. Differential regulation of TRPM channels governs electrolyte homeostasis in the *C. elegans* intestine. *Cell Metab* 2005;1:343–354. [PubMed: 16054081]
40. Xing J, Yan X, Estevez A, Strange K. Highly Ca²⁺-selective TRPM channels regulate IP₃-dependent oscillatory Ca²⁺ signaling in the *C. elegans* intestine. *J Gen Physiol* 2008;131:245–255. [PubMed: 18299395]
41. Kwan CS, Vazquez-Manrique RP, Ly S, Goyal K, Baylis HA. TRPM channels are required for rhythmicity in the ultradian defecation rhythm of *C. elegans*. *BMC Physiol* 2008;8:11. [PubMed: 18495023]
42. Nadler MJ, Hermosura MC, Inabe K, Perraud AL, Zhu Q, Stokes AJ, Kurosaki T, Kinet JP, Penner R, Scharenberg AM, Fleig A. LTRPC7 is a Mg-ATP-regulated divalent cation channel required for cell viability. *Nature* 2001;411:590–595. [PubMed: 11385574]
43. Schlingmann KP, Weber S, Peters M, Niemann Nejsum L, Vitzthum H, Klingel K, Kratz M, Haddad E, Ristoff E, Dinour D, Syrrou M, Nielsen S, Sassen M, Waldegger S, Seyberth HW, Konrad M. Hypomagnesemia with secondary hypocalcemia is caused by mutations in TRPM6, a new member of the TRPM gene family. *Nat Genet* 2002;31:166–170. [PubMed: 12032568]
44. Monteilh-Zoller MK, Hermosura MC, Nadler MJ, Scharenberg AM, Penner R, Fleig A. TRPM7 provides an ion channel mechanism for cellular entry of trace metal ions. *J Gen Physiol* 2003;121:49–60. [PubMed: 12508053]
45. Schmitz C, Perraud AL, Johnson CO, Inabe K, Smith MK, Penner R, Kurosaki T, Fleig A, Scharenberg AM. Regulation of vertebrate cellular Mg²⁺ homeostasis by TRPM7. *Cell* 2003;114:191–200. [PubMed: 12887921]
46. Chubanov V, Schlingmann KP, Waring J, Heinzinger J, Kaske S, Waldegger S, Mederos y Schnitzler M, Gudermann T. Hypomagnesemia with secondary hypocalcemia due to a missense mutation in the putative pore-forming region of TRPM6. *J Biol Chem* 2007;282:7656–7667. [PubMed: 17197439]
47. Thomas JH. Genetic analysis of defecation in *Caenorhabditis elegans*. *Genetics* 1990;124:855–872. [PubMed: 2323555]
48. Liu DW, Thomas JH. Regulation of a periodic motor program in *C. elegans*. *J Neurosci* 1994;14:1953–1962. [PubMed: 8158250]
49. Dal Santo P, Logan MA, Chisholm AD, Jorgensen EM. The inositol trisphosphate receptor regulates a 50-second behavioral rhythm in *C. elegans*. *Cell* 1999;98:757–767. [PubMed: 10499793]
50. Kindt KS, Viswanath V, Macpherson L, Quast K, Hu H, Patapoutian A, Schafer WR. *Caenorhabditis elegans* TRPA-1 functions in mechanosensation. *Nat Neurosci* 2007;10:568–577. [PubMed: 17450139]

51. Walker RG, Willingham AT, Zuker CS. A *Drosophila* mechanosensory transduction channel. *Science* 2000;287:2229–2234. [PubMed: 10744543]
52. Kindt KS, Quast KB, Giles AC, De S, Hendrey D, Nicastro I, Rankin CH, Schafer WR. Dopamine mediates context-dependent modulation of sensory plasticity in *C. elegans*. *Neuron* 2007;55:662–676. [PubMed: 17698017]
53. Barr MM, Sternberg PW. A polycystic kidney-disease gene homologue required for male mating behaviour in *C. elegans*. *Nature* 1999;401:386–389. [PubMed: 10517638]
54. Fares H, Greenwald I. Regulation of endocytosis by CUP-5, the *Caenorhabditis elegans* mucolipin-1 homologue. *Nat Genet* 2001;28:64–68. [PubMed: 11326278]
55. Hersh BM, Hartwig E, Horvitz HR. The *Caenorhabditis elegans* mucolipin-like gene cup-5 is essential for viability and regulates lysosomes in multiple cell types. *Proc Natl Acad Sci U S A* 2002;99:4355–4360. [PubMed: 11904372]
56. Bassi MT, Manzoni M, Monti E, Pizzo MT, Ballabio A, Borsani G. Cloning of the gene encoding a novel integral membrane protein, mucolipidin and identification of the two major founder mutations causing mucopolipidosis type IV. *Am J Hum Genet* 2000;67:1110–1120. [PubMed: 11013137]
57. Sun M, Goldin E, Stahl S, Falardeau JL, Kennedy JC, Acierno JS Jr, Bove C, Kaneski CR, Nagle J, Bromley MC, Colman M, Schiffmann R, Slaugenhaupt SA. Mucopolipidosis type IV is caused by mutations in a gene encoding a novel transient receptor potential channel. *Hum Mol Genet* 2000;9:2471–2478. [PubMed: 11030752]
58. Treusch S, Knuth S, Slaugenhaupt SA, Goldin E, Grant BD, Fares H. *Caenorhabditis elegans* functional orthologue of human protein h-mucolipin-1 is required for lysosome biogenesis. *Proc Natl Acad Sci U S A* 2004;101:4483–4488. [PubMed: 15070744]
59. Venkatachalam K, Long AA, Elsaesser R, Nikolaeva D, Broadie K, Montell C. Motor deficit in a *Drosophila* model of mucopolipidosis type IV due to defective clearance of apoptotic cells. *Cell* 2008;135:838–851. [PubMed: 19041749]
60. Pedersen SF, Owsianik G, Nilius B. TRP channels: an overview. *Cell Calcium* 2005;38:233–252. [PubMed: 16098585]
61. Zhang Z, Tang J, Tikunova S, Johnson JD, Chen Z, Qin N, Dietrich A, Stefani E, Birnbaumer L, Zhu MX. Activation of Trp3 by inositol 1,4,5-trisphosphate receptors through displacement of inhibitory calmodulin from a common binding domain. *Proc Natl Acad Sci U S A* 2001;98:3168–3173. [PubMed: 11248050]
62. Rohacs T, Lopes CM, Michailidis I, Logothetis DE. PI(4,5)P₂ regulates the activation and desensitization of TRPM8 channels through the TRP domain. *Nat Neurosci* 2005;8:626–634. [PubMed: 15852009]
63. Hofmann T, Obukhov AG, Schaefer M, Harteneck C, Gudermann T, Schultz G. Direct activation of human TRPC6 and TRPC3 channels by diacylglycerol. *Nature* 1999;397:259–263. [PubMed: 9930701]
64. Huang J, Liu CH, Hughes SA, Postma M, Schwiening CJ, Hardie RC. Activation of TRP channels by protons and phosphoinositide depletion in *Drosophila* photoreceptors. *Curr Biol* 20:189–197. [PubMed: 20116246]
65. Ramsey IS, Delling M, Clapham DE. An introduction to TRP channels. *Annu Rev Physiol* 2006;68:619–647. [PubMed: 16460286]
66. Kahn-Kirby AH, Dantzer JL, Apicella AJ, Schafer WR, Browse J, Bargmann CI, Watts JL. Specific polyunsaturated fatty acids drive TRPV-dependent sensory signaling in vivo. *Cell* 2004;119:889–900. [PubMed: 15607983]
67. Christensen AP, Corey DP. TRP channels in mechanosensation: direct or indirect activation? *Nat Rev Neurosci* 2007;8:510–521. [PubMed: 17585304]
68. Sharif-Naeini R, Dedman A, Folgering JH, Duprat F, Patel A, Nilius B, Honore E. TRP channels and mechanosensory transduction: insights into the arterial myogenic response. *Pflugers Arch* 2008;456:529–540. [PubMed: 18183414]
69. Zhou XL, Loukin SH, Coria R, Kung C, Saimi Y. Heterologously expressed fungal transient receptor potential channels retain mechanosensitivity in vitro and osmotic response in vivo. *Eur Biophys J* 2005;34:413–422. [PubMed: 15711808]

70. Sidi S, Friedrich RW, Nicolson T. NompC TRP channel required for vertebrate sensory hair cell mechanotransduction. *Science* 2003;301:96–99. [PubMed: 12805553]
71. Goodman MB, Schwarz EM. Transducing touch in *Caenorhabditis elegans*. *Annu Rev Physiol* 2003;65:429–452. [PubMed: 12524464]
72. Bounoutas A, Chalfie M. Touch sensitivity in *Caenorhabditis elegans*. *Pflugers Arch* 2007;454:691–702. [PubMed: 17285303]
73. Chalfie M. Neurosensory mechanotransduction. *Nat Rev Mol Cell Biol* 2009;10:44–52. [PubMed: 19197331]
74. Kaplan JM, Horvitz HR. A dual mechanosensory and chemosensory neuron in *Caenorhabditis elegans*. *Proc Natl Acad Sci U S A* 1993;90:2227–2231. [PubMed: 8460126]
75. Sawin ER, Ranganathan R, Horvitz HR. *C. elegans* locomotory rate is modulated by the environment through a dopaminergic pathway and by experience through a serotonergic pathway. *Neuron* 2000;26:619–631. [PubMed: 10896158]
76. Hart AC, Sims S, Kaplan JM. Synaptic code for sensory modalities revealed by *C. elegans* GLR-1 glutamate receptor. *Nature* 1995;378:82–85. [PubMed: 7477294]
77. Nauli SM, Alenghat FJ, Luo Y, Williams E, Vassilev P, Li X, Elia AE, Lu W, Brown EM, Quinn SJ, Ingber DE, Zhou J. Polycystins 1 and 2 mediate mechanosensation in the primary cilium of kidney cells. *Nat Genet* 2003;33:129–137. [PubMed: 12514735]
78. Sharif-Naeini R, Folgering JH, Bichet D, Duprat F, Lauritzen I, Arhatte M, Jodar M, Dedman A, Chatelain FC, Schulte U, Retailleau K, Loufrani L, Patel A, Sachs F, Delmas P, Peters DJ, Honore E. Polycystin-1 and -2 dosage regulates pressure sensing. *Cell* 2009;139:587–596. [PubMed: 19879844]
79. Jordt SE, McKemy DD, Julius D. Lessons from peppers and peppermint: the molecular logic of thermosensation. *Curr Opin Neurobiol* 2003;13:487–492. [PubMed: 12965298]
80. Patapoutian A, Peier AM, Story GM, Viswanath V. ThermoTRP channels and beyond: mechanisms of temperature sensation. *Nat Rev Neurosci* 2003;4:529–539. [PubMed: 12838328]
81. Groenestege WM, Thebault S, van der Wijst J, van den Berg D, Janssen R, Tejpar S, van den Heuvel LP, van Cutsem E, Hoenderop JG, Knoers NV, Bindels RJ. Impaired basolateral sorting of pro-EGF causes isolated recessive renal hypomagnesemia. *J Clin Invest* 2007;117:2260–2267. [PubMed: 17671655]
82. Thebault S, Alexander RT, Tiel Groenestege WM, Hoenderop JG, Bindels RJ. EGF increases TRPM6 activity and surface expression. *J Am Soc Nephrol* 2009;20:78–85. [PubMed: 19073827]
83. Zurborg S, Yurgionas B, Jira JA, Caspani O, Heppenstall PA. Direct activation of the ion channel TRPA1 by Ca²⁺. *Nat Neurosci* 2007;10:277–279. [PubMed: 17259981]
84. Doerner JF, Gisselmann G, Hatt H, Wetzel CH. Transient receptor potential channel A1 is directly gated by calcium ions. *J Biol Chem* 2007;282:13180–13189. [PubMed: 17353192]
85. Tang J, Lin Y, Zhang Z, Tikunova S, Birnbaumer L, Zhu MX. Identification of common binding sites for calmodulin and inositol 1,4,5-trisphosphate receptors on the carboxyl termini of trp channels. *J Biol Chem* 2001;276:21303–21310. [PubMed: 11290752]
86. Zhu MX. Multiple roles of calmodulin and other Ca(2+)-binding proteins in the functional regulation of TRP channels. *Pflugers Arch* 2005;451:105–115. [PubMed: 15924238]
87. Kwon Y, Hofmann T, Montell C. Integration of phosphoinositide- and calmodulin-mediated regulation of TRPC6. *Mol Cell* 2007;25:491–503. [PubMed: 17317623]
88. Caterina MJ, Schumacher MA, Tominaga M, Rosen TA, Levine JD, Julius D. The capsaicin receptor: a heat-activated ion channel in the pain pathway. *Nature* 1997;389:816–824. [PubMed: 9349813]
89. Moqrich A, Hwang SW, Earley TJ, Petrus MJ, Murray AN, Spencer KS, Andahazy M, Story GM, Patapoutian A. Impaired thermosensation in mice lacking TRPV3, a heat and camphor sensor in the skin. *Science* 2005;307:1468–1472. [PubMed: 15746429]
90. Smith PL, Maloney KN, Pothén RG, Clardy J, Clapham DE. Bisandrographolide from *Andrographis paniculata* activates TRPV4 channels. *J Biol Chem* 2006;281:29897–29904. [PubMed: 16899456]
91. Xu H, Delling M, Jun JC, Clapham DE. Oregano, thyme and clove-derived flavors and skin sensitizers activate specific TRP channels. *Nat Neurosci* 2006;9:628–635. [PubMed: 16617338]

92. Qin N, Neeper MP, Liu Y, Hutchinson TL, Lubin ML, Flores CM. TRPV2 is activated by cannabidiol and mediates CGRP release in cultured rat dorsal root ganglion neurons. *J Neurosci* 2008;28:6231–6238. [PubMed: 18550765]
93. Xu XZ, Li HS, Guggino WB, Montell C. Coassembly of TRP and TRPL produces a distinct store-operated conductance. *Cell* 1997;89:1155–1164. [PubMed: 9215637]
94. Strubing C, Krapivinsky G, Krapivinsky L, Clapham DE. TRPC1 and TRPC5 form a novel cation channel in mammalian brain. *Neuron* 2001;29:645–655. [PubMed: 11301024]
95. Hoenderop JG, Voets T, Hoefs S, Weidema F, Prenen J, Nilius B, Bindels RJ. Homo- and heterotetrameric architecture of the epithelial Ca²⁺ channels TRPV5 and TRPV6. *EMBO J* 2003;22:776–785. [PubMed: 12574114]
96. Chubanov V, Waldegger S, Mederos y Schnitzler M, Vitzthum H, Sassen MC, Seyberth HW, Konrad M, Gudermann T. Disruption of TRPM6/TRPM7 complex formation by a mutation in the TRPM6 gene causes hypomagnesemia with secondary hypocalcemia. *Proc Natl Acad Sci U S A* 2004;101:2894–2899. [PubMed: 14976260]
97. Zhang P, Luo Y, Chasan B, Gonzalez-Perrett S, Montalbetti N, Timpanaro GA, Cantero Mdel R, Ramos AJ, Goldmann WH, Zhou J, Cantiello HF. The multimeric structure of polycystin-2 (TRPP2): structural-functional correlates of homo- and hetero-multimers with TRPC1. *Hum Mol Genet* 2009;18:1238–1251. [PubMed: 19193631]
98. Garcia-Martinez C, Morenilla-Palao C, Planells-Cases R, Merino JM, Ferrer-Montiel A. Identification of an aspartic residue in the P-loop of the vanilloid receptor that modulates pore properties. *J Biol Chem* 2000;275:32552–32558. [PubMed: 10931826]
99. Voets T, Prenen J, Vriens J, Watanabe H, Janssens A, Wissenbach U, Bodding M, Droogmans G, Nilius B. Molecular determinants of permeation through the cation channel TRPV4. *J Biol Chem* 2002;277:33704–33710. [PubMed: 12093812]
100. Chung MK, Guler AD, Caterina MJ. Biphasic currents evoked by chemical or thermal activation of the heat-gated ion channel, TRPV3. *J Biol Chem* 2005;280:15928–15941. [PubMed: 15722340]
101. Xiao R, Tang J, Wang C, Colton CK, Tian J, Zhu MX. Calcium plays a central role in the sensitization of TRPV3 channel to repetitive stimulations. *J Biol Chem* 2008;283:6162–6174. [PubMed: 18178557]
102. Sambongi Y, Nagae T, Liu Y, Yoshimizu T, Takeda K, Wada Y, Futai M. Sensing of cadmium and copper ions by externally exposed ADL, ASE, and ASH neurons elicits avoidance response in *Caenorhabditis elegans*. *Neuroreport* 1999;10:753–757. [PubMed: 10208543]
103. Hilliard MA, Apicella AJ, Kerr R, Suzuki H, Bazzicalupo P, Schafer WR. In vivo imaging of *C. elegans* ASH neurons: cellular response and adaptation to chemical repellents. *EMBO J* 2005;24:63–72. [PubMed: 15577941]
104. Fukuto HS, Ferkey DM, Apicella AJ, Lans H, Sharmeen T, Chen W, Lefkowitz RJ, Jansen G, Schafer WR, Hart AC. G protein-coupled receptor kinase function is essential for chemosensation in *C. elegans*. *Neuron* 2004;42:581–593. [PubMed: 15157420]
105. Ferkey DM, Hyde R, Haspel G, Dionne HM, Hess HA, Suzuki H, Schafer WR, Koelle MR, Hart AC. *C. elegans* G protein regulator RGS-3 controls sensitivity to sensory stimuli. *Neuron* 2007;53:39–52. [PubMed: 17196529]
106. Jiang J, Li M, Yue L. Potentiation of TRPM7 inward currents by protons. *J Gen Physiol* 2005;126:137–150. [PubMed: 16009728]
107. Li M, Du J, Jiang J, Ratzan W, Su LT, Runnels LW, Yue L. Molecular determinants of Mg²⁺ and Ca²⁺ permeability and pH sensitivity in TRPM6 and TRPM7. *J Biol Chem* 2007;282:25817–25830. [PubMed: 17599911]
108. Kemp BJ, Church DL, Hatzold J, Conradt B, Lambie EJ. Gem-1 encodes an SLC16 monocarboxylate transporter-related protein that functions in parallel to the gon-2 TRPM channel during gonad development in *Caenorhabditis elegans*. *Genetics* 2009;181:581–591. [PubMed: 19087963]
109. Church DL, Lambie EJ. The promotion of gonadal cell divisions by the *Caenorhabditis elegans* TRPM cation channel GON-2 is antagonized by GEM-4 copine. *Genetics* 2003;165:563–574. [PubMed: 14573470]

110. Patapoutian A, Tate S, Woolf CJ. Transient receptor potential channels: targeting pain at the source. *Nat Rev Drug Discov* 2009;8:55–68. [PubMed: 19116627]
111. Nilius B, Owsianik G, Voets T, Peters JA. Transient receptor potential cation channels in disease. *Physiol Rev* 2007;87:165–217. [PubMed: 17237345]
112. Macpherson LJ, Dubin AE, Evans MJ, Marr F, Schultz PG, Cravatt BF, Patapoutian A. Noxious compounds activate TRPA1 ion channels through covalent modification of cysteines. *Nature* 2007;445:541–545. [PubMed: 17237762]
113. Hinman A, Chuang HH, Bautista DM, Julius D. TRP channel activation by reversible covalent modification. *Proc Natl Acad Sci U S A* 2006;103:19564–19568. [PubMed: 17164327]
114. Barr MM, DeModena J, Braun D, Nguyen CQ, Hall DH, Sternberg PW. The *Caenorhabditis elegans* autosomal dominant polycystic kidney disease gene homologs *lov-1* and *pkd-2* act in the same pathway. *Curr Biol* 2001;11:1341–1346. [PubMed: 11553327]
115. Qian F, Germino FJ, Cai Y, Zhang X, Somlo S, Germino GG. PKD1 interacts with PKD2 through a probable coiled-coil domain. *Nat Genet* 1997;16:179–183. [PubMed: 9171830]
116. Tsiokas L, Kim E, Arnould T, Sukhatme VP, Walz G. Homo- and heterodimeric interactions between the gene products of PKD1 and PKD2. *Proc Natl Acad Sci U S A* 1997;94:6965–6970. [PubMed: 9192675]
117. Hanaoka K, Qian F, Boletta A, Bhunia AK, Piontek K, Tsiokas L, Sukhatme VP, Guggino WB, Germino GG. Co-assembly of polycystin-1 and -2 produces unique cation-permeable currents. *Nature* 2000;408:990–994. [PubMed: 11140688]
118. Yu Y, Ulbrich MH, Li MH, Buraei Z, Chen XZ, Ong AC, Tong L, Isacoff EY, Yang J. Structural and molecular basis of the assembly of the TRPP2/PKD1 complex. *Proc Natl Acad Sci U S A* 2009;106:11558–11563. [PubMed: 19556541]
119. Giamarchi A, Feng S, Rodat-Despoix L, Xu Y, Bubenshchikova E, Newby LJ, Hao J, Gaudioso C, Crest M, Lupas AN, Honore E, Williamson MP, Obara T, Ong AC, Delmas P. A polycystin-2 (TRPP2) dimerization domain essential for the function of heteromeric polycystin complexes. *EMBO J* 29:1176–1191. [PubMed: 20168298]
120. Grimm DH, Cai Y, Chauvet V, Rajendran V, Zeltner R, Geng L, Avner ED, Sweeney W, Somlo S, Caplan MJ. Polycystin-1 distribution is modulated by polycystin-2 expression in mammalian cells. *J Biol Chem* 2003;278:36786–36793. [PubMed: 12840011]
121. Peden EM, Barr MM. The KLP-6 kinesin is required for male mating behaviors and polycystin localization in *Caenorhabditis elegans*. *Curr Biol* 2005;15:394–404. [PubMed: 15753033]
122. Hu J, Bae YK, Knobel KM, Barr MM. Casein kinase II and calcineurin modulate TRPP function and ciliary localization. *Mol Biol Cell* 2006;17:2200–2211. [PubMed: 16481400]
123. Bae YK, Kim E, L'Hernault SW, Barr MM. The CIL-1 PI 5-phosphatase localizes TRP Polycystins to cilia and activates sperm in *C. elegans*. *Curr Biol* 2009;19:1599–1607. [PubMed: 19781942]
124. Nicot AS, Fares H, Payraastre B, Chisholm AD, Labouesse M, Laporte J. The phosphoinositide kinase PIKfyve/Fab1p regulates terminal lysosome maturation in *Caenorhabditis elegans*. *Mol Biol Cell* 2006;17:3062–3074. [PubMed: 16801682]
125. Bierut LJ, Madden PA, Breslau N, Johnson EO, Hatsukami D, Pomerleau OF, Swan GE, Rutter J, Bertelsen S, Fox L, Fugman D, Goate AM, Hinrichs AL, Konvicka K, Martin NG, Montgomery GW, Saccone NL, Saccone SF, Wang JC, Chase GA, Rice JP, Ballinger DG. Novel genes identified in a high-density genome wide association study for nicotine dependence. *Hum Mol Genet* 2007;16:24–35. [PubMed: 17158188]
126. Mellem JE, Brockie PJ, Zheng Y, Madsen DM, Maricq AV. Decoding of polymodal sensory stimuli by postsynaptic glutamate receptors in *C. elegans*. *Neuron* 2002;36:933–944. [PubMed: 12467596]
127. O'Hagan R, Chalfie M, Goodman MB. The MEC-4 DEG/ENaC channel of *Caenorhabditis elegans* touch receptor neurons transduces mechanical signals. *Nat Neurosci* 2005;8:43–50. [PubMed: 15580270]
128. Liu J, Ward A, Gao J, Dong Y, Nishio N, Inada H, Kang L, Yu Y, Ma D, Xu T, Mori I, Xie Z, Xu XZ. *C. elegans* phototransduction requires a G protein-dependent cGMP pathway and a taste receptor homolog. *Nat Neurosci*. 2010 In press.

129. Goodman MB, Hall DH, Avery L, Lockery SR. Active currents regulate sensitivity and dynamic range in *C. elegans* neurons. *Neuron* 1998;20:763–772. [PubMed: 9581767]
131. Kang L, Gao J, Schafer WR, Xie Z, Xu XZS. *C. Elegans* TRP family protein TRP-4 is a pore-forming subunit of a native mechanotransduction channel. *Neuron* 2010;67:381–391. [PubMed: 20696377]

A, a dendrogram plot of *C. elegans* TRP superfamily. The relationship between each TRP channel is indicated by the branch length in point accepted mutations (PAM) units. B, schematic representation of a TRP subunit. Extracellular Na⁺ and Ca²⁺ flux through the putative pore between S5 and S6. C, a schematic drawing of *C. elegans* (modified from www.wormatlas.com). D, a schematic showing a cross section of the worm body (modified from Edwards & Wood, 1983).