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Function and regulation of TRP family channels in *C. elegans*

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Abstract

Seventeen transient receptor potential (TRP) family proteins are encoded by the *C. elegans* genome, and they cover all of the seven TRP subfamilies, including TRPC, TRPV, TRPM, TRPN, TRPA, TRPP and TRPML. Classical forward and reverse genetic screens have isolated mutant alleles in every *C. elegans trp* gene, and their characterizations have revealed novel functions and regulatory mechanisms of TRP channels. For example, the TRPC channels TRP-1 and TRP-2 control nicotine-dependent behavior, while TRP-3, a sperm TRPC channel, is regulated by sperm activation and required for sperm-egg interactions during fertilization. Similar to their vertebrate counterparts, *C. elegans* TRPs function in sensory physiology. For instance, the TRPV channels OSM-9 and OCR-2 act in chemosensation, osmosensation and touch sensation, the TRPA member TRPA-1 regulates touch sensation, while the TRPN channel TRP-4 mediates proprioception. Some *C. elegans* TRPM, TRPP and TRPML members exhibit cellular functions similar to their vertebrate homologues and have provided insights into human diseases, including polycystic kidney disease, hypomagnesemia and mucolipidosis type IV. The availability of a complete set of *trp* gene mutants in conjunction with its facile genetics makes *C. elegans* a powerful model for studying the function and regulation of TRP family channels *in vivo*.

Introduction

TRP proteins represent a superfamily of cation channels that are conserved from worms to humans (17,58,78). They form seven subfamilies: TRPC (TRP-Canonical), TRPV (TRP-Vanilloid), TRPM (TRP-Melastatin), TRPN (TRP-NompC), TRPA (TRP-Ankyrin), TRPP (TRP-Polycystin), and TRPML (TRP-MucoLipin) (78). The first *trp* mutant was identified in 1969 in *Drosophila*, which displays a transient receptor potential phenotype in electroretinogram (ERG) recoding (15). Two decades later, Montell & Rubin cloned the *trp* gene by germ-line transformation and found that it encodes a putative membrane protein with homology to voltage-gated calcium channels (55). Subsequent functional studies indicate that *Drosophila* TRP proteins form calcium-permeable cation channels both *in vivo* and *in vitro* (30,86).

Genetic screens and database search have identified 17 *trp* genes in *C. elegans*. Together they cover all of the seven TRP subfamilies (Fig 1A) (41,78). All TRP channels likely consist of four subunits, and each subunit contains six putative transmembrane segments (S1-S6) with the hydrophobic region between S5 and S6 forming the pore loop and both the N- and C-termini residing in the cytoplasmic side (Fig 1B) (78).

Benefiting from its facile genetics and short generation time (~3 days), *C. elegans* has become an increasingly popular model organism for the study of various biological

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questions. Most *trp* genes in *C. elegans* show expression in the nervous system. Despite its simple nervous system, *C. elegans* expresses complex behaviors, ranging from sensory, motor, mating, social, drug dependence behaviors to learning and memory (18,25). In the case of sensory behaviors, worms can sense a wide range of chemicals that trigger olfactory and taste responses, and mechanical forces that evoke touch behavior and proprioception (18,52). Worms also possess the sense of light (22,80), and engage in phototaxis behavior that is mediated by light-sensitive neurons and channels (80). This wealth of simple behavioral assays, together with a small and very well characterized nervous system, has greatly facilitated *in vivo* characterization of gene functions in *C. elegans*, particularly those genes with a role in the nervous system. Indeed, unlike mammalian TRP channels which have been extensively studied in heterologous systems, characterization of *C. elegans* TRP channels has mostly been carried out *in vivo*. Mutant alleles have been isolated for every *trp* gene, and most of them exhibit discernable phenotypes. Here we give a brief review of TRP family channels in *C. elegans*, mainly focusing on the *in vivo* function and regulation of these channels.

TRPC channels

The first *C. elegans* TRP homologue (ZC21.2) was reported by Wes *et al*. and Zhu *et al*. in 1995 (82,90). This TRP shares the highest homology with the *Drosophila* TRP and TRPL, and was later designated as TRP-1, the founding member of *C. elegans* TRPCs (87). In addition to TRP-1, two additional TRPC members, TRP-2 and TRP-3, are present in *C. elegans*. Some known features of these TRP channels are summarized in table 1. Similar to their *Drosophila* and mammalian homologues, these TRPC channels contain 2-4 ankyrin repeats and a coiled-coil domain in their N-terminus and a highly conserved TRP domain in their C-terminus (87).

Both TRP-1 and TRP-2 are expressed in multiple types of neurons, including interneurons, motor neurons, pharyngeal neurons and sensory neurons (14,25). Mutant alleles of *trp-1* and *trp-2* are viable and superficially wild-type without strong defects in locomotion and egg-laying behavior. This is rather surprising, considering their wide expression in the nervous system. Nevertheless, in an effort to establish *C. elegans* as a model for nicotine dependence, an unexpected function of TRP-1 and TRP-2 has been revealed (25). Similar to other established rodent models for nicotine dependence (21), *C. elegans* displays locomotion response to acute nicotine treatment, develops tolerance upon prolonged nicotine exposure, becomes sensitized to nicotine after repetitive nicotine treatment, and reacts to nicotine withdrawal (25). Interestingly, null mutations in *trp-1* and *trp-2* greatly reduce these behavioral responses to nicotine. In contrast, mutations in another TRPC member, *trp*-3, do not affect nicotine responses (25). In addition, some nicotinic acetylcholine receptors (nAChRs, e.g. ACR-15) are required for nicotine responses in *C. elegans* (25). TRP-1 and TRP-2 are not required for the expression of these nAChRs, but appear to functionally regulate the activity of nAChRs directly or indirectly. The precise mechanism by which TRPCs modulate nicotinic signaling is not clear. It is also unclear whether TRP-1 and TRP-2 function as heteromeric channels like their mammalian homologues (86). When expressed in HEK293 cells, TRP-2 behaves as a receptor-operated cation channel coupled to the Gq-PLCβ pathway, a feature shared by mammalian TRPCs (25,78). Mutations in Gq/*egl-30* and PLCβ/*egl-8* lead to a strong defect in nicotine responses (25). Expression of the human TRPC3 in *C. elegans* can rescue the nicotine phenotype in *trp-2* mutant worms, suggesting functional conservation of TRPC channels in nicotine responses. Interestingly, a recent genome-wide association study has identified TRPC7 as a candidate gene regulating nicotine dependence in humans (7). In similar studies, TRPC4 has been linked to multiple types of drug dependence (37). These results raise the possibility that TRP channels may play a role in drug dependence in mammals.

Unlike TRP-1 and TRP-2, TRP-3 is specifically enriched in sperm (87). In HEK293 cells, TRP-3 promotes both receptor-operated and store-operated calcium entry, suggesting that TRP-3 may form a calcium-permeable channel in sperm. Consistent with its expression pattern, TRP-3 mutant alleles are sterile due to a defect in sperm (87). TRP-3 mutant sperm are motile, can bind to oocytes, but cannot fertilize oocytes, suggesting a defect in sperm-egg fusion. During sperm-egg interactions, binding of sperm ligand to its oocyte receptor may signal the opening of TRP-3, and the ensuing calcium influx may then trigger a series of signaling events culminating in gamete fusion. The ligand-receptor pair in sperm and oocytes has not been identified. Candidates include SPE-9, an EGF repeats-containing sperm protein which may serve as the sperm ligand, and EGG-1 and EGG-2, two LDL receptor repeats-containing egg proteins which may act as the egg receptor for SPE-9 (40,65).

TRP-3 proteins initially reside in some endoplasmic reticulum (ER)/Golgi-derived intracellular membranous organelles (MOs) in spermatids and later translocate to the plasma membrane upon sperm activation, leading to an increase in TRP-3 activity (87). Similar phenomena have been observed with several mammalian and fly TRP channels (78). Mouse TRPC2 has been shown to function as a sperm cation channel promoting calcium influx that triggers acrosome reaction in sperm (39). Although a defect in fertility has not been reported in knockout mice lacking individual TRPC channels, these channels may function redundantly to regulate fertilization in mammals. Indeed, most, if not all, mammalian TRPCs are expressed in sperm and have been suggested to play a role in sperm acrosome reaction, motility and sperm-egg fusion (76).

TRPV channels

osm-9 (*osm*otic avoidance abnormal) encodes the founding member of *C. elegans* TRPVs and is the first *trp* gene that has been functionally characterized in *C. elegans* (14). Subsequent database search has identified four additional *trpv/ocr* (*o*sm-9/*c*apsaicin receptor *r*elated) genes: *ocr-1* to *ocr-4* (73). Some important features of *C. elegans* TRPV channels are summarized in table 2.

osm-9 is expressed in multiple types of sensory neurons such as AWA, AWC, ASH, ADL, ADF, etc (14,73). In addition, *osm-9* is expressed in neuroendocrine cells in the gonad and rectal gland cells. Wild-type worms are attracted to volatile chemicals (chemosensation) through AWA and AWC neurons while avoiding high osmolarity (osmosensation), nose touch stimuli (mechanosensation) and chemical repellents (chemosensation) primarily through ASH neurons (3). *osm-9* and *ocr-2* mutants are defective in most, if not all, of the AWA- and ASH-mediated sensory responses (14,73). Thus, OSM-9 and OCR-2 may function as a polymodal sensor or modulator for chemosensation, osmosensation and mechanosensation in *C. elegans*. These functions appear to be mediated by distinct domains. For example, the N-terminal domain of OCR-2 is critical for osmosensation but not for chemosensation (67). This polymodal feature is reminiscent of that found in some mammalian TRPV channels, for example, TRPV1 that senses and integrates multiple types of noxious stimuli such as proton, heat and capsaicin (74). Remarkably, expression of human TRPV4 in ASH can functionally rescue the defects of *osm-9* mutants in osmosensation and mechanosensation (53).

OSM-9 and OCR-2 are also involved in social feeding behavior (19). In *C. elegans*, social feeding is promoted by adverse or stressful environmental cues. Two types of nociceptive neurons, ASH and ADL, play a central role in sensing harsh environment (19). Loss of OSM-9 or OCR-2 suppresses social feeding behavior in social strains (19). Worms avoid high O_2 level (29). Mutant alleles of *osm-9* and *ocr-2* are defective in this avoidance

behavior (59). OSM-9/OCR-2 channels have also been implicated in a form of sexual attraction behavior in which males are attracted to hermaphrodites presumably by sensing pheromones from hermaphrodites (84).

Although OSM-9 is required for responding to odorants (e.g. diacetyl and pyrazine) in AWA neurons, it is probably not the initial detector. G protein-coupled receptors (GPCRs) are likely the primary binding sites for these odorants at least for diacetyl, as a GPCR family gene *odr-10* is essential for diacetyl-triggered response *in vivo* and *in vitro* (3). In addition, chemosensory behaviors mediated by AWA and ASH depend on Gi-like proteins such as ODR-3 and GPA-3 (3). Moreover, a GPCR kinase (GRK-2) and RGS protein (RGS-3) regulate some of OSM-9-dependent behaviors (26,27), further suggesting that OSM-9 acts downstream of GPCRs. Regulation by G protein signaling has also been demonstrated in mammalian TRPVs, e.g. TRPV1 (10). Interestingly, some worm TRPV channels control GPCR expression in an activity-dependent manner. For example, *osm*-9 single and *ocr-2;ocr-1* double mutants abolish the expression of the diacetyl receptor ODR-10 in AWA neurons (73). Thus, TRPVs and chemoreceptors appear to regulate each other and may function in a cooperative fashion in chemosensation. As is the case with some mammalian TRPVs (6), OSM-9 and OCR-2 play a critical role in mechanosensation and are required for sensing nose touch (73). However, it is not clear whether they act as mechanoreceptors for nose touch or function downstream of mechanoreceptors.

GPCRs are not the only targets whose expression levels are regulated by OSM-9 and OCR-2 channels in an activity-dependent manner. In ADF neurons, OSM-9 and OCR-2 are important for serotonin (5HT) biosynthesis (89). The expression of *tph-1*, which encodes a key 5HT biosynthesis enzyme tryptophan hydroxylase, appears to be regulated by these two TRPV channels in ADF (89). Mutations of these two *trpv* genes greatly reduce the expression of *tph-1* and 5HT. Ectopic expression of mammalian TRPV2 can rescue the 5HT biosynthesis but not osmosensation or chemosensation phenotype in *ocr-2* mutants (67). A possible downstream effector of TRPV channels is *unc-43*, the only *C. elegans* CaMKII (89). One simple explanation is that OSM-9 and OCR-2 channels induce a Ca^{2+} influx, which activates CaMKII. CaMKII then stimulates *tph-1* transcription and 5-HT synthesis.

As discussed above, in many cells OSM-9 and OCR-2 function in a cooperative manner. In fact, all *ocr*-expressing neurons also express *osm-9*, but not *vice versa* (73). In cells co-expressing multiple TRPV channels, these channels may form heteromeric channels, which is common for many mammalian and fly TRP channels (28,51,69,86). In AWA and ASH neurons, OSM-9 and OCR-2 may directly interact to form heteromeric channels (73). The presence of one subunit is required for targeting the other to the cilia of these neurons (73). In a set of uterus-associated neuroendocrine cells, OCR-1, OCR-2 and OCR-4 appear to form heteromers without the involvement of OSM-9 (38). These three OCR channels regulate egg-laying behavior by acting downstream of G protein signaling to modulate neurotransmitter release from these endocrine cells (38). In a separate study, OCR-2 has been found to regulate peptide-hormone secretion and L1 larva starvation survival in ADL neurons, and this function is independent of OSM-9, OCR-1 and OCR-4 (50). Thus, *C. elegans* TRPV channels may form heteromeric channels in a cell-specific manner. Nevertheless, biochemical evidence supporting TRPV heteromerization has not been described. Notably, loss of OCR-2 extends adult lifespan, revealing a novel function of TRP family channels in longevity (50).

Many compounds from natural plants have been reported as agonists for mammalian TRPV channels, for instance, capsaicin (for TRPV1), camphor (for TRPV1 and TRPV3), and bisandrographolide (for TRPV4) (8,56,66). Similar pharmacological tools are still lacking for *C. elegans* TRPV channels. However, some 20-C polyunsaturated fatty acids (PUFAs)

may be endogenous modulators for these TRPV channels (42). For example, eicosapentaenoic acid (EPA) evokes calcium transients in ASH neurons that express OSM-9 and OCR-2, and these calcium transients are missing in *osm-9* mutants (42). While alternative explanations remain, one possibility is that OSM-9 channels may be directly gated by PUFAs. This can be tested in heterologous systems. However, functional expression of TRPVs (e.g. OSM-9 and OCR-2) in heterologous systems has been reported to be unsuccessful (14,73). It is possible that heterologous systems may lack accessory subunits and/or certain post-translational modification mechanisms that are needed for OSM-9/OCR-2 to function properly. Nevertheless, activation by PUFAs and other endogenous lipids is common for many mammalian and *Drosophila* TRP channels. For example, PUFAs directly activate TRP and TRPL channels in *Drosophila* (12), products of lipoxygenases directly activate rat TRPV1 (35), and anandamide and AA can activate mouse TRPV4 through their downstream metabolites epoxyeicosatrienoic acids (81).

While *C. elegans* TRPVs share many functional characteristics with their mammalian counterparts, there are differences between the two. For example, several mammalian TRPVs are gated by temperature (78); however, no *C. elegans* TRPV channel has been implicated in thermosensation, raising the possibility that TRPV channels in *C. elegans* may not directly participate in heat-sensing.

TRPM channels

The *C. elegans* genome encodes four TRPM members, *gon-2* (abnormal *gon*ad development), *gtl-1* (*g*on-*t*wo *l*ike), *gtl-2*, and *ced-11*(*ce*ll *d*eath abnormal). Table 3 summarizes some features of these channels. *gon*-2 alleles were isolated in a genetic screen for mutants with defects in gonad development (70). This gene was then found to encode a TRPM-like channel protein in *C. elegans* (83). Based on sequence alignment, GON-2 exhibits high homology to mammalian TRPM6 and TRPM7 channels but lacks the C-terminal kinase domain. GON-2 is highly expressed in the gonad and intestine where it promotes cell division and Mg^{2+} uptake, respectively (70,72,83). Mutations in *gon-2* cause an abnormal delay or absence of post-embryonic mitotic cell divisions in the gonad (70). It is plausible that cation influx through GON-2 may promote cell division. (83). Vertebrate TRPM7 also functions in development (36,78). Mutations in *gem-4* (*gon-2 e*xtragenic *m*odifier), a gene encoding the copine family of calcium-dependent phosphatidylserine binding proteins, can suppress the *gon-2* phenotype (11). As GEM-4 is predicted to be associated with the plasma membrane, one intriguing possibility is that GEM-4 may directly inhibit GON-2 activity.

GON-2 and GTL-1 govern Mg^{2+} homeostasis in the intestine. In worms lacking both GON-2 and GTL-1, a severe Mg^{2+} deficiency has been observed (72). Whole-cell recoding of cultured worm intestine cells shows that GON-2 mediates an outwardly rectifying non-selective cation current that is tightly regulated by Mg^{2+}, while GTL-1 underlies the Mg^{2+} responsiveness of the outwardly rectifying current (72). GON-2 and GTL-1 are also important for Ni^{2+} uptake by the intestine (72), a feature that has been observed with mammalian TRPM7. Similarly, mammalian TRPM6 and TRPM7 control Mg^{2+} homeostasis, and mutations in human TRPM6 have been identified in patients with hypomagnesemia and secondary hypocalcemia (62). Knocking out TRPM7 from a chicken B cell line leads to cell death, which can be rescued by Mg^{2+} supplement (63). Thus, it seems that the role of TRPM channels in Mg^{2+} homeostasis is conserved between *C. elegans* and vertebrates. Nevertheless, a recent study with TRPM7 conditional knockout mice shows that this is not the case in mice (36). In TRPM7-deficient thymocytes, both the acute uptake of Mg^{2+} and maintenance of cellular Mg^{2+} level are normal (36).

Posterior body-wall muscle contraction occurs rhythmically every 45-50 seconds to control defecation in *C. elegans*. This rhythmic activity is coupled to Ca^{2+} oscillations in intestinal cells (16,71,85). Mutations in *gon-2* and *gtl-1* disrupt the rhythmic activity and defecation, indicating an important role of these two TRPM channels in this motor program (48,72,85). Interestingly, mouse TRPM7 also plays a similar role in intestinal pacemaker cells (43). GON-2 and GTL-1 exhibit a high Ca^{2+} selectivity with a P_{Ca2+}:P_{Mg2+}>10 (72,85). Ca^{2+} influx through GON-2 and GTL-1 may directly activate IP_3 receptors (IP_3Rs) on the ER membrane to control Ca^{2+} oscillation frequency (23,48,85).

Relatively little is known about the other two *trpm* genes in *C. elegans*, *gtl-2* and *ced-11*. *gtl-2* is highly related to *gtl-1*. *ced-11* mutants are defective in programmed cell death (34,41). Although *ced-11* is predicted to encode a TRPM-like protein (31,34,41), the exact role of *ced-11* in programmed cell death remains unclear.

TRPN channels

TRP-4, the sole TRPN channel in *C. elegans*, shares ~40% sequence identity with zebrafish TRPN-1 and *Drosophila* NOMPC, both of which are mechanosensitive channels (64,79). Expression of TRP-4 can be detected in CEP, ADE, and PDE dopamine neurons, as well as DVA and DVC interneurons (52,79). Dopamine neurons are mechanosensory neurons with a morphology analogous to that of vertebrate hair cells in the inner ear (52,60). These neurons sense mechanical attributes imposed by the surface material on which worms navigate (60). As a result, worms slow down their locomotion speed when moving into areas with rough texture (e.g. bacteria lawn), a phenomenon called basal slowing response (60). TRP-4 is required for basal slowing response and acts in dopamine neurons to mediate this response, suggesting that TRP-4 is a mechanosensitive channel in dopamine neurons (52). This is further supported by calcium imaging experiments showing that gentle nose touch can induce calcium transients in the dopamine neuron CEP (44).

While the function of TRP-4 in the mechanosensory dopamine neurons is anticipated, the presumed identity of DVA and DVC as interneurons offers no clue as to what functions TRP-4 could mediate in these neurons. Notably, *trp-4* mutants express another interesting phenotype: mutant worms exhibit an abnormal body posture during locomotion, indicating a defect in proprioception (52). While proprioception has long been proposed to act in *C. elegans* to control locomotion, no proprioceptor has been identified in *C. elegans*, raising the question of whether proprioception is employed by *C. elegans* to regulate its locomotion behavior. TRP-4 offers a unique opportunity to address this question because of its relatively limited expression pattern and the proprioception phenotype observed in its mutant. It appears that TRP-4 acts in a single neuron DVA to regulate body posture during locomotion, and that body stretch stimulates DVA activity in a TRP-4-dependent manner (52). This identifies DVA as the first stretch-sensitive proprioceptor neuron in *C. elegans*, indicating that propricoption is indeed present in *C. elegans* to control locomotion. It is not known whether fish and fly TRPN channels regulate propriopcetion. Notably, *nompC* mutants exhibit an uncoordinated phenotype, raising the possibility that TRPN channels may also control proprioception in flies (79). DVA is unlikely the only proprioceptor neuron in *C. elegans*, as *trp-4* mutants and DVA-ablated worms retain the ability of executing coordinated sinusoidal movement (52). Additional proprioceptors must be present in *C. elegans* to mediate this function. Candidates include the undifferentiated processes of ventral cord motor neurons (9).

TRPA channels

Two *trpa* genes, *trpa-1* and *trpa-2* are present in the *C. elegans* genome. Some of their features are shown in table 4. The function and expression pattern of TRPA-2 have not been

described. TRPA-1 is expressed in multiple tissues, including pharyngeal muscle, body-wall muscle, rectal gland cells, vulval epithelium, amphid neurons, and phasmid neurons (45). This wide expression pattern is distinct from that of mouse TRPA1 which is enriched in sensory neurons (68). Loss-of-function mutations in *trpa-1* cause defects in mechanosensory behaviors, including head withdrawal and nose touch response (45). Interestingly, TRPA-1 acts in OLQ and IL neurons but not ASH neurons (45). Calcium imaging studies demonstrate that nose touch induces calcium transients in OLQ neurons. Although *trpa-1* mutant worms respond normally to the initial nose touch stimulus, they show a defect in sensing subsequent nose touch stimuli, indicating an important role for this channel in touch sensation in OLQ neurons (45). In heterologous systems (CHO cells), TRPA-1 can be activated by mechanical stimuli, suggesting that TRPA-1 may function as a mechanosensitive channel in *C. elegans* (45). Mammalian TRPA1 has also been implicated in mechanosensation (49). In CHO cells, TRPA-1 can act downstream of GPCRs (45), a feature that has also been observed with mammalian TRPA1 (78).

Mammalian TRPA1 can be directly activated by a large number of structurally unrelated chemicals that act by covalently modifying cysteine (Cys) residues located in the N-terminus of the channel (33,54). However, these residues are not conserved in *C. elegans* TRPA-1. It is possible that *C. elegans* TRPA-1 may not be sensitive to some of the mammalian TRPA1 agonists.

TRPP channels

Mammalian TRPPs are further divided into two groups. The polycystic kidney disease-1 PC-1/TRPP1 proteins contain 11 transmembrane domains and are structurally distant from TRP family channels. The other group, PC-2/TRPP2/PKD-2 proteins, consists of six transmembrane domains and is structurally related to other TRP channels. Homologues of both mammalian TRPP1 and TRPP2 are present in the *C. elegans* genome (*lov-1* and *pkd-2*, respectively). As TRPP1-like proteins are no longer considered as TRP channels (78), we will mainly focus on TRPP2/PKD-2.

PKD-2 is co-localized with LOV-1 in male-specific sensory neurons (5). *lov-1* and *pkd-2* single and double mutants exhibit identical male-specific mating defects, indicating that PKD-2 and LOV-1 act in the same pathway (4). Mammalian PC-1 and PC-2/TRPP2 also function in the same signaling cascade, perhaps as a heteromeric channel complex (13,17,78). In *C. elegans*, PKD-2 proteins are enriched in the cilia, and cilia targeting of PKD-2 is essential for PKD-2 function in male mating, revealing a critical functional site for PKD-2 (5). Subsequently, mammalian TRPP2/PC-2 has also been found to be targeted to the primary cilia of renal epithelia and interact with PC-1 to form a mechanosensitive channel (88). Thus, sensory function and cilia localization of TRPP2 appear to be evolutionarily conserved. Aided by powerful molecular genetic tools, a number of genes regulating cilia targeting of PKD-2 and LOV-1 have been identified in *C. elegans*. For example, KLP-6/kinesin-3, KIN-10/casein kinase-2 and TAX-6/calcineurin, all of which have mammalian homologues, regulate PKD-2 cilia targeting and function (2). Clearly, *C. elegans* presents a powerful genetic model for studying cilia development and function.

Mammalian TRPP2 has been shown to form Ca^{2+}-permeable channels both on ER and plasma membrane (46,57). *C. elegans* PKD-2 also promotes Ca^{2+} release from ER stores in dissociated *C. elegans* cells, although the signaling events triggering PKD-2 activation remain unknown (47). The male neurons expressing PKD-2 are mechanosensory/chemosensory neurons (5). Interestingly, when expressed in the cilia of collecting duct-derived epithelial cells of mouse kidney, TRPP2 mediates a flow-induced Ca^{2+} entry (57), suggesting that TRPP2 channels may form a stretch-activated cation channel in the cilia.

TRPML channels

Mutations in mucolipin-1 (TRPML1) lead to an autosomal recessive lysosomal storage disease, mucolipidosis type IV (MLIV) (1). *cup-5*, the *C. elegans* ortholog of mammalian *trpml1*, was identified by two independent groups through positional cloning (24,32). Ectopic expression of human TRPML1 can rescue *cup-5* mutant phenotypes (32).

Mammalian TRPML1 is ubiquitously expressed in the late endosomes and lysosomes of all tissues where it forms a Fe^{2+} release channel (20). CUP-5 is widely expressed in multiple cell types, including coelomocytes, a group of scavenger cells that continuously endocytose fluid from the pseudocoelom (24). Mutations in *cup-5* cause accumulation of large vacuoles composed of hybrids of late endosomes and lysosomes (75). CUP-5 is essential for lysosome biogenesis/function, which may hold true for mammalian TPRML1 (75). In addition to a defect in lysosome biogenesis/function, loss of CUP-5 leads to lethality and accumulation of apoptotic cells (32). These features have also been observed in MLIV patients, as well as in a *Drosophila* model of MLIV which shows that defective clearance of apoptotic cells underlies motor defects in flies lacking TRPML1 (77).

A genetic screen for suppressors of *cup-5* has identified an ABC transporter MRP-4 (61). Lack of MRP-4 suppresses the lysosomal degradation defect and the corresponding lethality in *cup-5* mutant worms. MRP-5 is localized to the endolysosomal compartments where it may function to uptake various substrates. Loss of CUP-5 leads to up-regulation of MRP-5, which may contribute to the lysosomal degradation defect. Currently, there is no effective treatment for MLIV. These results identify MRP-4/ABC transporter as a potential target for treating this deadly disease.

Concluding remarks

TRP channels play important roles in sensing a wide range of physical and chemical stimuli from both external and internal sources (13,17,78). Functional studies have implicated *C. elegans* TRP channels in a variety of behavioral and physiological processes (41). In particular, worm TRP channels are extensively involved in regulating sensory perception, including chemosensation, osmosensation, touch sensation and proprioception. In this respect, TRP channels are molecular sensors for *C. elegans*, a feature shared by their mammalian and fly counterparts (13,17,78). Thus, TRP channels play evolutionarily conserved roles in the animal kingdom. A unique property of some mammalian TRP channels (e.g. TRPV, TRPA and TRPM) is that they can be activated or modulated by multiple types of sensory stimuli, which makes them polymodal sensors (58). This also appears to be case for some *C. elegans* TRPV channels. Polymodal sensitivity may be a common feature for some TRP channels.

Characterization of *C. elegans trp* mutants have also revealed novel biological functions of TRP channels such as drug dependence, sperm-egg fusion, social feeding, proprioception, longevity, apoptosis, cilia function, etc. The precise mechanisms underlying most of these TRP functions remain to be elucidated. It would be interesting to see whether some of these functions are conserved in vertebrates.

Thus far, very few *C. elegans* TRP channels have been characterized in heterologous systems. Electrophysiological analysis of *C. elegans* TRP channels in native tissues has not been described. As such, very little is known about the biophysical properties, particularly the gating mechanisms, of most *C. elegans* TRP channels. Nevertheless, because of the thorough understanding of *C. elegans* biology and the wealth of genetic tools, *C. elegans* provides an excellent animal model to study the biological function and regulation of TRP channels *in vivo*.

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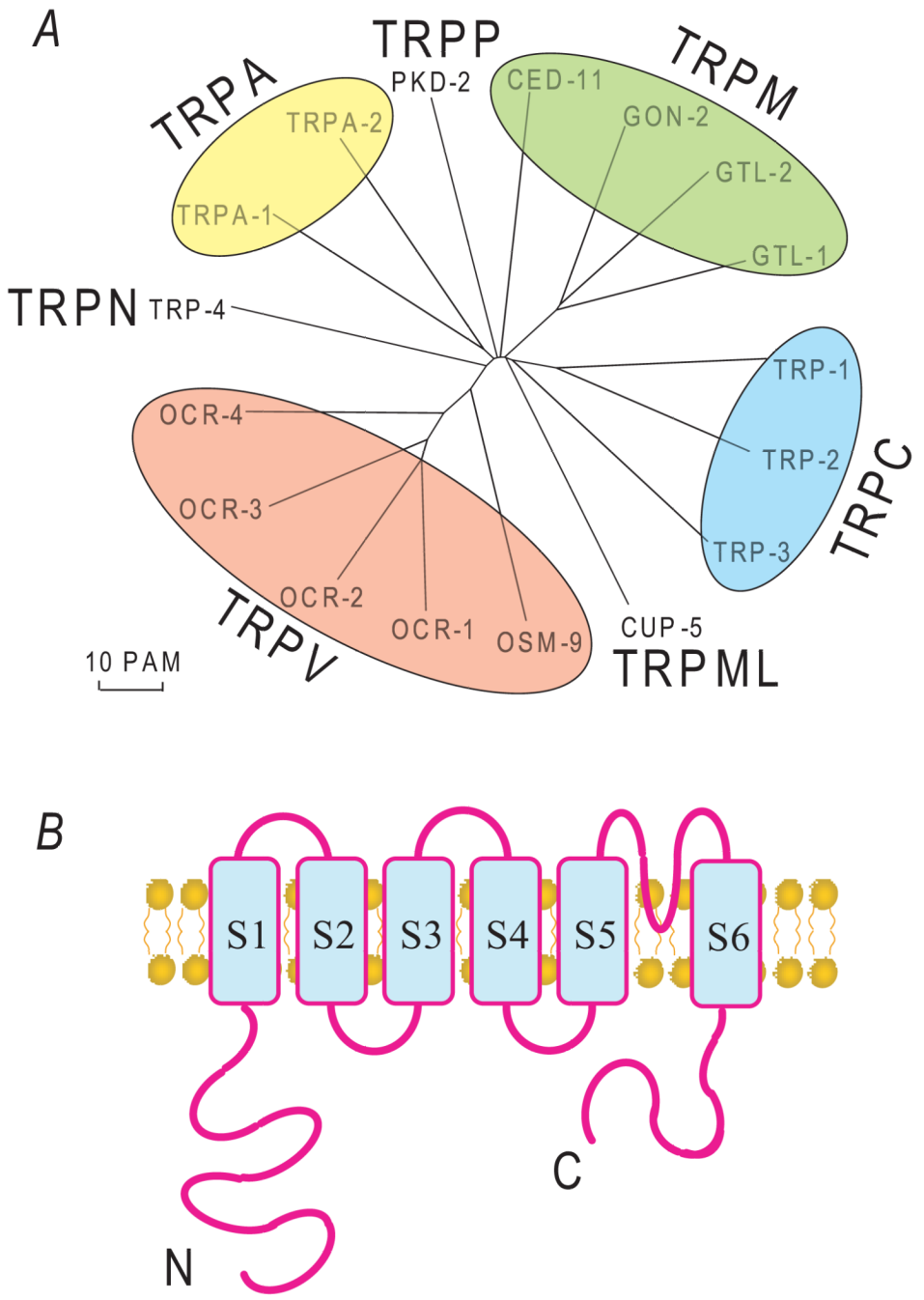

Figure 1. TRP channels in *C. elegans*

A, the amino acid sequences of 17 *C. elegans* TRP channels were aligned up using ClustalW. Unrooted dendrogram plot was generated using on-line multiple sequence alignment service (http://align.genome.jp/). The evolution distance is indicated by the branch length in point accepted mutations (PAM) units. ***B***, a schematic showing predicted topology of a TRP channel subunit with six transmembrane domains (S1-S6) and a pore loop buried in membrane lipids.

Table 1

TRPC channels in *C. elegans*

	trp-1	**trp-2**	**trp-3**
Accession no. (Swiss-Port)	P34586	Q8I6Y9	Q21070
Expression	interneurons motor neurons pharyngeal neurons sensory neurons muscles	similar to *trp-1*	sperm
Function	nicotine -dependence	nicotine -dependence	sperm-egg fusion
Regulation	nicotine, Gq/11, PLCβ heteromerization?	nicotine, Gq/11, PLCβ heteromerization?	receptor- and store-operated, translocation regulated by sperm activation
Reference	(13,24,86)	(13,24,86)	(86)

Table 2

TRPV channels in *C. elegans*

	osm-9	**ocr-1**	**ocr-2**	**ocr-3**	**ocr-4**
Accession no. (Swiss-Port)	O17469	P90784	O61220	Q22374	Q9N3Y9
Expression	multiple neurons, endocrine cells, rectal gland cells	AWA, ADL, endocrine cells	AWA , ADL, ASH, ADF, PHA, PHB, endocrine cells	rectal gland cells	OLQ, endocrine cells
Function	chemo-, mechano-, osmo-sensations, social feeding, gene expression, sexual attraction,	chemo-sensation, egg-laying	chemo-, osmo-, mechano-sensations, egg-laying, social feeding, gene expression, hormone secretion, longevity	NA	egg-laying
Regulation	PUFAs ODR-10, ODR-3 RGS-3, GRK-2, heteromeri-zation	heteromeri-zation	PUFAs ODR-10, ODR-3, heteromeri-zation	NA	heteromeri-zation
Reference	(13,18,37) (41,59,73) (83,88)	(37,73)	(18,37,41) (48,59,73)	(73)	(37,73)

Table 3

TRPM channels in *C. elegans*

	gon-2	**gtl-1**	**gtl-2**	**ced-11**
Accession no. (Swiss-Port)	Q93971	Q17652	Q20766	P34641
Expression	gonad, intestine	intestine	excretory canal, pharynx	widely expressed during embryogenesis
Function	cell division, Mg^{2+} homeostasis, defecation rhythm	Mg^{2+} homeostasis, defecation rhythm	NA	apoptosis
Regulation	GEM-4, Mg^{2+}	Mg^{2+}	NA	NA
Reference	(70,72,84)	(84)		(30)

Table 4

TRPN, TRPA, TRPP and TRPML channels in *C. elegans*

	TRPN	TRPA		TRPP	TRPML
	trp-4	**trpa-1**	**trpa-2**	**pkd-2**	**cup-5**
Accession no. (Swiss-Port)	Q9GRV5	Q18297	Q21517	Q9U1S7	Q8T666
Expression	dopamine neurons, DVA, DVC, etc.	sensory neurons, muscles, other tissues	NA	male specific sensory neurons	multiple cells
Function	proprioception, basal slowing response	nose touch sensation, head withdrawal	NA	mating behavior	lysosomal function, apoptosis
Regulation	stretch, mechanical attributes from texture	mechanical stimuli, G protein signaling	NA	LOV-1, KLP-6, KIN-10, TAX-6	pH, MRP-4
Reference	(50)	(44)		(2,3,6,56)	(23,31,75)