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TRP CHANNELS IN *C. ELEGANS*

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■ **Abstract** The TRP (transient receptor potential) superfamily of cation channels is present in all eukaryotes, from yeast to mammals. Many TRP channels have been studied in the nematode *Caenorhabditis elegans*, revealing novel biological functions, regulatory modes, and mechanisms of localization. *C. elegans* TRPV channels function in olfaction, mechanosensation, osmosensation, and activity-dependent gene regulation. Their activity is regulated by G protein signaling and polyunsaturated fatty acids. *C. elegans* TRPPs related to human polycystic kidney disease genes are expressed in male-specific neurons. The KLP-6 kinesin directs TRPP channels to cilia, where they may interact with F0/F1 ATPases. A sperm-specific TRPC channel, TRP-3, is required for fertilization. Upon sperm activation, TRP-3 translocates from an intracellular compartment to the plasma membrane to allow store-operated Ca^{2+} entry. The TRPM channels GON-2 and GTL-2 regulate Mg^{2+} homeostasis and Mg^{2+} uptake by intestinal cells; GON-2 is also required for gonad development. The TRPML CUP-5 promotes normal lysosome biogenesis and prevents apoptosis. Dynamic, precise expression of TRP proteins generates a remarkable range of cellular functions.

OVERVIEW: *C. ELEGANS* AS A MODEL SYSTEM FOR UNDERSTANDING TRP FUNCTION

An astonishing variety of biological functions are associated with the conserved TRP (transient receptor potential) channel superfamily, a class of channels defined by sequence similarity to the *Drosophila* phototransduction channel TRP (1, 2). TRPs assemble into homo- and heterotetramers to form cation-selective ion channels that can be regulated by thermal stimuli, mechanical stimuli, lipids, lipid derivatives, voltage, pH, phosphorylation, and intracellular Ca^{2+} stores (3). Some TRPs serve as integrators of multiple regulatory pathways, and others are activated by one predominant pathway. TRP proteins are linked to many sensory modalities: vertebrate heat sensation (4–8), cold sensation (9, 10), osmosensation (11, 12), pheromone sensation (13) and hearing (14); insect phototransduction (1, 15, 16), mechanosensation (17), thermosensation (18) and hearing (19); and nematode olfaction, mechanosensation, and osmosensation (20–22). Although TRP

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functions have been studied most extensively in sensory neurons, vertebrate TRP channels also regulate cardiovascular (23, 24), renal (25), and lysosomal functions (26).

The TRP superfamily can be divided into seven families of channels based on sequence similarity. In humans, six TRP families encode a total of 28 channel subunits: TRPC (classical/short; seven members including a pseudogene), TRPV (vanilloid; six members), TRPM (melastatin/long; eight members), TRPML (mucolipin; three members), TRPP (polycystin; three members), and TRPA (one member) (27). Nonmammalian vertebrates also have a TRPN family (one member) (28). All TRP members have six predicted transmembrane domains; several families have a variable number of ankyrin motifs, suggested to participate in protein-protein interactions (Figure 1). Outside of these core regions, members of individual TRP families may share other motifs, such as coiled-coil domains. *Caenorhabditis elegans* has members of all seven known TRP families as well as novel TRP genes (Figure 1), and mutants are available for many of these loci. Because of the simple anatomy of *C. elegans*, the functions of these channels can be studied at single-cell resolution. Several *C. elegans* TRP channels have been studied in nonneural tissues, which may provide insight into analogous cellular functions of mammalian relatives. *C. elegans* studies of TRP channels have focused less on the molecular gating and biophysical properties of the channels and more on their integration into cellular pathways and neural circuits. As such, they are a useful complement to biophysical and pharmacological studies of mammalian counterparts.

C. ELEGANS TRPV CHANNELS FUNCTION IN OLFACTION AND NOCICEPTION

The TRPV gene *osm-9* was identified contemporaneously with its mammalian homolog TRPV1 (VR1), defining the first typical family beyond TRPC channels (4, 20). *osm-9* mutants have abnormal olfactory responses to all odors sensed by a class of ciliated neurons referred to as AWA neurons (20). The OSM-9 protein is localized to AWA sensory cilia (Figure 2), consistent with a role in olfactory signal transduction. In addition, *osm-9* mutants have a near-complete defect in the functions of ciliated sensory neurons called ASH neurons that act as polymodal nociceptors. ASH neurons mediate behavioral avoidance of high osmolarity, mechanical stimuli, noxious odors, heavy metals, bitter substances, and acid pH (20, 29–31). The OSM-9 protein is localized to ASH sensory cilia and is required for primary ASH sensory signal transduction—a nociceptive function analogous to the function of mammalian TRPV1 (32).

In addition to *osm-9*, the *C. elegans* genome encodes four other TRPV genes: *ocr-1*, *ocr-2*, *ocr-3*, and *ocr-4* (21). Each *ocr* gene is expressed in a subset of the cells that express *osm-9*, suggesting that *ocr* genes usually function together with *osm-9*. This prediction is valid for the *ocr-2* gene, which is expressed with *osm-9*

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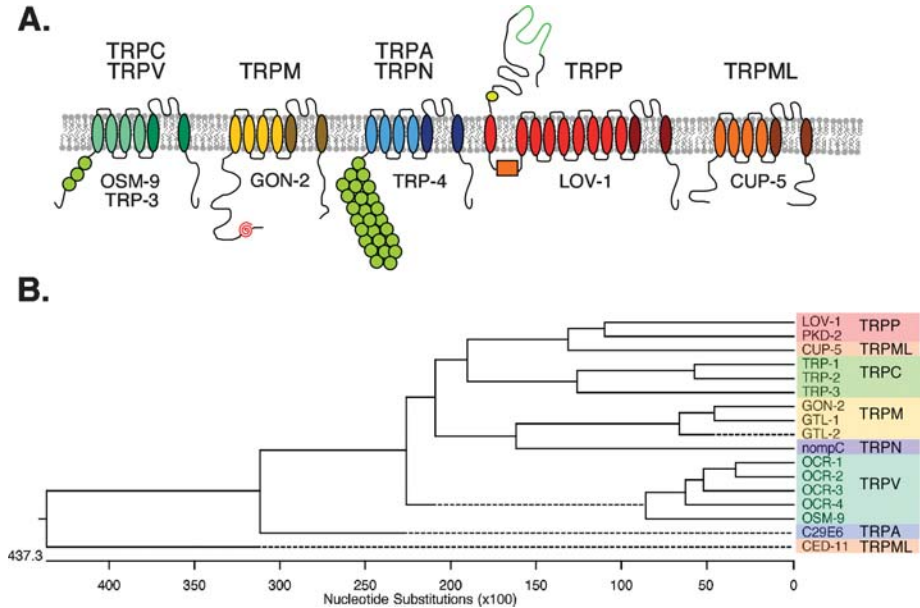

Figure 1 TRP structure and select *C. elegans* TRP channels. (*A*) Schematic domain structures for selected *C. elegans* TRP proteins. The cytoplasmic N′ region of several TRP families contains a variable number of ankyrin repeats (*green circles*). The TRPP protein LOV-1 has a large extracellular domain containing serine/threonine-rich (*green*) and GPS (*yellow*) regions as well as a total of 11 predicted transmembrane domains. Channel regions have six transmembrane domains, with S5 and S6 gate domains flanking a pore-loop selectivity filter. The transmembrane domains and pore loop have the strongest conservation among TRP family channels. The cytoplasmic C′ region varies among families and may contain lipid-binding motifs (*orange box*), coiled-coil domains (*red coil*), or other functional structures. (*B*) Alignment of *C. elegans* TRP channels. Conserved transmembrane regions were identified with SMART analysis and refined with NCBI CDD/reverse psi-BLAST. ClustalW was used to align transmembrane domains, and the results are presented as a phylogram. *C. elegans* has at least six candidate TRP genes from novel families that are entirely uncharacterized; these are omitted from the figure for clarity and are not discussed in the text.

in the ASH and AWA sensory neurons (Figure 2). Animals mutant for *ocr-2* have defects in nociception and olfaction that are similar to, though slightly less severe than, the defects in *osm-9* mutants. The similar mutant phenotypes of *osm-9* and *ocr-2* suggest that these genes may form heteromeric channels in ASH and AWA, although there is no direct biochemical evidence for this association. Increasing evidence suggests that many TRP channels may be heteromeric, including channels combining *Drosophila* TRP and TRPL as well as channels combining mammalian TRPC1 and TRPC5 (33, 34).

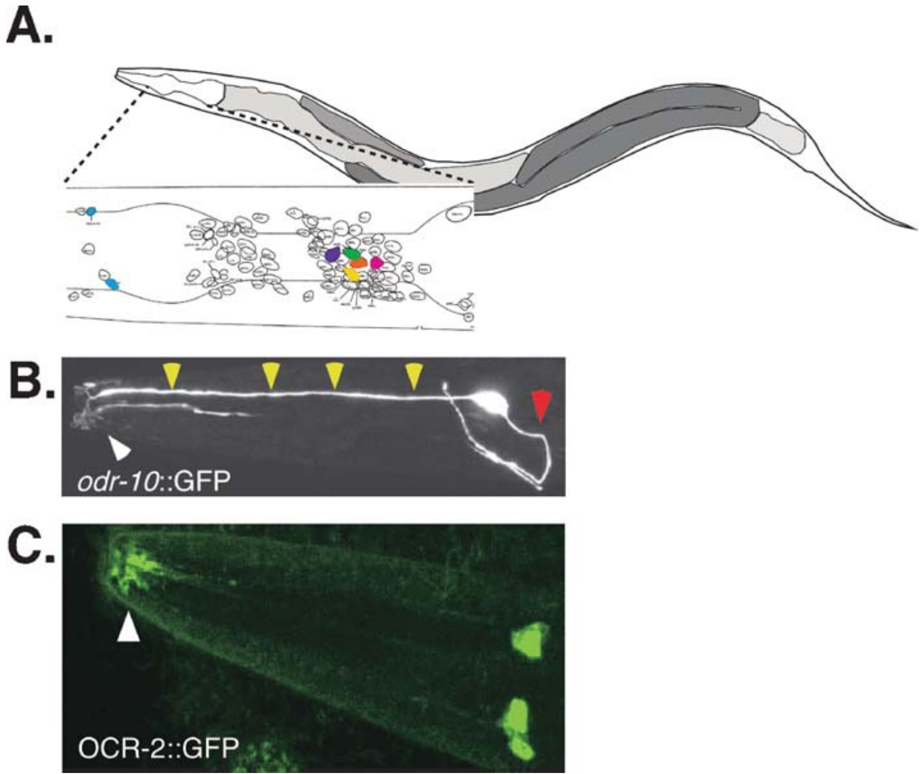

Figure 2 *C. elegans* TRPV proteins are expressed in sensory cilia. (*A*) Schematic diagram of a hermaphrodite *C. elegans*, highlighting a subset of anterior neurons with TRPV channel expression that are mentioned in the text (AWA, *green*; ASH, *orange*; ADF, *purple*; ASE, *pink*; AWC, *yellow*; OLQ, *blue*). (*B*) Confocal image of an AWA olfactory neuron expressing GFP driven by the *odr-10* promoter. The axon (*red arrow*), dendrite (*yellow arrows*), and sensory cilia (*white arrow*) are visible. (*C*) Confocal image of ASH and AWA sensory neurons expressing an OCR-2::GFP fusion protein. Note prominent expression of the OCR-2 protein in cilia (*arrowhead*) and cell bodies; the axons and dendrites have little OCR-2 protein.

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In AWA and ASH neurons, both OSM-9 and OCR-2 proteins are enriched in sensory cilia (21). OSM-9 and OCR-2 mutually depend on each other for localization to cilia rather than to the cell body. Some neurons normally express the *osm-9* gene in the absence of any *ocr* gene, and in these neurons, OSM-9 protein is found in the cell body. However, ectopic expression of OCR-2 in one such cell class, the AWC chemosensory neurons, is sufficient to drive OSM-9 to the cilia. These findings suggest a physical interaction between the OSM-9 and OCR-2 subunits that mediates their localization.

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G PROTEIN–COUPLED LIPID SIGNALING PATHWAYS REGULATE TRPV CHANNEL SIGNALING

OSM-9 and OCR-2 have not been amenable to electrophysiological analysis in heterologous cells, and as a result, the molecular regulation of OSM-9/OCR-2 is only partly understood. In AWA olfactory neurons, *osm-9* and *ocr-2* act downstream of G protein–coupled odorant receptors, probably as the olfactory transduction channel (20, 35). A similar role downstream of G protein–coupled receptors is likely in some forms of ASH nociception, particularly the avoidance of noxious odors (36). The role of OSM-9/OCR-2 in detecting physical stimuli such as high osmolarity and nose touch may mean that these channels directly sense force. The cytoplasmic OSM-10 protein is required only for osmosensation, suggesting that a specialized sensory apparatus helps OSM-9/OCR-2 sense osmotic stimuli (37).

Genetic analysis indicates that sensory G proteins may activate OSM-9 and OCR-2 by mobilizing specific polyunsaturated fatty acids (PUFAs). *C. elegans* mutants in the omega-3 lipid desaturase enzyme *fat-3* are deficient in long-chain PUFAs. Like TRPV mutants, *fat-3* mutants show pronounced defects in ASH nociceptive behaviors and AWA olfactory behaviors as well as primary defects in ASH sensory transduction measured by Ca^{2+} imaging (38). PUFAs stimulate rapid, TRPV-dependent Ca^{2+} transients in the ASH neurons and induce TRPV-dependent avoidance behaviors indicative of ASH activation. A battery of PUFA biosynthetic mutants, as well as acute rescue of *fat-3* mutants with dietary lipid supplementation, have implicated the omega-3 and omega-6 PUFAs arachidonic acid and eicosapentaenoic acid in OSM-9 TRPV signaling. The exact enzyme that mobilizes these PUFAs downstream of G proteins is unknown. The physiological mechanisms underlying the documented human health benefits of dietary omega-3 fatty acids are mysterious. By analogy with *C. elegans*, TRP channels that act in inflammation and cardiovascular regulation may represent molecular targets for dietary PUFAs in humans.

TRPV CHANNELS REGULATE TRANSCRIPTION AND MODULATE COMPLEX BEHAVIORS

In addition to their roles in sensory transduction, *osm-9*, *ocr-2*, and *ocr-1* regulate the transcription of sensory genes. *osm-9* and *ocr-2* mutants have reduced expression of the G protein–coupled receptor ODR-10 (which recognizes the odorant diacetyl) in AWA olfactory neurons (21). *ocr-1*, which is expressed in AWA but has no detectable role in AWA olfactory signaling, also affects the level of *odr-10* expression. *osm-9* and *ocr-2* also stimulate expression of the serotonin biosynthetic gene *tph-1* (encoding tryptophan hydroxylase) in ADF neurons, a pair of ciliated chemosensory neurons (39). *osm-9* and the *ocr* genes are likely to act in activity-dependent gene expression pathways that link sensory stimulation to patterns of gene expression. The Ca^{2+}/calmodulin-dependent kinase CaMKII

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functions downstream of OSM-9 and OCR-2 in the signaling pathway from sensory transduction to gene expression in ADF neurons (39). In one straightforward model, Ca^{2+} entry through OSM-9/OCR-2 channels could activate CaMKII to initiate transcriptional changes.

The ability of OCR-2 to regulate gene expression in ADF neurons can be separated from some of its other sensory functions. A point mutation in an N-terminal helical region of OCR-2 eliminates its ability to stimulate *tph-1* expression but does not diminish AWA olfactory function or cilia localization of the OCR-2 protein (40). Conversely, inserting the N-terminal helical region of OCR-2 into the related OCR-4 protein makes OCR-4 competent to stimulate *tph-1* expression.

In addition to their primary sensory roles, OSM-9 TRPV channels can affect sensory adaptation after prolonged exposure to an odor or taste. *osm-9* is expressed in many *C. elegans* ciliated neurons whose sensory transduction is mediated by cGMP and cGMP-gated channels (20). In two of these cGMP signaling neurons, the AWC olfactory neurons and the ASE gustatory neurons, *osm-9* is not required for primary sensory signaling but is required for sensory adaptation (41, 42). Neurons that use TRPV channels in adaptation express only *osm-9*, whereas neurons in which TRPV channels are primary transduction channels express both *osm-9* and at least one *ocr* gene. This distinction may be related to the preferential ciliary localization of OSM-9/OCR-2 complexes, as described above.

Another modulatory function for *osm-9* and *ocr-2* is their ability to regulate aggregation, or social behavior (43). Some natural isolates of *C. elegans* form aggregates of dozens of animals when they forage on bacteria, the "social" phenotype (44). Mutations in *osm-9* or *ocr-2* suppress aggregation, at least partly because of TRPV function in the ASH nociceptive neurons (43). Aggregation requires at least three different classes of sensory neurons, including TRPV-dependent nociceptive neurons, oxygen-sensing neurons that signal using a soluble guanylate cyclase (45), and a third neuronal class (46). TRPV-dependent nociception, oxygen sensation, and signals from food are integrated to produce context-dependent aggregation behavior.

PURSUING THE MAMMALIAN ANALOGY: ORTHOLOGY BETWEEN TRPVS?

Sequence analysis suggests that the common ancestor of mammals and invertebrates had one or two TRPV genes; there are no clear orthologies between individual mammalian and nematode TRPVs. Nonetheless, experiments using heterologous expression of mammalian channels in *C. elegans* neurons have revealed functional analogies between different mammalian TRPVs and *C. elegans* TRPVs.

The first experiment of this type involved the expression of rat TRPV1 in ASH nociceptive neurons (21). TRPV1 has a role in pain sensation, responding to irritants such as capsaicin. Rat TRPV1 expressed in ASH functions as a capsaicin-gated channel and can cause *C. elegans*, which is normally oblivious to capsaicin,

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to avoid the irritant. The behavioral response to this artificial activation of ASH is strikingly similar to the avoidance of repellents normally sensed by ASH. When expressed in ASH, rat TRPV1 functions independently of native ASH signal transduction pathways and cannot substitute for the normal functions of either *osm-9* or *ocr-2* (21).

By contrast, expression of the rat osmosensory channel TRPV4 in ASH nociceptive neurons can rescue the osmosensitivity and mechanosensitivity of *osm-9* mutants, although the channel cannot rescue their G protein–mediated odorant responses (47). TRPV4 requires endogenous ASH signaling molecules to perform this function, but it changes the threshold for osmosensation to match the mammalian threshold rather than that of *C. elegans*. Thus, TRPV4 functions as a partial *osm-9* ortholog, while retaining a distinct sensory signature. These results place TRPV4, and by implication OSM-9, very close to the primary event in osmosensation.

Finally, expression of mouse or human TRPV2 in ADF neurons can partially rescue the defect in *tph-1* gene expression that is observed in *ocr-2* mutants (40). As does endogenous *ocr-2*, TRPV2 requires *osm-9* for full function in ADF, again suggesting that TRPV2 can be integrated into endogenous *C. elegans* signaling pathways. The endogenous function of mammalian TRPV2 is not understood; potential analogies with OCR-2 may be explored further.

TRPP CHANNELS ARE REQUIRED FOR MALE MATING BEHAVIOR

Mutations in the two genes PKD1 and PKD2 account for 95% of the occurrences of human autosomal dominant polycystic kidney disease, one of the most common inherited genetic disorders (48). PKD1 and PKD2 encode the polycystins, large multidomain proteins that define the TRPP family of channels. Polycystic kidney disease is associated with fluid-filled cysts in the kidneys and other tissues. The mammalian polycystin-1 and polycystin-2 proteins are present in the cilia of renal cells (49, 50), where they have been proposed to act in intracellular traffic, fluid accumulation, or ion transport, or as generators or sensors of force. *C. elegans* has homologs of each of these genes, which are called *lov-1* (PKD1) and *pkd-2* (PKD2) (Figure 3). These TRPP proteins underlie the behavior that male worms exhibit when they encounter a hermaphrodite.

Male *C. elegans* use an elaborate sensory apparatus in their tail to execute a stereotyped search for the hermaphrodite vulva. This search is followed by spicule insertion and sperm release (51). *lov-1* and *pkd-2* males have defective responses to contact with a hermaphrodite, whereas other TRP mutants such as *osm-9* have normal male mating behavior (22, 52). *lov-1* and *pkd-2* are expressed in the cilia of the male-specific CEM, HOB, and ray neurons, which may have mechanosensory functions (22, 52). *lov-1; pkd-2* double mutants show the same behavioral defects as do the single mutants, consistent with the possibility that each has essential

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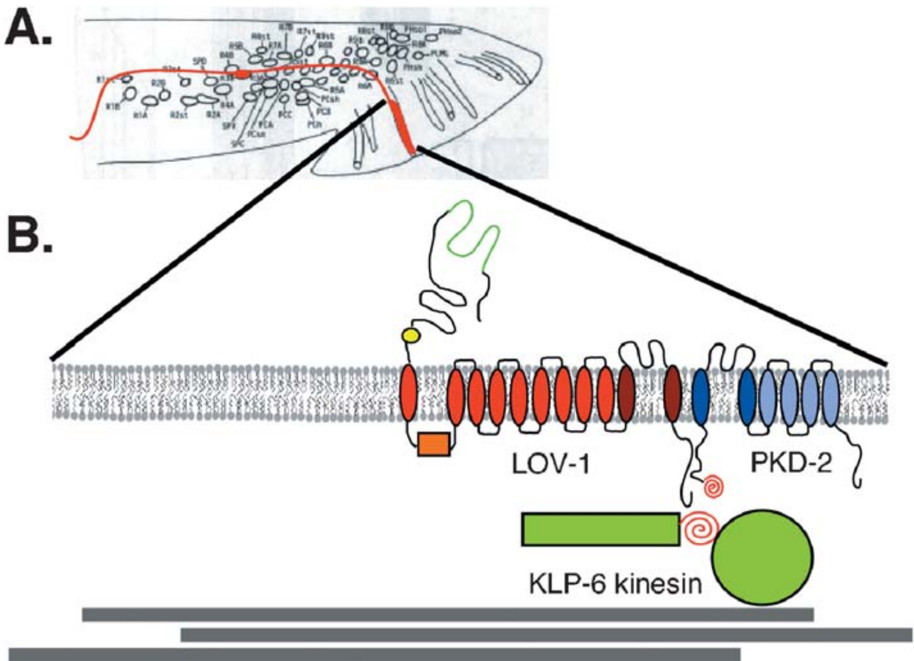

Figure 3 Polycystin localization in the cilia of male-specific neurons: (*A*) Schematic diagram of male tail, highlighting one of the ray neurons that expresses *lov-1* and *pkd-2* TRPP proteins. The cilia extend into the fan-shaped male tail used for mating. (*B*) Enlarged view of ray neuron sensory cilia and proposed LOV-1/PKD-2 interactions. The KLP-6 kinesin is required for TRPP cilia localization, perhaps by transporting a LOV-1/PKD-2 complex to cilia along microtubules (*gray lines*). Red coils, coiled-coil domains; orange box, PLAT domain.

functions in the same signaling complex. Like their mammalian orthologs, PKD-2 and LOV-1 proteins are enriched in sensory cilia and require intact cilia for their function (53, 54). Cilia morphology appears normal in *lov-1* and *pkd-2* mutants, suggesting that they have an acute sensory role rather than a function in ciliogenesis.

The relationship between human kidney function and *C. elegans* mating is most easily explained by suggesting a special relationship between TRPP channels and force-sensing cilia. In this scenario, TRPP channels sense both fluid flow in the kidneys and mechanical stimuli during mating. A similar role is suggested by the role of TRPP channels in early vertebrate development. Ciliated cells in Hensen's node of vertebrates establish the left-right asymmetry of the developing embryo (55, 56). Some of these nodal cilia are motile, despite a 9 + 0 arrangement of microtubules that is typical for nonmotile cilia (a morphology shared by *C. elegans* cilia). Mouse polycystin-2 mutants have defects in left-right asymmetry, and polycystin-2 is expressed in nodal cilia, consistent with a role in left-right

patterning (57). The polycystin complex is thus a candidate to generate or sense motility in nodal cilia.

TRPP CILIA LOCALIZATION AND A POSSIBLE RELATIONSHIP WITH THE F0/F1 ATPASE

The mechanisms by which membrane proteins such as LOV-1 and PKD-2 are localized to cilia are only partly understood. Targeted transport vesicles may carry G protein–coupled receptors and TRPV channels from the Golgi to the base of the cilia; an AP-1 adaptor complex appears to be essential for cilia-directed transport (58). Within cilia, proteins are transported by the intraflagellar transport (IFT) protein complex, with kinesins that move to the cilia tip and a dynein that moves back to the base of the cilia (59, 60). An uncharacterized transition occurs between the dendrite and the base of the cilia to allow membrane proteins access to the cilia. A genetic screen for mutants with *pkd-2*-like mating defects uncovered one potential player in this process, the kinesin KLP-6, which affects PKD-2 localization to cilia (61) (Figure 3). KLP-6 is related to the axonal synaptic vesicle transport kinesin UNC-104/Kif1A. In *klp-6* mutants, PKD-2 often accumulates at the base of the cilia rather than the cilia proper, and it is also more prevalent in the dendrites. Cilia morphology is normal in *klp-6* mutants, implicating *klp-6* in the function rather than development of the cilia. *lov-1*, *pkd-2*, and *klp-6* are all expressed in a subset of ciliated neurons, most prominently in the male mating neurons. These results raise the possibility that various motor proteins may have selective transport properties in different ciliated cells.

A priority in the further understanding of TRPPs is the identification of additional signaling components in the TRPP complex. Within the LOV-1 (polycystin-1) protein is a cytoplasmic loop called the PLAT (polycystin/lipoxygenase/a-toxin) domain. A yeast two-hybrid screen with the LOV-1 PLAT domain yielded an F1 ATP synthase subunit, ATP-2 (62). Human polycystin-1 can also bind ATP-2. The F0/F1 ATPase is an essential component of the mitochondrial respiratory chain, and because mitochondria are absent from cilia, this interaction looks odd, perhaps spurious. However, unlike other mitochondrial enzymes, both ATP-2 and the transmembrane F0 subunit ASG-2 can be detected in cilia, and surface expression of the F0/F1 ATPase has been reported in mammalian cells as well (63, 64). Reducing ATPase function in male sensory neurons with RNAi attenuates male mating, leading Hu & Barr (62) to suggest that ATPase function in cilia may promote LOV-1/PKD-2 function. The F0/F1 ATPase is best known for its coupling of a mitochondrial pH gradient to ATP production in respiration, and the presence of this ATPase in cilia may be indicative of a high ATPase requirement in this compartment (62). Alternatively, cilia may use the F0/F1 ATPase in a distinct capacity, such as its capacity to act as an ATP- and pH-regulated molecular motor (65, 66).

Genetic and biochemical studies should identify additional components of the TRPP signaling complex. For example, microarray analysis has identified four

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genes that are coexpressed with *lov-1* and *pkd-2* in male-specific neurons (67); Portman & Emmons (67) propose that these novel secreted proteins are components of an extracellular force-sensing matrix surrounding sensory cilia.

TRPC AND TRPM CHANNELS: A FERTILE FIELD

The TRPC protein encoded by *trp-3/spe-41* is found exclusively in sperm and is required for a late step in fertilization (68) (Figure 4). Both male and hermaphrodite *C. elegans* produce sterile sperm in *trp-3* mutants. Unlike TRPP *lov-1* and *pkd-2* mutants, male *trp-3* mutants execute normal behavioral mating and transfer sperm to hermaphrodites during mating. Moreover, *trp-3* mutants have motile, morphologically normal sperm. These sperm are even capable of competing with other sperm for a position in the spermatheca, a small compartment near the oocytes where hermaphrodites store sperm prior to fertilization. These experiments suggest that *trp-3* sperm have problems at a step between contact with the oocyte and fertilization.

Ca^{2+} imaging of normal *C. elegans* sperm reveals increased Ca^{2+} influx if internal Ca^{2+} stores are depleted with drugs such as thapsigargin (68). This influx is diagnostic of store-operated Ca^{2+} channels, an important class of homeostatic channels found in many cell types. In *trp-3* mutant sperm, this influx is lost, suggesting that TRP-3 functions as a store-operated channel in *C. elegans* sperm. When heterologously expressed in HEK293 cells, TRP-3 promotes Ca^{2+} influx in response to store depletion and Gq pathway activation. Studies of mammalian TRPC subunits have provided conflicting evidence about the role of Ca^{2+} stores in regulating this family (69), so it is gratifying to see that a native TRPC protein functions as a store-operated channel in its endogenous context.

The subcellular localization of TRP-3 is developmentally regulated, providing an additional layer of channel regulation (68). The TRP-3 protein is found in vesicular compartments of immature spermatids and translocates to the plasma membrane in mature sperm during sperm activation. Mammalian TRPC5 and *Drosophila* TRPL (TRP-like) dynamically regulate their subcellular localization upon stimulation, and similar possibilities have been suggested for other TRP channels as well (34, 70). Regulated surface expression may be an exciting common property of TRPC channels. It is intriguing that several TRPC subunits are expressed in human sperm, hinting that *C. elegans* and humans may share ancient cellular mechanisms of fertilization (71).

C. elegans has two other TRPC proteins encoded by *trp-1* and *trp-2*. Mutant phenotypes have not been described for these two genes. *trp-1* is expressed in many motor neurons and interneurons as well as vulval and intestinal muscles (20).

In a different fertility-related function, the TRPM family member *gon-2* is required during mid-larval stages for proper development of gonadal tissues (72). In *gon-2* mutants, germ cells fail to proliferate and mature, a defect that could be either intrinsic to the germ cells or associated with other tissues that regulate the germ line (73).

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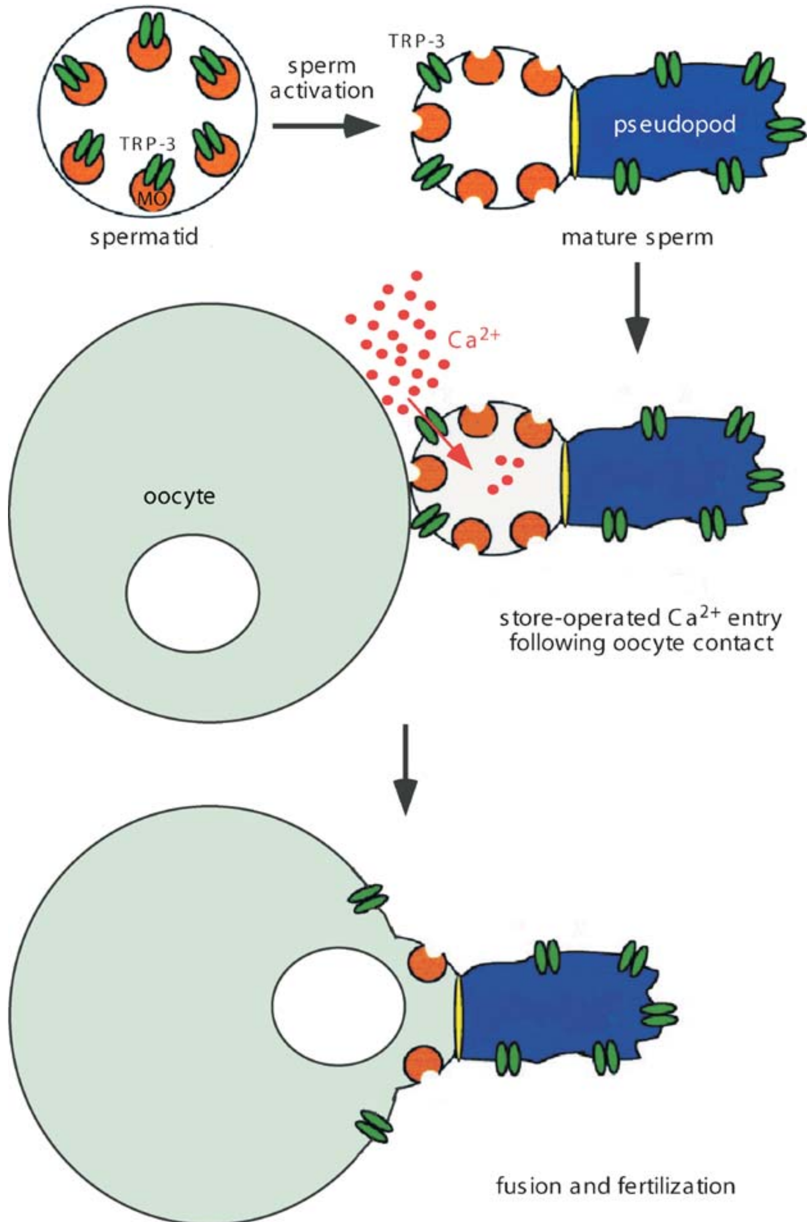

Figure 4 TRP-3 functions as a store-operated channel in sperm. In immature spermatids, TRP-3 (*green*) is sequestered inside cytoplasmic membranous organelles (*orange*). Following sperm activation, TRP-3 is found on the plasma membrane of sperm, including the pseudopod region. Upon contact with an oocyte, Ca^{2+} enters sperm through TRP-3 channels, followed by fusion with the oocyte and fertilization. Figure modified from Reference 68.

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Mutations in *gem-4* suppress *gon-2* reduction-of-function alleles, restoring the mutants to fertility. *gem-4* encodes a widely expressed member of the copine family of Ca^{2+}-dependent phospholipid-binding proteins (74). *gem-4* fails to suppress the strongest *gon-2* mutations, suggesting that it acts by modulating *gon-2* activity. Because of its lipid-binding, Ca^{2+}-binding, and Mg^{2+}-binding motifs, GEM-4 has been suggested to regulate membrane trafficking of GON-2 (74).

Both GON-2 and the TRPM channel GTL-1 have roles in Mg^{2+} uptake by intestinal cells and in Mg^{2+} homeostasis (74a). These channels are localized to the apical surface of intestinal epithelial cells, in which they take up ions from dietary sources. GTL-1 appears to form a constitutively active channel for Ca^{2+} and Mg^{2+}, whereas GON-2 forms an outwardly rectifying channel for Ca^{2+} and Mg^{2+} that is strongly inhibited by intracellular Mg^{2+}. Animals with mutations in both genes exhibit arrested development in low Mg^{2+} but can be rescued if grown in high external Mg^{2+}. Mutations in the human TRPM6 gene result in familial hypomagnesemia with secondary hypocalcemia owing to poor Mg^{2+} uptake in the intestine. Thus, for TRPM channels, as for TRPML channels (see below), the physiological functions are strikingly comparable in nematodes and humans.

cup-5: A LYSOSOMAL TRPML WITH LINKS TO APOPTOSIS

Another family of TRP channels, the TRPMLs or mucolipins, is implicated in the rare human familial disorder mucolipidosis type IV. Human patients exhibit early-onset mental retardation and ophthalmic defects, including retinal degeneration, owing to lysosomal sorting and lysosomal storage defects. TRPML channels may be the most primitive of all of the TRPs, as yeast express a mechanosensitive, Ca^{2+}- and pH-regulated TRP channel in the lysosome-like vacuole (75–77).

C. elegans has one TRPML gene, *cup-5*, whose reduction-of-function mutants have an endocytosis defect in coelomocytes, scavenger cells that filter soluble proteins from the *C. elegans* body cavity (78). *cup-5* is expressed in many cell types and localizes to internal vesicles that are most likely to be lysosomes and late endosomes. *cup-5* mutants have abnormally large internal vacuoles and an inappropriate accumulation of proteins that should have been degraded in lysosomes. Animals bearing null mutants in *cup-5* have a maternal-effect lethal phenotype, with excessive apoptosis and many cells with large, malformed lysosomes and vacuoles (79). On the basis of these cell-biological criteria, the *C. elegans* phenotype closely matches the pathology of human mucolipidosis. Indeed, mammalian TRPML1 expressed from a heat-shock promoter rescues the lethality of *cup-5* mutants, consistent with an orthologous function (79). Similarly, coelomocyte expression of mammalian TRPML1 or TRPML3 rescues the *cup-5* endocytosis defects (80).

Detailed analysis of *cup-5* mutants, using subcellular markers and electron microscopy, indicates that their primary cellular defect is in lysosome biogenesis

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and that the accumulated organelles in *cup-5* mutants have mixed properties of late endosomes and lysosomes (79, 80). Thus, human and *C. elegans* mucolipins may share a function in lysosome biogenesis. Human TRPML1 expressed in liposomes forms a cation channel that is inhibited at low pH (81); perhaps a change in CUP-5/TRPML1 activity accompanies or defines the maturation of lysosomes.

cup-5 mutants have been isolated in a genetic screen for mutations that stimulate apoptosis (79). Animals bearing null mutants in *cup-5* have high levels of apoptosis even in the presence of a death-preventing *bcl2 (egl-9)* mutation. Hersh et al. (79) suggest that apoptosis is secondary to the *cup-5* defect in lysosome and vacuole formation. A worm TRPM subunit, *ced-11*, has been identified as an apoptosis mutant with abnormal cell corpses (G. Stanfield & H.R. Horvitz, personal communication), but the mechanism for this phenotype has not been described.

C. ELEGANS TRPS AND OPEN QUESTIONS

The study of *C. elegans* has already shed light on numerous aspects of TRP channel function and localization. The diverse *C. elegans* TRP channels offer avenues for illuminating additional questions. Because it is relatively easy to examine subcellular localization of *C. elegans* proteins in live animals, this should be a particularly valuable system for studying mechanisms of surface expression, trafficking to sensory cilia, and regulated translocation of TRP channels. An open area to explore is the relationship between channel trafficking and cellular function. For example, when channels such as TRP-3 in spermatids are contained in intracellular compartments, are they sequestered or are they actively producing cationic currents?

C. elegans has been an outstanding model for studying mechanosensation mediated by the Deg/EnaC channel family (reviewed in Reference 82); in the future, it may be a useful model with which to study possible mechanosensory functions of TRPs. One avenue to explore is the proposed mechanosensory and osmosensory function of OSM-9/OCR-2 channels in ASH nociception. Other TRP channels may also have mechanosensitive functions; for example, the TRPV gene *osm-9* is expressed, together with the uncharacterized TRPV gene *ocr-4*, in OLQ, PVD, and FLP mechanosensory neurons. Another candidate mechanosensor is the *C. elegans* TRPN protein Y71A12B.4/*trp-4*, the ortholog of *Drosophila* and zebrafish mechanoreceptive channels of the nompC family (17). *trp-4* is expressed in CEP and ADE neurons, which are thought to detect the light mechanosensory stimulus provided by a bacterial lawn (83). Mutants in *ocr-4* and *trp-4* have not yet been described.

Several *C. elegans* TRP genes are completely uncharacterized. These include one TRPA family member, C29E6.2, which shares 88% identity with the candidate *Drosophila* thermosensory channel ANKTM1, as well as several uncharacterized TRPC, TRPM, and TRPV family members. Six additional TRP genes in the *C. elegans* genome are apparently unrelated to the existing seven TRP families, and these could open up entirely new areas of TRP biology. The continuing analysis of

C. elegans TRP channels should raise and answer new questions while providing a physiological and cellular context for TRPs.

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