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TRANSDUCING TOUCH IN *CAENORHABDITIS ELEGANS*

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■ **Abstract** Mechanosensation has been studied for decades, but understanding of its molecular mechanism is only now emerging from studies in *Caenorhabditis elegans* and *Drosophila melanogaster*. In both cases, the entry point proved to be genetic screens that allowed molecules needed for mechanosensation to be identified without any prior understanding of the likely components. In *C. elegans*, genetic screens revealed molecules needed for touch sensation along the body wall and other regions of force sensitivity. Members of two extensive membrane protein families have emerged as candidate sensory mechanotransduction channels: *mec-4* and *mec-10*, which encode amiloride-sensitive channels (ASCs or DEG/ENaCs), and *osm-9*, which encodes a TRP ion channel. There are roughly 50 other members of these families whose functions in *C. elegans* are unknown. This article classifies these channels in *C. elegans*, with an emphasis on insights into their function derived from mutation. We also review the neuronal cell types in which these channels might be expressed and mediate mechanotransduction.

INTRODUCTION

Sensation relies on the ability of specialized receptor cells to generate electrical responses to physical stimulation. Such responses are called receptor potentials and are initiated by transducer molecules that detect physical stimulation and produce a change in membrane permeability. This review concerns cells and molecules that sense touch and body movements generated by external forces and by self-produced movements. Although electrical responses to force were first measured more than 75 years ago (1, 2), surprisingly little is known about the molecules that transduce mechanical energy, and even less is known about how they work. Recent efforts to identify and study these molecules have focused on animals used for behavioral genetics: nematode worms (*Caenorhabditis elegans*), fruit flies (*Drosophila melanogaster*), and mice. Behavioral genetics in zebrafish

(*Brachydanio rerio*) and analysis of nonsyndromic, inherited deafness in humans also hold the promise of identifying molecules needed for mechanotransduction in vertebrate hair cells (3, 4). This article reviews behavioral, ultrastructural, and molecular aspects of mechanosensation in *C. elegans*, emphasizing prospects for discovering the molecular events that give rise to the sensation of touch and force in this simple animal.

As of this writing, all potential mechanotransducer channels identified in nematodes and fruit flies are related either to DEG/ENaC channels or to TRP channels (Table 1). The DEG/ENaC and TRP channel proteins are encoded by large gene families in worms, flies, and mammals; these proteins form cation-selective channels that are comparatively insensitive to membrane voltage. The DEG/ENaC family was named for the first two sub-families identified: degenerins, *C. elegans* proteins that can mutate to cause cell swelling and degeneration (5, 6, 18) and epithelial Na^+ channels (ENaC) (19, 20). A third sub-family called ASICs for acid-sensitive ion channels has also been identified (21). Here, we refer to these proteins as amiloride-sensitive channels or ASCs, a name used by Interpro (Acc. # IPR001873) (22) that recognizes the fact that all of these ion channels are blocked by the diuretic, amiloride. The TRP family was named for the first member identified: a *Drosophila* protein needed for sustained photoreceptor responses, encoded by the *trp* (*transient receptor potential*) locus (23, 24). Protein sequence analysis divides TRP channels into six conserved subfamilies (25–27): three subfamilies, currently denoted as TRPC, TRPV, and TRPM (27, 28), related to canonical TRP proteins; and three additional subfamilies, TRPN, TRPP, and TRPML (26, 27), which are more divergent. Some TRP ion channels are polyfunctional proteins, containing both an ion channel domain and an enzymatic domain (28).

TABLE 1 ASC and TRP ion channels in force sensing

Channel	Species	Sensory modality	Reference
ASC ion channels			
MEC-4	*C. elegans*	Touch receptor	(5)
MEC-10	*C. elegans*	Touch receptor	(6)
UNC-8	*C. elegans*	Proprioceptor	(7)
UNC-105	*C. elegans*	Proprioceptor	(8)
ASIC2[a]	Mouse	Touch (RA receptors)	(9)
ASIC3[b]	Mouse	Touch (RA & AM receptors)	(10)
		Ischemic pain	(11)
TRP ion channels			
OSM-9	*C. elegans*	Touch receptor	(12)
NOMPC	Drosophila	Touch receptor (insect type I)	(13)

[a]Also called BNC1 (14), BNaC1 (15), and MDEG (16).

[b]Also called DRASIC (17).

MODES OF MECHANICAL COUPLING

The simplest transducer complex is composed entirely of a mechanosensitive (MS) ion channel gated by application of force within the plane of the plasma membrane (Figure 1*a*). Many ion channels sense changes in membrane tension (29), but few ion channels are known to exploit this sensitivity for their cellular function. One example is the MscL channel of *Escherichia coli*, which opens in response to membrane tensions close to the lytic limit (30) and contributes to turgor regulation in bacteria (31, 32). Sensitivity to membrane tension implies that the closed and open conformations of MS channels occupy different areas in the plane of the plasma membrane. Indeed, MscL gating is estimated to involve an in-plane area increase of 6.5 nm^2 (30). The converse also holds: i.e., if the open state occupies a larger in-plane area than the closed state, then it should be possible to open the channel by stretching the plasma membrane, provided the force required to open the channel is less than the bilayer's lytic limit. Stretch-sensitive MS channels have been detected in many eukaryotic cells, including sensory neurons. Examples include some channels of unknown cellular function, such as the tandem pore K^+ channels TREK-1 (33) and TRAAK (34), as well as some with known, nonsensory

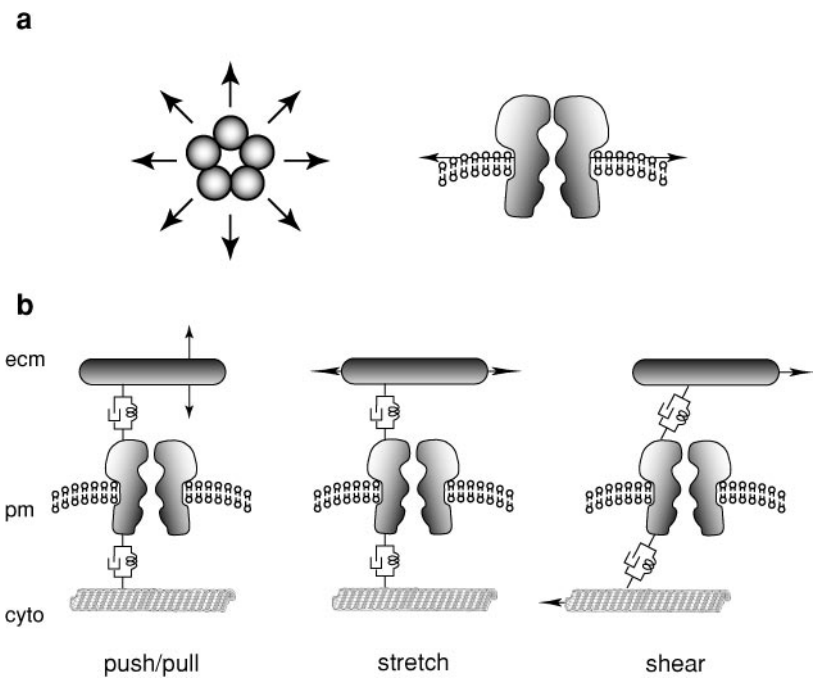


Figure 1 Modes of mechanical coupling. (*a*) Mechano-sensitive channel, gated by membrane tension. (*b*) Tethered modes of mechanical coupling. Abbreviations: ecm, extracellular matrix; pm, plasma membrane; cyto, cytoskeleton.

functions, including NMDA-gated channels (35) and *Shaker* K^+ channels (36). Thus sensitivity to membrane stretch could reflect the physiological gating stimulus, a side effect of conformational changes associated with gating, or both. In the absence of independent knowledge of a given channel's cellular function, it is impossible to distinguish between these possibilities. Thus sensitivity to membrane stretch is not, by itself, sufficient evidence that a given channel functions as a sensory mechanotransduction channel.

More complex or tethered models of sensory mechanotransduction hypothesize that force is converted into displacement of a transducer channel by virtue of relative movements between external structures in the extracellular matrix (ecm) and the cytoskeleton (cyto) (Figure 1*b*). This mechanical model, based on studies of mechanotransduction in vertebrate hair cells (37, 38), connects the ecm and cyto to the transducer channel with linkages represented by a spring and a dashpot in parallel. To generate displacement of the transducer channel's gate, the linkages must differ in their stiffness. Thus differences in the performance of individual touch- and force-sensitive cells can arise not only from variations in the mechanical sensitivity of the transducer channel itself, but also from variations in mechanical coupling.

In principle, force can push, pull, shear, or stretch the transducer channel. Mammalian hairs and insect bristles transform force and displacement applied across the body surface into displacement at the base of the hair or bristle, pushing nerve endings against surrounding structures. Such compression activates neurons that innervate bristles and campaniform sensilla in insects and is thought to activate transducer complexes (39, 40). Although *C. elegans* lacks hairs and bristles, neurons that innervate sensilla arrayed around the worm's mouth resemble *Drosophila* bristle mechanosensory neurons in their ultrastructure. The position of these neurons suggests that they, too, may be activated by compression perpendicular to the long axis of the sensory cilia. By contrast, sound stretches and compresses *Drosophila* sound receptors (scolopidia) parallel to the long axis of the cilium. Genetic analysis suggests that bristles and scolopidia rely on many of the same proteins for their function (41), however, despite differences in the mode of mechanical coupling (Table 2).

Touch and force sensation have been studied in several metazoans, including invertebrates such as crayfish, crickets, flies, and spiders, and vertebrates such as frogs, mice, and humans. Differences in the modes of mechanical coupling complicate efforts to compare the sensitivities of mechanosensory cells. For example, responses of crayfish stretch receptors are frequently measured as a percentage of resting length (e.g., Reference 47), whereas responses of insect bristle receptors are measured as a function of deflection (e.g., Reference 48). Measuring responses as a function of applied force makes it possible to compare sensitivities. In general, mechanosensory cells can sense forces over a range of approximately two orders of magnitude. Absolute sensitivity, however, varies widely (Table 2). Differences in absolute sensitivity may reflect differences in mechanical coupling, the sensitivity of the sensory mechanotransduction complex, or both factors.

TABLE 2 Sensitivities of selected touch- and force-sensitive neurons

Sense organ	Species and/or common name	$F_{1/2}$ (mN)	Reference
Slit sense organ	*Cupiennius salei* (wandering spider)	0.026	(42)
Cercal thread hairs	*Acheta domestica* (house cricket)	0.18	(39)
Nematocyte	*Stauridiosarsia producta* (hydra)	0.0002	(43)
Stretch receptor	*Procambarus alleni* (crayfish)	0.21	(44)
Muscle spindle	Frog	5.28	(1)
Glabrous skin	Human	0.54–7.5	(45)
Glabrous skin	Mouse	2.8–13.0	(46)

CELLS THAT SENSE FORCE IN *C. ELEGANS*

On the Natural Environment of *C. elegans*

Wild *C. elegans* live in soil and eat bacteria. They crawl on the damp surfaces of soil particles, held in place by surface tension produced by thin water films. While navigating this environment, *C. elegans* experiences external forces produced by surface tension, by colliding with adjacent soil particles and other animals, as well as internal forces generated by its own movement. Movement is accompanied by waves of alternating dorsal and ventral muscle contractions (49). Such movements could activate neuronal and muscle stretch receptors, providing ongoing feedback for movement control. In the laboratory, *C. elegans* leave visible, sinusoidal tracks as they crawl through a bacterial lawn on the surface of an agar plate. Differences in internal force sensing produced by mutations have been inferred by analyzing tracks (7). External force sensing is studied by observing how animals respond to touch along the body wall (gentle and harsh touch) and at the tip of head (nose touch) and to substrate acceleration (tap). The responses are simple: Adult animals withdraw from touches and reverse direction in response to tap (50). Gentle touch also modifies egg laying (51), pharyngeal pumping (52), and resets the defecation cycle (53).

Figure 2 shows neurons identified as mechanosensory by anatomical criteria (49). In adult hermaphrodites, 22 cells have ciliated sensory endings, 18 of which are associated with sensory organs or sensilla arrayed around the buccal opening (49, 54, 55). Adult males have 48 additional ciliated sensory neurons that innervate the male tail, hook, post-cloacal sensilla, and spicules (56), male-specific structures essential for efficient mating. Males have an additional set of fourfold symmetric cephalic sensilla whose ciliated endings are exposed to the external environment (55). Upon contact with hermphrodites, males search for the vulva, insert their spicules, and transfer sperm. Male mating behavior requires the male-specific sensilla (57), most of which are believed to be mechanosensory. Male sensory neurons exposed to the external environment could be polymodal, recognizing both physical contact and a chemical signal.

C. elegans and insect cuticular sensilla share a common anatomical plan (Figure 2*b*); they are composed of one or more ciliated sensory dendrites, a socket cell that joins the sensillum to the hypodermis, and a glial-like sheath cell (54, 55). Some sensory neurons are encapsulated by the cuticle, whereas others are contained within a channel open to the external environment. The amphids are the largest sensilla; each amphid contains 12 sensory neurons, 4 of which are encapsulated, and 8 of which are exposed to the outside. The 6 non-ciliated mechanosensory cells extend long, microtubule-filled neurites in close apposition to the animal's hypodermis and cuticle. These cells are called touch cells because they are needed for the response to gentle touch along the body wall (52) and are among the best-studied neurons in the *C. elegans* nervous system.

Touch Cells

Touch cell neurites are filled with atypical, large-diameter microtubules arrayed such that their distal ends are in close apposition to the cell membrane (Figure 2*c*,*d*). The junction between these microtubules and the cell membrane was proposed to be the site of a sensory mechanotransduction complex (58, 59). Laser ablation by Chalfie et al. (52) revealed that one pair of touch cells (PLML and PLMR) is responsible for touch sensation along the posterior half of the animal, whereas a second pair (ALML and ALMR) mediates touch sensation along the anterior half of the animal together with a third, unpaired cell (AVM). A sixth, unpaired cell (PVM) has the same ultrastructural features as the other touch cells, but killing PVM produces no detectable defect in touch sensation (52, 60, 61). When all 6 cells are killed by a laser or by a toxic gene product, animals fail to respond to gentle touch, but retain the ability to respond to strong stimuli (52, 62). Intact, wild-type animals can reliably detect 10 μN touches, whereas animals lacking touch cells because of toxic mutations in the *mec-4* gene respond to forces in excess of >100 μN (I. Chin, M.B. Goodman & M. Chalfie, unpublished data). Such large forces are probably detected by the PVD cells, because killing these cells in animals that lack touch cell function eliminates harsh touch sensitivity (62). PVD cells are bipolar neurons with long, undifferentiated neurites that run along the lateral body wall. Like the 6 touch cells, PVD expresses the MEC-3 LIM homodomain protein (62). Loss of *mec-3* function eliminates sensitivity to forces up to 2000 μN (I. Chin, M.B. Goodman & M. Chalfie, unpublished data).

ASH and Others

Three classes of ciliated sensory neurons mediate sensitivity to nose touch: ASH, FLP, and OLQ (70). ASH, FLP, and OLQ innervate distinct sensilla at the tip of the nose (Figure 2*a*). The ciliated endings of ASHL/R are in the left and right amphid sensilla, where they are exposed to the external environment through a channel in the amphid sheath cell (49). The ASH cells are considered polymodal sensory neurons because they are needed for the sensation of nose touch (63),

high osmolarity (64), and noxious chemicals (65). All three types of stimuli evoke qualitatively similar behaviors: Upon encountering a noxious stimulus, animals halt forward movement, back up, and then turn away. ASH also contributes to avoidance of acid pH (66) and toxic concentrations of Cd^{2+} and Cu^{2+} (67). In this way, ASH resembles vertebrate sensory neurons that sense noxious force, heat, and chemicals in the skin. Like ASH, the FLP cells are bilaterally symmetric, with sensory endings in the left and right labial sensilla (49). The OLQ cells, by contrast, are fourfold symmetric, with sensory endings in a set of sensilla distributed around the mouth (left, dorsal, right, and ventral) (49). Unlike ASH, neither FLP nor OLQ has sensory endings exposed to the external environment.

CEP, ADE, and PDE

C. elegans hermaphrodites slow their forward motion upon entering a lawn of bacteria. This basal slowing response requires dopamine and eight putative mechanosensory neurons: the four CEPs, the two ADEs, and the two PDEs (68). Consistent with a role for dopamine in the basal-slowing response, these eight cells are the only dopaminergic neurons in hermaphrodites (69). The CEP, ADE, and PDE neurons have ciliated sensory endings embedded in different regions of the cuticle. The four CEP neurons have sensory endings in the outer labial sensilla, distributed in a fourfold symmetric pattern around the buccal opening (Figure 2*a*), whereas ADE and PDE have sensory endings embedded along lateral midlines located anteriorly and posteriorly, respectively. Sawin et al. (68) proposed that CEP, ADE, and PDE mediate basal slowing by sensing the mechanical effects of crawling through bacteria. The evidence in support of this idea is twofold. First, the slowing response evoked by bacteria is mimicked by sterile Sephadex G-200 beads, which are unlikely to present a chemical stimulus and are too large to ingest (50–100 μm). Second, Sephadex-mediated slowing also requires CEP, ADE, and PDE. In addition, animals with unilateral ablations exhibit the basal-slowing response only when crawling on the intact, unoperated side.

Other Cells

The IL1 cells are a set of six bipolar neurons that have sensory endings in the inner labial sensilla and also form neuromuscular junctions. Like ventral cord motor neurons, the six IL1 cells are interconnected by gap junctions (49). Together with OLQ and the RMD motor neurons, the IL1 cells regulate the rate of spontaneous foraging (70). The IL1 and OLQ neurons have also been suggested to mediate responses to touch along the dorsal and ventral surface of the nose.

Male-Specific Sensilla

Approximately half of the male-specific neurons (46 of 87) are ciliated sensory neurons that innervate the male tail, hook, post-cloacal sensilla, and spicules (56, 71). Thirty-six neurons innervate nine pairs of sensory rays (2 neurons/ray) in the male

tail. All these neurons have ciliated endings contained within channels, except for the neurons (which are encapsulated) that innervate ray 6 (56). Rays 1, 5, and 7 open to the animal's dorsal side and are necessary for males to recognize contact with hermaphrodites along this surface (57). Rays 2, 4, and 8 open ventrally and appear to act in concert with sensory neurons that innervate the hook, post-cloacal sensilla, and spicules to recognize hermaphrodite contact along the ventral surface (57). Two sensory neurons, HOA and HOB, innervate the hook and contribute to vulva location (57). Four neurons, SPDL/R and SPVL/R, innervate the spicule (56) and contribute to spicule insertion and sperm release (64). These sensory neurons are believed to detect the mechanical effects of hermaphrodite contact, vulva location, and spicule insertion.

Stretch Receptors

Several types of *C. elegans* motor neurons extend long, undifferentiated processes that run parallel to the animal's body axis. These regions may function as unconventional stretch receptors (L. Byerly & R.L. Russell, cited in Reference 49). If true, then some *C. elegans* neurons could serve as both sensory neurons and motor neurons. In the case of the ventral cord motor neurons (VA, DA, VB, and DB), such stretch receptive regions could encode local body curvature and translate this signal directly into localized changes in motor activity. Such signals could also contribute to the generation and maintenance of propagating waves of body flexion by spreading to adjacent body regions through the gap junctions that connect motor neurons within each class (49). Two additional classes of motor neurons, SMB and SMD, send processes posteriorly along sub-lateral nerve cords, where they are ideally situated to monitor bend in the anterior body (49). In males, the spicule motor neuron (SPC) may also provide proprioceptive information (56). Thus there are seven classes of motor neurons that could sense stretch during locomotion.

SENSORY MECHANOTRANSDUCTION BY ASC COMPLEXES

Reconstituting a Transduction Complex from *C. elegans* Touch Cells

Genetic screens for touch-insensitive *C. elegans* identified 12 *mec* (for mechanosensory abnormal) genes needed for the function but not the development of the touch cells (72, 73). Nearly all these genes have been cloned and characterized. These genes encode proteins needed to form the specialized cytoskeleton and extracellular matrix of touch cells, two DEG/ENaC channel proteins, and two cytoplasmic regulators (Figure 3*a*). All of the cloned genes are expressed in the touch cells except for *mec-5*, which is expressed by epidermal cells that envelope touch cell neurites (74). A loss-of-function mutation in a single *mec* gene is sufficient to

eliminate touch sensitivity, indicating that these genes function non-redundantly and suggesting that all 12 proteins are needed for touch cell function. Gene interaction studies carried out by Chalfie and colleagues (6, 75) were critical in formulating the first molecular model of a metazoan sensory mechanotransduction complex.

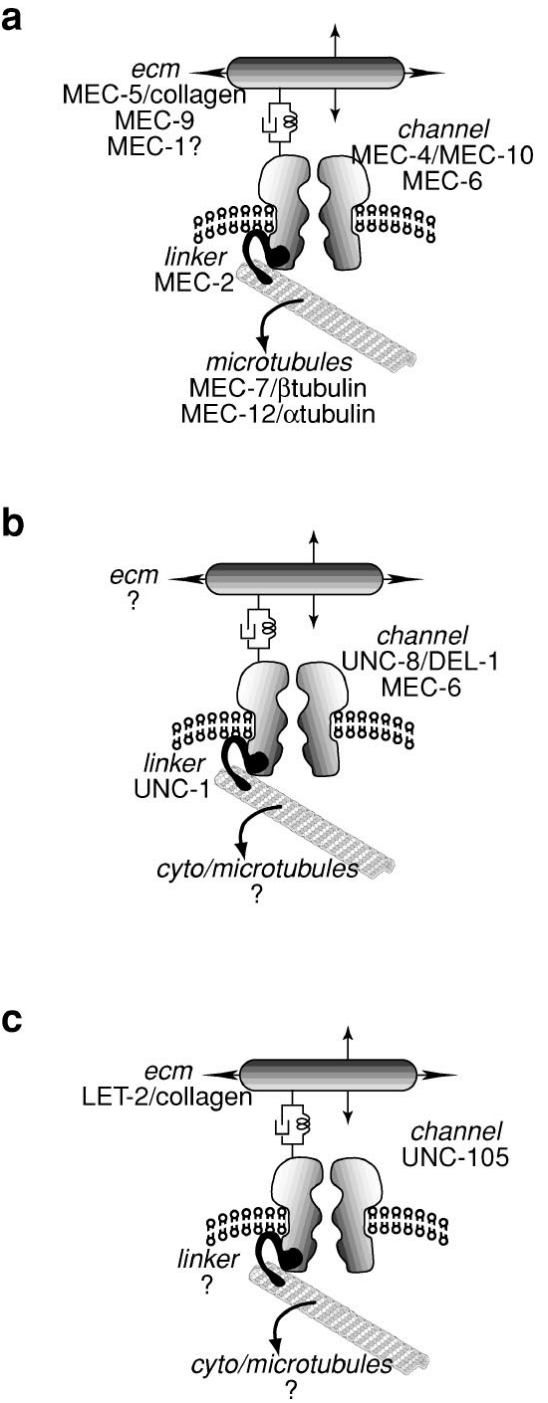
Efforts to reconstitute this complex in heterologous cells are underway. Thus far, these studies show that the ASC proteins, MEC-4 and MEC-10, are sufficient to form a heteromeric, amiloride-sensitive Na^+ channel (76). The accessory proteins, MEC-2 and MEC-6, increase current amplitude without affecting the steady-state surface expression of either MEC-4 or MEC-10 (76, 77). Consistent with gene interactions in vivo and functional interactions in heterologous cells, all four proteins appear to bind one another (76, 77).

Other ASC Complexes

Similar complexes may exist in *C. elegans* motor neurons (7) and body wall muscle (8, 78), which are known to express homologs of some, but not all, of the genes needed for touch cell function (Figure 3*b*,*c*). Multidendritic or type II sensory neurons in *Drosophila* innervate the larval cuticle and express two ASC genes, *rpk* (*Ripped Pocket*) and *ppk* (*Pickpocket*), proposed to encode transducer channels (79). At present, there is no direct evidence that these neurons sense touch in *Drosophila* or that *rpk* and *ppk* are needed for touch sensation. Nonetheless, responses to force have been recorded from equivalent neurons in *Manduca* larvae (80), supporting the idea that type II sensory neurons in insects employ a similar touch-transducing complex as the one proposed for *C. elegans* touch cells. ASC complexes might also mediate sensory mechanotransduction proprioceptive neurons of the tropical wandering spider (*Cupiennius salei*), because transduction currents in these neurons are Na^+ selective and blocked by amiloride (81).

AMILORIDE-SENSITIVE CHANNELS

ASC proteins assemble as homomultimers or heteromultimers to form non-voltage-gated, Na^+ channels blocked by the diuretic, amiloride. They share a common topology consisting of two transmembrane domains separated by a long extracellular domain that contains at least two cysteine-rich domains (Figure 4); *C. elegans* ASC proteins also contain a third, non-conserved cysteine-rich domain. Structure-function studies of vertebrate ENaCs have identified conserved residues near the second transmembrane domain important for gating, ion selectivity, and amiloride blockade (82). These residues are mutated in several alleles of ASC-encoding genes in *C. elegans* (domain 4, Figure 4), indicating that they are critical for ASC function in *C. elegans*, as well as for channel biophysics and pharmacology in heterologous cells. Dominant alleles of *mec-4* and *deg-1* that cause cell degeneration encode substitutions of a conserved alanine (indicated in *red*); this phenotype led to the hypothesis that the presence of bulky



side chains produces hyperactive channels (5, 18). Consistent with this idea, introducing bulky moieties at homologous positions in ENaC subunits was found to increase open probability (P_o) (83). A conserved domain in the intracellular NH_2 terminus of ASC proteins is also critical for function (domain 1, Figure 4). A loss-of-function mutation in the homologous region of the human βENaC gene is associated with the salt-losing syndrome, PHA1 (84); mutant ENaC channels exhibit a reduced P_o when expressed in *Xenopus* oocytes (85), implicating this domain in some aspect of channel gating. Recently, it was shown that overexpressing the NH_2 terminus of MEC-4 disrupts touch-sensitivity in wild-type animals and reduces cell death in animals expressing MEC-4(A713V). Both effects were eliminated by introducing the *mec-4*(*u25*) T91I and *mec-4*(*u339*) S92F substitutions into the NH_2-terminal fragment, suggesting that these residues may be involved in protein-protein interactions (86). Although the first transmembrane domain is poorly conserved among ASC proteins, there is a highly conserved region nearby (domain 2, Figure 4). Gain-of-function mutations in *unc-105* alter a proline residue in this domain (8) and result in hypercontracted animals (87). Expression of mutant UNC-105 channels in *Xenopus* oocytes showed that the *unc-105*(*n490*) P134S substitution alters channel gating (78). At present, there are no other *C. elegans* mutant alleles that encode amino acid changes in this domain or any evidence indicating that this domain contributes to gating in vertebrate ASCs.

The subgroup of *C. elegans* ASC proteins that includes MEC-4 and MEC-10 (Figure 5) contains an extracellular regulatory domain or ERD (domain 3, Figure 4). A role for this domain in channel gating was proposed on the basis of the *deg-1*(*u506*) A393T mutation, which causes cellular degeneration but only when homozygous. Introduction of the equivalent mutation into *mec-4* or deletion of nine residues in this domain produced a similar degeneration phenotype (88), supporting the inference that this domain negatively regulates the channel. Garcia-Añoveros et al. (88) proposed that this domain could be sensitive to mechanical manipulation and provide the molecular substrate for the mechanosensory function of MEC-4 and MEC-10. Interestingly, the ERD is restricted to a subgroup of seven *C. elgans* ASC proteins: MEC-4, MEC-10, UNC-8, DEG-1,

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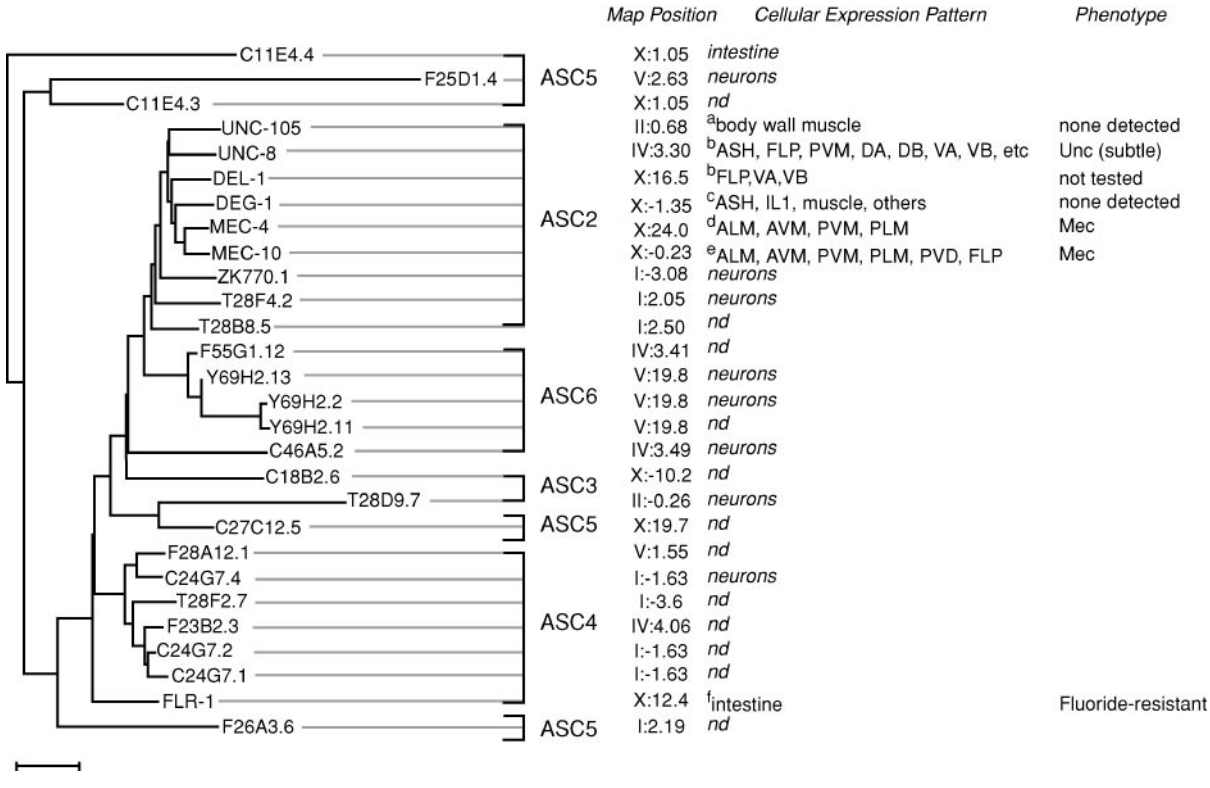
Figure 3 ASC channel complexes. (*a*) Touch cell complex, adapted from Gu et al. (75). In this model, the *ecm* contains MEC-5, MEC-9, and possibly MEC-1; the sensory mechanotransduction channel is formed by MEC-4, MEC-10, and possibly MEC-6; MEC-2 enhances channel activity and links the channel to specialized microtubules containing MEC-*7*/β-tubulin and MEC-12/α-tubulin. (*b*) Motor neuron stretch receptor complex. ecm components are not known; channel hypothesized to be formed by UNC-8, DEL-1, and MEC-6; linked to the cytoskeleton by UNC-1. (*c*) Muscle stretch receptor complex. ecm contains LET-2/collagen channel formed by UNC-105; linkers and cytoskeletal components have not been identified.



DEL-1, UNC-105, and ZK770.1. It is absent from the vertebrate ASC proteins, ASIC2 and ASIC3, proposed to contribute to touch sensation in mice (9, 10). From this analysis, it is tempting to speculate that (*a*) the ERD could represent a nematode-specific specialization for mechanical sensitivity and that (*b*) *C. elegans* ASC proteins that form sensory mechanotransduction channels are restricted to this subgroup.

To learn more about conservation of ASC proteins across species, we searched proteins predicted from the sequences of two invertebrate genomes (*C. elegans* and *Drosophila*) and three vertebrate genomes (human, mouse, and the Japanese pufferfish, *Fugu rubripes*). No genes predicted to encode ASC proteins were found in the *Arabdopsis thaliana* genome, indicating that ASCs may be absent from plants. We found 28 and 25 predicted *asc* genes in the genomes of *C. elegans* and *Drosophila*, respectively. Fewer genes were found in the vertebrate genomes: 9 in humans, 8 in mouse, and 7 in *Fugu*. Including three FMRF-gated ASCs identified in mollusks (*Helix aspersa*, *Helisoma trivolvis*, and *Lymnaea stagnalis*), the ASCs we analyzed fell into six subfamilies (see supplemental material: follow the Supplemental Material link on the Annual Reviews homepage at http://annualreviews.org/); three appeared to be nematode-specific (ASC2, ASC4, and ASC6), one was represented in nematodes, mammals, and fish (ASC3), one in insects, nematodes, and fish (ASC5), and one in mammals and mollusks (ASC1). Thus ASC proteins are highly divergent among species. Despite this, many residues important for ion channel function are conserved across species (see above).

Approximately two thirds of the 28 predicted *C. elegans asc* genes are found on either the first chromosome (8 genes) or the X chromosome (9 genes). No *asc* genes were detected on the third chromosome. We found two clusters of predicted *asc* genes; one located on chromosome I (C24G7.1, C24G7.2, and C24G7.4, map position = I:−1.63) and one on chromosome V (Y69H2.13, Y69H2.2, Y69H2.11, map position = V:19.8). Both clusters encode related ASC proteins; the C24G7 proteins are 22.8% identical, whereas the Y69H2 proteins are 28.4% identical. These

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Figure 5 *C. elegans* ASC proteins. ASCs denoted by classical locus names (three-letter plus number abbreviations) or by molecular sequence names (cosmid name). Proteins predicted to be encoded by the *C. elegans* genome were obtained from "wormpep81" (104) and scanned for ASC motifs using hidden Markov model (HMM) searches (HMMER 2.2 g) (105) or position-specific iterated BLAST searches (psi-BLAST) (106). Global HMMs for ASC families were obtained from PFAM 7.3 (ASC.hmm) (107). psi-BLAST for ASC proteins used residues 444–740 of MEC-4 as a query sequence. Dendrograms generated by ClustalW 1.82 (108) using full protein sequences, 10,000 bootstraps, and distance correction. Genomic locations and cellular expression patterns extracted from WormBase (WS81) (104); data in italics derived from DNA microarray data (89).

clusters could represent gene duplication events. Twelve *C. elegans asc* genes are either known to be expressed in neurons (*mec-4*, *mec-10*, *deg-1*, *unc-8*, *del-1*) or clustered with neuronal genes in analyses of DNA microarray experiments (89), consistent with possible roles for ASC proteins in sensory mechanotransduction and other aspects of neuron function.

Loss-of-function mutations in the 6 *asc* genes defined by behavioral genetics produce either subtle defects or no detectable phenotype (Figure 5). The absence of a detectable mutant phenotype could indicate that some *asc* genes function redundantly, perhaps by forming heteromeric channels with other ASC proteins. Theoretically, the 28 putative ASC proteins could form 406 distinct ion channels in *C. elegans* (28 homomeric channels and 378 heteromeric channels formed by two ASC proteins). The actual number of ASC channels formed in vivo is likely to be smaller, however, owing to distinct expression patterns for each gene and the capacity of some, but not all, ASC proteins to form homomeric channels. For example, MEC-4 and MEC-10 are co-expressed in all six touch cells and form heteromeric channels in *Xenopus* oocytes. In oocytes, MEC-4, but not MEC-10, can form homomeric channels (76). However, homomeric MEC-4 channels are unlikely to exist in vivo because every cell that expresses MEC-4 also expresses MEC-10. MEC-10, by contrast, is expressed in four additional cells (the FLPs and PVDs) and is likely to associate with one or more additional ASC proteins in these cells.

SENSORY MECHANOTRANSDUCTION BY TRP CHANNELS

A TRP Channel (NOMPC) in *Drosophila* Bristles

Screens for *Drosophila* larvae with defects in mechanosensation and uncoordinated adults identified several genes that can mutate to produce defects in electrical responses of bristles (90) and in responses to sound (41). Defects in courtship behaviors (which rely on the flies' ability to hear) were also observed. One of these genes, *nompC*, encodes a TRP channel protein. In *nompC* mutant flies, bristle displacement evoked mechanosensory currents that were either ~10% of their wild-type amplitude or adapted ~fivefold faster than wild-type currents (13). This study provides the most direct evidence that a TRP channel functions as a sensory mechanotransduction channel. The *C. elegans* ortholog of NOMPC, encoded by Y71A12B.4 (41% identical), is expressed in CEP and ADE, which are ciliated mechanosensory neurons needed for the basal slowing response to food and to Sephadex beads (68). The intracellular NH_2 terminals of NOMPC and Y71A12B.4 contain 29 ankyrin (ANK) repeats, 33-residue motifs that mediate protein-protein interactions (91). At present, it is not known if either NOMPC or its *C. elegans* ortholog form ion channels, if these channels are gated by force, or if the channels are localized to ciliated endings, as expected for a transducer channel.

A Polymodal *C. elegans* TRP

Wild-type *osm-9* and *ocr-2* are required for all of the sensory functions of the polymodal ASH neurons and the odor-sensing AWA neurons (12, 92). Both OSM-9 and OCR-2 co-localize to ciliated endings in ASH and AWA, where they are likely to assemble into a single transduction channel (92). How could a single channel contribute to both chemotransduction and mechanotransduction? A speculative hypothesis is that the putative OSM-9/OCR-2 channel is activated indirectly by tightly coupled receptors in ASH and AWA. To ensure rapid activation, the channel could associate with this hypothetical receptor in a sensory transduction complex, as proposed for phototransduction in *Drosophila* (93). Alternatively, the channel could be gated both by chemical ligands and mechanical force. In any case, behavioral analyses of *osm-9* and *ocr-2* mutant animals support the idea that a single TRP channel can subserve multiple sensory functions.

A Sexy TRP

TRP proteins also appear to be critical for normal mating behaviors in *C. elegans* males. This complex behavior relies on the function of male-specific sensory neurons that express the TRP proteins, LOV-1 and PKD-2 (94, 95). Mutations in *lov-1*, *pkd-2*, or both genes produced equally severe phenotypes, supporting the idea that LOV-1 and PKD-2 act together. In addition, both proteins were co-expressed in the same sensory neurons and concentrated in ciliated endings, where they could assemble into a single sensory receptor channel.

TRP ION CHANNELS

TRP ion channel proteins share a common predicted topology composed of an intracellular NH_2-termimal domain that can include one or more ANK repeats, six transmembrane domains, and a poorly conserved, intracellular CO_2H-terminal domain (25, 26, 28). ANK repeats appear to be important for function in vivo because *osm-9*(*n1516*) and *osm-9*(*n2743*) affect a glycine residue conserved in the ankyrin repeats of all *C. elegans* TRPV proteins (12). Like the ASC proteins, TRP proteins appear to be absent from plants; none were found in searches of the *A. thaliana* genome. By contrast with ASC proteins, all six subfamilies are represented by predicted protein sequences in *C. elegans*, *Drosophila*, *Fugu rubripes*, and humans (Table 3). At least one mutation in a *C. elegans* TRP gene (*cup-5*) can be functionally complemented by a transgene expressing its human ortholog, MCOLN1 (96). This suggests that the six TRP subfamilies were present and had already developed specific functions, in an ancestor common to both vertebrates and invertebrates (97). In addition to these conserved families, one subfamily was detected only in nematodes (Table 3). This last subfamily of channel proteins are good candidates for mediating nematode-specific biological functions.

Searches of the *C. elegans* genome sequence reveal 24 genes predicted to encode TRP ion channel proteins (Figure 6). Nearly half of these genes are found on chromosome IV (10 of 23). TRP-encoding genes do not appear in clusters; even the

TABLE 3 TRP channels in *C. elegans*, *Drosophila*, *Fugu rubripes*, and *Homo sapiens*

Subfamily	*Caenorhabditis elegans*	*Drosophila melanogaster*	*Fugu rubripes*	*Homo sapiens*
TRPC	3	3	8	6
TRPV	5	2	4	6
TRPM	4	1	15	9
TRPN	3	5	1	1
TRPP	2	3	5	5
TRPML	1	1	5	2
C. elegans-specific	6	—	—	—
Total	24	15	38	29

closely related TRPV genes (*osm-9*, *ocr-1*, *ocr-2*, *ocr-3*, and *ocr-4*) are distributed throughout the genome. All of the TRPV genes are expressed in sensory neurons except for OCR-3 (12, 92). As noted above, OSM-9 and OCR-2 are proposed to form a sensory transduction channel in AWA and ASH. Similarly, the TRPP genes, *lov-1* and *pkd-2*, are co-expressed in male-specific sensilla, organs needed for normal mating behavior (94, 95), and could form a sensory transduction channel in male-specific sensory neurons. Not all TRP proteins are expressed in neurons. For example, the TRPML gene, *cup-5*, is expressed in coelomocytes and appears to be needed for normal endocytosis and lysosomal function (96, 98). *gon-2* encodes a TRPM protein needed for normal gonad development (99). In addition, two TRP proteins may be expressed in sperm (K01A11.4, C05C12.3), since these genes cluster with sperm-specific mRNAs in DNA microarray experiments (89). Thus TRP ion channels are likely to subserve diverse cellular functions in *C. elegans*.

Almost nothing is known about currents carried by *C. elegans* TRP channels. Thus far, *trp*-dependent ionic currents have not been studied using either in vivo or in vitro electrical recordings. Nor has ion channel activity been observed for any *C. elegans* TRP channels in heterologous cells. Recent efforts to express OSM-9 and OCR-2 in *Xenopus* oocytes and HEK-293 cells have not been successful (92). Genetic experiments show that channels formed by these TRPV proteins must differ from those formed by mammalian TRPV1, since expressing mammalian TRPV1 in ASH failed to restore osmotic sensitivity to *osm-9* and *ocr-2* mutants. TRPV1 was functional in *C. elegans* neurons, however, because this maneuver transformed wild-type, capsaicin-insensitive animals into animals that avoided capsaicin (92).

SUMMARY AND FUTURE DIRECTIONS

The putative sensory mechanotransduction channels described here would have been extremely difficult to identify by methods other than classical genetics. Our understanding of how they work and the extent to which mechanisms of

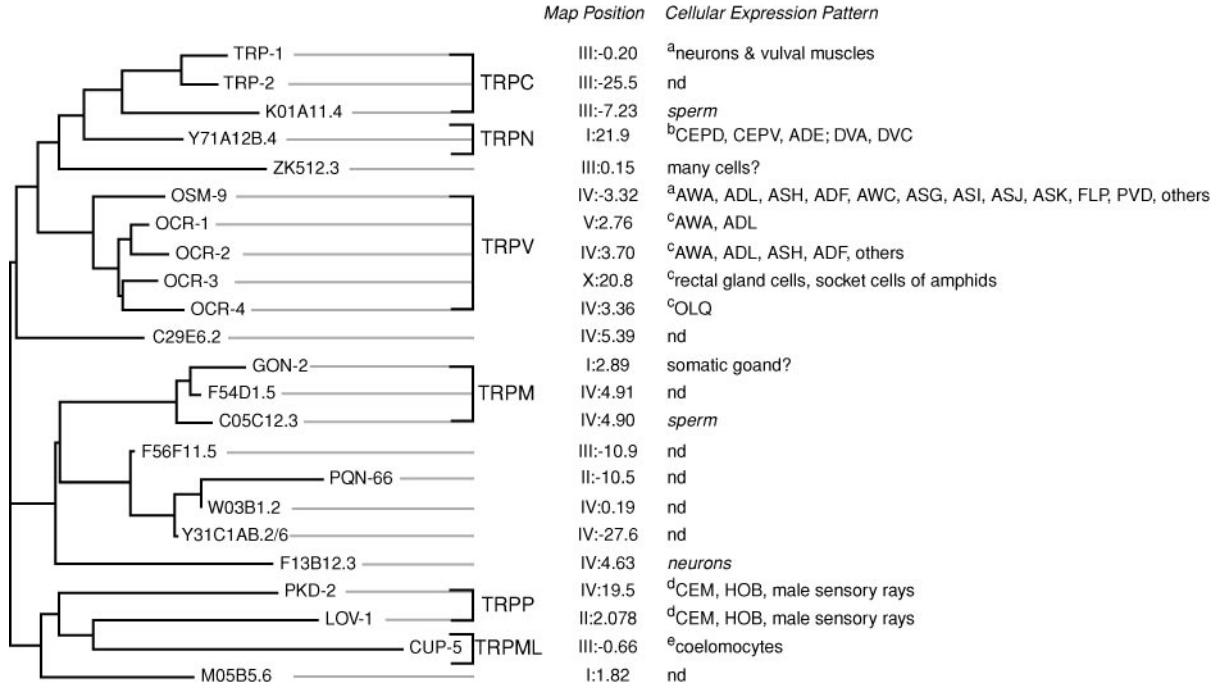

Figure 6 *C. elegans* TRP proteins. TRPs denoted by classical locus names (three-letter plus number abbreviations) or by molecular sequence names (cosmid name). Proteins were identified and used to generate dendrogram using the same methods as described for ASC proteins (see Figure 5). Genomic locations and cellular expression patterns extracted from [a](12), [b](13), [c](92), [d](94, 95), and WormBase (WS81; 104); data in italics derived from DNA microarray data (83).

mechanotransduction are shared among diverse mechanosensory neurons and conserved across species is only beginning. Even in a comparatively simple animal such as *C. elegans*, mechanosensory neurons differ in their behavioral functions, morphologies, and ultrastructure. There are several lines of work that should expand our understanding, and *C. elegans* is ideally suited for this task.

Many potential, but uncharacterized, sensory transduction channels are encoded by the *C. elegans* genome; one example, Y71A12B.4, is a strong candidate for being a mechanoreceptor but has so far been missed by classical genetics. Systematic determination of channel expression patterns by GFP transgenes, followed by site-selected deletion mutagenesis, should help to make behavioral functions clear. However, behavioral analysis alone cannot determine if a given channel acts as a sensory transducer or if the channel provides an essential function for cellular signaling following transduction. This important question could be resolved using in vivo electrical (100) or optical (101) recordings from identified *C. elegans* neurons. At present, such evidence is lacking even for the well-characterized ASC complex of *C. elegans* touch cells.

In vertebrate hair cells, transduction occurs extraordinarily rapidly (<100 μs) and is hypothesized to involve direct gating of the transducer channel by force (38, 102). It is important to remember, however, that direct mechanical gating may not be universal and that some transducer channels could be activated indirectly. In either case, the molecular substrates of mechanical gating are unknown. Missense mutations isolated in genetic screens could prove instructive in this regard, especially considering that these alterations in amino acid sequence are guaranteed to produce defects in some aspect of synthesis, trafficking, or function. Single-channel studies of these mutants hold the promise of discovering molecular determinants of gating and permeation.

Dissection of the sensory mechanotransduction channel is itself only a starting point. As discussed above, mechanoreceptor proteins in metazoa are unlikely to have the simplicity of proteins such as *E. coli* MscL. They are instead likely to work as part of intricate protein machines, anchored on both sides of the membrane to structural elements of the cytoskeleton and extracellular matrix. Strong bases for identifying such machines in *C. elegans* touch cells are the extensive genetic analyses and transcriptional profiling of these cells (72, 103). Recent studies in heterologous cells have demonstrated both functional and physical interactions between MEC-4, MEC-10, MEC-2, and MEC-6 (76, 77). Comparable knowledge of the potential components of sensory transduction complexes is currently lacking for other mechanosensory neurons in *C. elegans*. Efforts to uncover these components using classical genetics have been disappointing thus far. As a result, it may be necessary use alternative approaches such as the determination of mechanosensory neuron-specific gene expression (103). Understanding of the molecular events that give rise to the sensation of touch is poised to expand in the near future, particularly through the parallel approaches of in vivo physiology and heterologous reconstitution studies that rely on genetic data, which have successfully identified proteins and functional domains critical for mechanosensation.

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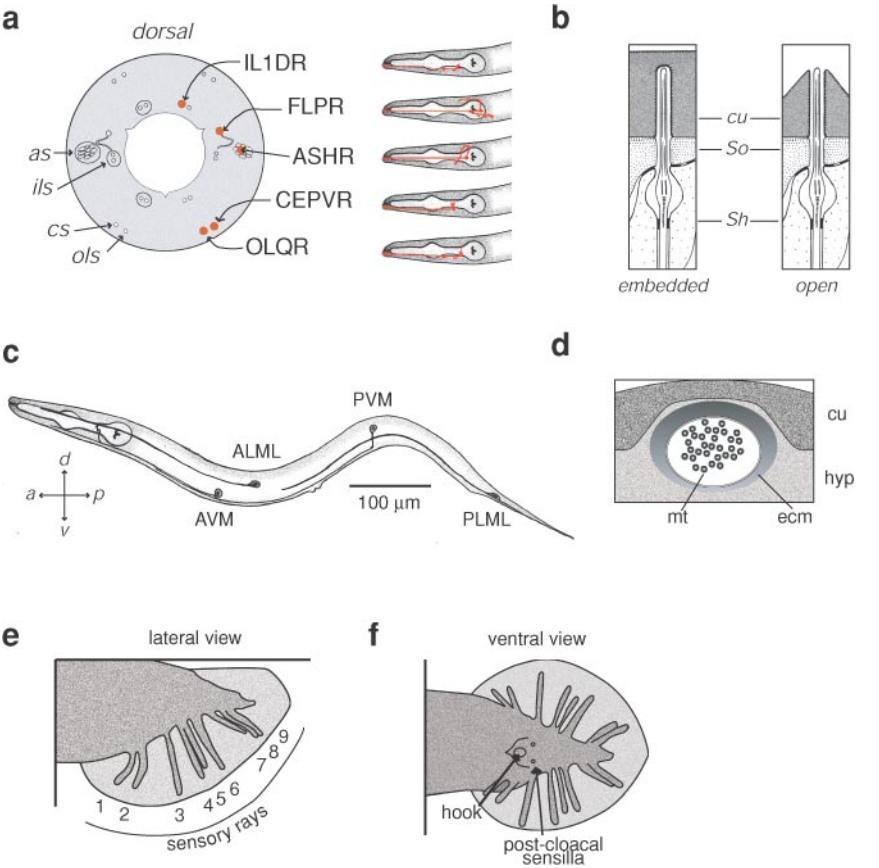

Figure 2 Mechanosensory cells of *C. elegans*. (*a*) Anterior sensilla diagrammed in a cross section near the anterior tip of *C. elegans* (*left*) and positions of mechanosensory neurons that innervate the sensilla (*right*). (*b*) Sensory endings embedded in the cuticle (*left*) and open to the outside (*right*). (*c*) Touch cells. Diagram, adapted from (59), shows the left side of an adult animal. (*d*) Cross section of a touch neurite. (Adapted from http://www.wormatlas.org.) (*e*) Sensory rays in the male tale, lateral view. (*f*) Male-specific sensilla, ventral surface of the male tail. Abbreviations: cu, cuticle; So, socket cell; Sh, sheath cell; hyp, hypodermis; ecm, extracellular matrix; mt, 15-protofilament microtubules; as, amphid sensillum; ils, inner labial sensillum; cs, cephalic sensillum; ols, outer labial sensillum.

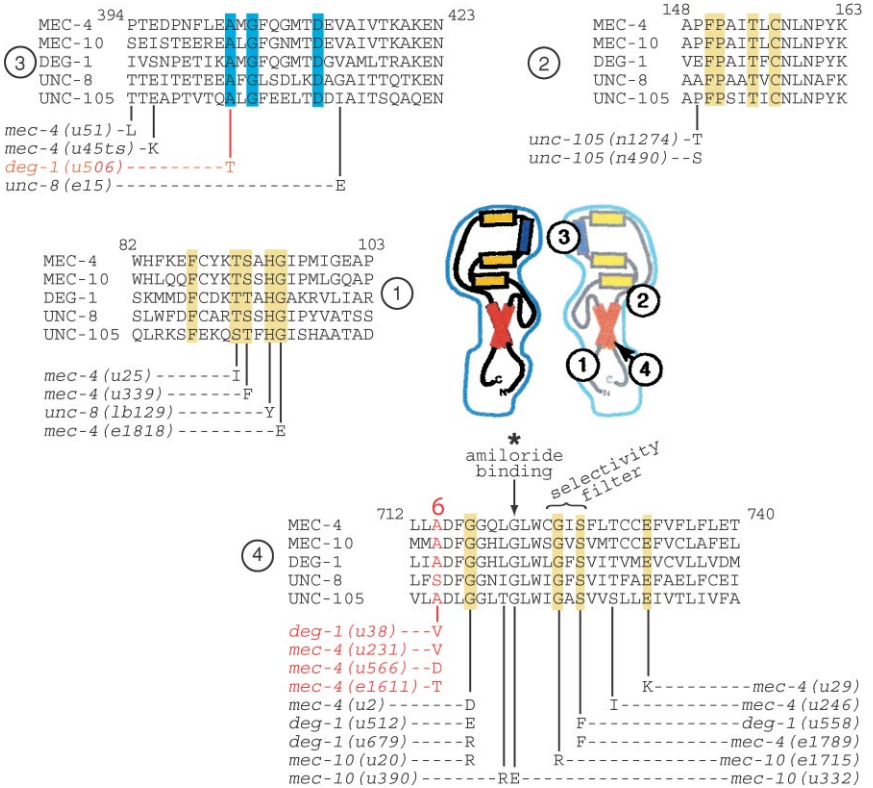

Figure 4 Clusters of point mutations in ASCs. Cysteine-rich and transmembrane domains shown in yellow and red, respectively. Extracellular regulatory domain (blue) is found in 7 ASC proteins (MEC-4, MEC-10, DEG-1, DEL-1, UNC-8, UNC-105, and ZK770.1). Residues conserved in vertebrate ASCs highlighted in yellow, in *C. elegans* ASCs highlighted in blue. Residues implicated in gating and degeneration (X), amiloride binding (*), and selectivity (bracket). Missense mutations reproduced from (86) for MEC-4, (6) for MEC-10, (78) for DEG-1, (7) for UNC-8, and (8) for UNC-105.

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