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How does morphology relate to function in sensory arbors?

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Abstract

Sensory dendrites fall into many different morphological and functional classes. Polymodal nociceptors are one subclass of sensory neurons, which are of particular note due to their elaborate dendritic arbors. Complex developmental programs are required to form these arbors, and there is striking conservation of morphology, function, and molecular determinants between vertebrate and invertebrate polymodal nociceptors. Based on these studies, we argue that arbor morphology plays an important role in the function of polymodal nociceptors. Similar associations between form and function may explain the plethora of dendrite morphologies seen among all sensory neurons.

Introduction

Pioneering work by Ramón y Cajal revealed that neurons adopt many diverse morphological forms [1]. This diversity is clearly demonstrated by the diversity of dendritic arbors (Glossary) found in neurons of the central nervous system (CNS), and by the many forms of peripheral sensory dendritic arbors. In both cases, these dendritic arbors receive multiple inputs, and in the case of peripheral sensory neurons, their arbors physically define their sensory fields.

The range of signals perceived by a dendritic arbor is principally determined by the channels and receptors that it expresses. But if input collection is the sole function of these arbors, then an arbor's function will depend only on the gross size of the area covered by it and on the density and type of receptors expressed on it. In contrast, we argue that the precise morphological form of sensory arbors also contributes to the ability of sensory neurons to perceive external stimuli. Indeed, it was previously suggested that the exact form of the dendritic arbor can affect summation and propagation of synaptic stimuli perceived by distal dendrites at the site of action potential initiation, and therefore can control the transmission efficacy of each stimulus [2]. However, the relationship between dendritic-arbor-form and signal propagation is still unclear. On the one hand, voltage-gated ion channels in CNS dendrites can function to dampen propagation effects [3]. On the other hand, recent evidence suggests a role for dendritic arbors in computing synaptic signals (reviewed in [4]). In any case, the sheer diversity and complexity of sensory dendritic arbors and the tight regulation of their development (reviewed in [5]) suggest that we should look for a link between form and function of these arbors.

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Indeed, detailed analysis of GFP reporters for the DES-2 protein or for the F49H12.4 promoter expressed in PVD demonstrated a complex, but well-ordered, array of dendrites that formed repeating “menorah-like” structures covering the animal’s body [7,9] (Figs 1 and 2). In addition, electron microscopic analyses have shown that the terminal (quaternary) branches are as thin as 30–60nm, less than half the diameter of any other known neurite [10]. These fine branches are exceptionally wispy, lying within a very thin hypodermal sheet and showing no prominent cytoskeletal elements inside, or extracellular matrix (ECM)-derived structures outside, as well as no periodic attachments to surrounding tissues [10] (Figure 2). By comparison, the dendrites of the well characterized touch receptor neurons (TRN) (Table 2) of *C. elegans* contain prominent microtubule bundles and are deeply invested into a thick epidermal layer [22,23]. Furthermore, the TRN neurons display a thickened basement membrane (mantle) and periodic electron-dense attachments to anchor themselves to the outer cuticle (Table 2) [23].

Drosophila larvae, like *C. elegans*, provide an experimentally accessible system for the analysis of neuronal form, function, and development. Sensory dendrites innervating the larval surface are conveniently organized in two dimensions beneath a transparent skin [24]. Anatomical studies have classified these neurons according to whether their dendrites have, or lack, encapsulation. Free endings, lacking encapsulation, have been further classified according to their degree of arborization, leading to four classes of dendritic arborization (DA) neurons [25]. Functional analysis of these DA neuron classes shows that class IV (DA-IV) neurons, the most highly branched class, are polymodal nociceptors, while class I neurons, the least branched class, function as proprioceptors [26,27] (Table 1 and Fig 3a). Specifically, DA-IV neurons are responsible for the sensation of noxious heat, high-threshold mechanical stimuli, parasitoid wasps, and noxious light [13,14,27,28]. Moreover, similar to mammalian polymodal nociceptors, their sensitivity to heat can be modulated by signals caused by tissue damage [15].

In mammals, somatosensory neurons innervating the skin have sensory endings that are either encapsulated (known as Ruffini’s end organ, Meissner’s corpuscle or Merkel disk) or free [1]. Neurons having free sensory endings are a heterogeneous group whose morphology is difficult to characterize. Currently, sensory neurons innervating the skin are classified using several features: morphology, conductance, sensory modalities, and molecular markers. Encapsulated sensory endings are associated with fast conducting fibers (ie. A β) and are low threshold mechanoreceptors. In contrast, sensory endings lacking encapsulation (ie. free endings) are associated with slow conducting fibers that are poorly myelinated (A δ -fibers) or unmyelinated (C-fibers) (Table 1 and Fig 3). These free endings mostly sense noxious signals and function as polymodal nociceptors. For example, many A δ neurons sense sharp pressure and cold, while many C-fibers respond to heat, high threshold mechanical stimuli, and chemical stimuli (reviewed in [6,29]). Interestingly, neurons having “free” endings are mostly multi-dendritic [30–34], although it should be noted that naming sensory arbors of these neurons “multi-dendritic” may be confusing since the peripheral (sensory) branch of these neurons conducts action potentials, and therefore is sometimes considered an axon rather than a dendrite.

Taken together, morphological analysis of polymodal nociceptors in vertebrates and invertebrates highlights two shared morphological features: free endings lacking encapsulation and a multi-dendritic arbor. Further support for conservation of these features in evolution comes from another model organism, the leech *Hirudo medicinalis*, whose polymodal nociceptors (N-cells) also have a multi-dendritic arbor lacking encapsulation (Table 1) [35,36]. Unfortunately, details on the morphology of N-cells are poorly defined, possibly due to the small caliber of their terminal dendrites [35]. Detailed morphological data is, however, available for leech P-cells (Table 1). These neurons are responsible for

sensation of pressure and have well ordered multi-dendritic arbors (Fig 3b) [37]. It is important to point-out one well-characterized exception to this conservation, the *C. elegans* ASH (Amphid Single-cillium H) neurons. These neurons are polymodal, sensing noxious mechanical and chemical stimuli applied to the nose, but unlike other polymodal nociceptors are not multi-dendritic [17,38–40] (Tables 1 and 2).

Development of multi-dendritic sensory arbors in *C. elegans* and *Drosophila*

PVD development in *C. elegans* involves the progressive addition of more branches, starting at the second larval stage and ending late in the fourth larval stage, the last stage of larval development [7,9,11] (Fig 1). Development of PVD branches is temporally ordered: primary branches appear first, secondaries and tertiaries later, and quaternaries appear last (see Fig 2 for branch numberings). Branch formation is dynamic and shows self-avoidance: both secondary and quaternary branches grow and retract to finally form a regularly spaced array of parallel branches, and growing tertiary branches retract their ends to avoid contact with tertiary branches from neighboring neurons [9]. Thus PVD development is a dynamic process that is likely to depend on mechanisms of self-avoidance and competition to form a well-ordered and regularly spaced array of non-overlapping branches [9] (Fig 1).

PVD development is likely to depend on both extrinsic and intrinsic factors. External guideposts for PVD development may include processes of adjacent neurons, the overlying seam cells, the borders of muscle quadrants, and/or ECM components [9,10]. Important internal factors may include multiple transcription factors, signaling molecules, cytoskeletal proteins, and regulators of cytoskeleton dynamics [7,9,11]. Three molecules have been studied in detail. MEC-3 (MECHANOSensory abnormality) is a LIM homeodomain transcription factor required for proper development of several mechanosensory neurons and is needed for appearance of PVD side branches [9,16,21,41]. Loss of the EFF-1 (Epithelial Fusion Failure) fusogen leads to ectopic branching of PVD processes and to considerable disorganization these processes [7], while BICD-1 (BICAudal D), a dynein accessory factor, is known to regulate the number and position of PVD branches [11].

Detailed analyses of the development of *Drosophila* DA neurons have led to the identification and characterization of many more regulators of dendritic arbor morphology. These include transcription factors [42–44], molecules involved in vesicle trafficking [45–47], components of signaling pathways [48–50], cell adhesion proteins [51–53], regulators of the actin cytoskeleton, and regulators of RNA trafficking and translation [54]. This large array of molecules and diverse cellular pathways regulates many different aspects of dendritic development: the number of dendrites, their position, their morphology, their length, self-avoidance between dendrites of the same neuron, tiling of neighboring arbors belonging to neurons of the same class, and continued maintenance of dendrites.

Overall, recent studies demonstrate that both *Drosophila* and *C. elegans* have well-ordered and molecularly complex developmental programs responsible for formation of the multi-dendritic sensory arbors of polymodal nociceptors. This tight regulation of arbor morphology suggests that the exact shape of the sensory arbor is important for functional reasons. Indeed, differences in arborization patterns of different DA neuron classes are also tightly regulated at the molecular level [42–44]. Specifically, the transcription factors Knot/Collier and Cut control dendrite numbers and dendrite length to regulate class specific arborization patterns in *Drosophila* DA neurons [42–44]. Therefore, we suggest that the morphology of sensory arbors is tightly regulated in order to enable their function. Although much less is known about the molecular details governing the development of sensory

neurons in leech, evidence for well-ordered sensory arbors and for active self-avoidance has been reported in the leech *Haementeria ghilianii* [55,56].

Molecules and morphological features enabling mechanosensation

Early analysis of PVD function showed that, together with TRNs, they mediate the response to high-threshold prodding to the midbody [16]. Further analysis showed increased Ca^{2+} levels inside PVD neurons following strong mechanical stimuli [8]. MEC-10 and DEGT-1 (DEG/ENaC involved in Touch), both DEG/ENaC subunits, were identified as likely subunits of the PVD mechanosensory channel, and were found to colocalize to puncta on the primary and tertiary branches of PVD [8] (Fig 2).

The *Drosophila* DA-IV neurons also respond to high threshold mechanical stimuli [13], and like PVD neurons, depend on a DEG/ENaC subunit, Pickpocket, for this function [14]. Similar to MEC-10 and DEGT-1, Pickpocket was demonstrated to be localized to puncta on the dendritic arbor of sensory neurons [57]. It is important to note that heterologous expression of DEG/ENaC subunits, which have been suggested to function as mechanosensors, has not yet demonstrated their gating by mechanical stimuli [57,58]. Thus, gating of these channels by mechanical stimuli is likely to require accessory structures and proteins that are absent in heterologous expression systems.

Involvement of DEG/ENaC channels in mechanosensation has also been suggested for mammalian low-threshold and high-threshold mechanoreceptors [59,60]. However, genetic knockout studies are inconsistent with a central role for this family of receptors in mammalian mechanosensation, possibly due to molecular redundancy [61,62]. Indeed, a recent study showed that the Piezo-2 protein is responsible for a subset of mechanically activated currents in mammalian mechanosensors [63]. Piezo-2, a novel multipass membrane protein, is expressed in mammalian mechanosensory neurons, including some polymodal nociceptors [63]. Members of the Piezo family are found across the animal kingdom, including *C. elegans* and *Drosophila* [63], however their function in invertebrates is yet unknown.

Mechanosensory neurons are mostly associated with specialized ECM and/or cytoskeletal structures, which have been suggested to enable their function (reviewed in [64,65]). Specifically, *C. elegans* has multiple mechanosensory neurons; these neurons, with the exception of DVA (DorsoVentral A) and PVD, contain cilia or specialized large diameter microtubule bundles (Table 2) [40]. Deflection of the single cilium in the CEP (CEPhalic cilium) neuron by pressure application was observed to produce ion currents in this neuron, consistent with cilium's suggested role in enabling mechanosensation [66]. Similarly, MEC-7, which encodes a microtubule subunit specific to TRNs, has been suggested to be involved in mechanosensation. Mutations in *mec-7* resulted in the elimination of TRN-specific 15-protofilament microtubules [67]. These microtubules are attached to the membrane of TRNs at multiple sites and were suggested to gate the mechanosensory channel [23,68]. However, the membrane-attached ends of these microtubules do not co-localize with the mechanosensory channels, as measured by coimmunofluorescent and immuno-electron microscopy (EM) studies, nor does elimination of MEC-7 abolish all mechanically activated currents [68,69]. Such findings suggest that specialized microtubules are unlikely to directly gate mechanosensory channels, nor are they absolutely necessary for activation of these channels. Nevertheless, elimination of MEC-7 leads to greatly diminished responses to mechanical stimuli, and to a significantly higher threshold for activation of these responses, demonstrating the importance of MEC-7 for mechanosensation [69]. MEC-5, which encodes a collagen needed for mechanosensation [70], has also been found to not directly co-localize with the mechanosensory channel [68]. Thus, direct gating via

microtubules or the ECM appears unlikely. Instead, it has been suggested that mechanical force applied to TRNs is transmitted via the microtubule bundles onto the membrane leading to local membrane stretch at the site of microtubule attachment sites, and thus, to stretch-activated channel opening [68].

PVD neurons, unlike other mechanosensitive neurons, do not contain cilia or other specialized microtubules, and are not encapsulated. Instead, we suggest that the morphology of PVD neurons and the organization of their processes serve as an alternative means for directing stretch forces onto the mechanosensory channels. Specifically, quaternary branches are embedded in a thin hypodermal layer between muscles and the animal's outer envelope [10] (Fig 2). This position serves to anchor the quaternary dendrites between two relatively strong rigid structures, the muscle sarcomeres and the cuticle. In light of this, large displacement of the animal's outer envelope by strong mechanical stimuli is likely to displace one quaternary branch relative to its neighbor, thereby stretching the tertiary processes linking one quaternary to its neighbor (Figure 2). By extension, it is also possible that such a displacement displaces one menorah relative to its neighbor, thereby stretching the primary branches linking one menorah to its neighbor. Importantly, the two subunits of the PVD mechanosensory channel are not found on its terminal (ie. quaternary) branches. Therefore, these branches are unlikely to function as mechanosensors themselves. Indeed, our proposed model suggests that these dendrites only serve as anchors whose displacement by local pressure transmits pulling forces onto tertiary and primary branches. Moreover, subunits of the mechanosensory channel are found in puncta on the primary and tertiary branches [8], and are thus in the right position to sense stretching of these processes (Fig 2). Additional support for our model comes from the analysis of worms lacking *eff-1*, a protein essential for cell fusion. Such mutants were observed to have highly disorganized PVD branches, and were also defective for mechanosensation [7]. Further support for this model requires similar analyses of the many other mutations known to affect PVD morphology, such as BICD-1 [11] and others [9].

Interestingly, studies of mammalian high-threshold mechanoreceptors are consistent with a mechanism whereby forces applied to external rigid structures result in one branch of a high threshold mechanoreceptor being pulled relative to other branches. Specifically, high threshold mechanoreceptors in joints are embedded within dense collagenous tissues, such as fibrous capsules or ligaments, and in the skin they are tethered to the basal lamina of the epidermis via collagen fibers [30,32](Fig 3c). By analogy, we propose that (low or high threshold) mechanosensation in other multi-dendritic neurons can also be achieved by local forces causing independent motions of branching dendrites spanning a large area, where these dendrites are independently embedded within, or tethered to, rigid structures. For instance, leech *Hirudo medicinalis* P-cells have many evenly spaced terminal dendrites that are embedded inbetween muscle layers [37]. Instances of low threshold mechanosensors that are multi-dendritic include T-cells in leech, DA class I neurons in *Drosophila*, and Palisade neurons in mammals (Fig 3d)[26,27,71,72].

Multi-dendritic neurons and temperature sensation

PVD neurons, like multi-dendritic sensory neurons in *Drosophila*, leech, and mammals, respond to both high-threshold mechanical stimuli and to noxious temperatures [8,13,36,73]. Cold sensation in PVD neurons has been determined to be mediated by TRPA-1 (Transient Receptor Potential Ankyrin), a member of the TRP (Transient Receptor Potential) channel family previously suggested to function in cold sensation in other species [8,74]. Mutation of TRPA-1 does not affect the responses of PVD neurons to mechanical stimuli [8], and expression of this channel in other neurons (ie. FLP and ALM), or in mammalian cells, also enables a response to cold [8].

The role of TRP channels in thermosensation, like the role of DEG/ENaC channels in mechanosensation, has been evolutionarily conserved. Specifically, thermoTRPs belonging to the TRPA, TRPM, and TRPV branches of the TRP ion-channel family have been shown to function in temperature sensation in *Drosophila* (Painless is a TRPA homolog) [13] and in mammalian polymodal nociceptors [75–79]. However, the precise role of thermo-TRPs in mammalian nociception, and particularly of TRPA1 in the sensation of noxious cold, is under debate [80–82]. One perplexing issue is that gating of thermoTRPs by temperature seems to be different in heterologous systems compared to the *in vivo* situation.

Heterologous expression studies show that thermoTRPs respond to temperature, suggesting that they are directly gated by temperature [8,74–76]. *In vivo*, chemical signals produced by inflammation or tissue damage facilitate temperature-dependent activation of thermoTRPs, and may lower the threshold for their activation by hot or cold. Indeed, knockout of TRPV1 in mice has been shown to eliminate inflammatory heat hyperalgesia, but does not eliminate nociceptor heat sensation; defects in the response to heat are only seen at temperatures far exceeding the threshold for activation of this receptor [75,83]. Multiple lines of evidence suggest roles for chemical signals in temperature sensation by TRP channels. Firstly, TRPA1 has been shown to function downstream of a G-protein coupled receptor (GPCR) and phospholipase C (PLC) cascade in *Drosophila* temperature discrimination [84]. Secondly, heat-dependent release of lipid metabolites from skin has been shown to be sufficient for TRPV activation [85]. Thirdly, agonist application is needed for significant cold-activated responses of TRPA [86], and lastly, the neuroactive steroid pregnenolone sulfate synergizes with heat to activate TRPM3 [79].

The role of PVD's complex arbor in its ability to sense and respond to temperature remains unclear. Two facts argue against a role of PVD's form in cold sensation. First, TRPA-1 also functions as a cold-sensor when expressed in a heterologous system [ie. human embryonic kidney (HEK) cells] [8] and in ALM neurons [8], which have simple unbranched sensory processes. Second, TRPA-1 is apparently localized to the cell body and not to sensory dendrites [8]. However, it is possible that the inability to detect GFP-tagged TRPA-1 in sensory dendrites of PVD was due to low expression levels, as other TRPA-1 homologs have been detected in sensory dendrites [13,87]. It is also notable that other known thermosensors are either multi-dendritic or have numerous villi (eg. AFD in *C. elegans*) [13,32,88]. Thus, one possibility is that a high surface-to-volume ratio may enhance the ability of a cell to sense temperature. Another possibility is that the placement of multiple terminal branches along the outer surface of the animal may enhance their sensitivity to temperature changes in the outside environment of the animal, rather than monitoring internal temperature. Other explanations are also possible, but further studies are needed to evaluate the role of PVD morphology in thermosensation.

Chemosensitivity of polymodal nociceptors

In mammals, polymodal nociceptors associated with C-fibers often function as chemosensors sensitive to ATP, protons, and other molecules that are released or secreted by nearby cells upon tissue damage or inflammation [73,89–91]. Chemicals acting on polymodal nociceptors either activate them directly or sensitize them to thermal or mechanical stimuli [92,93]. The heat response of *Drosophila* DA-IV neurons, like responses of mammalian C-fibers, is sensitized by tissue damage. Specifically, ultraviolet light-mediated damage to the overlying epidermis leads to release of cytokines that regulate the heat response of these neurons [15]. Leech nociceptors have also been demonstrated to be sensitive to chemicals (i.e protons) [36]. Protons are likely to be released from injured cells, and thus, may function as signals of tissue damage. Studies have yet to demonstrate that *C. elegans* PVD and FLP neurons are responsive to chemicals, however, the possibility cannot be ruled out entirely. To detect chemical signals, sensory dendrites of polymodal nociceptors

need to be exposed to the external milieu, and thus need to be free of a protective capsule. It is important to note that naming the sensory endings of mammalian nociceptors as “free” or “bare” is misleading, as their terminals are known to be ensheathed by Schwann cells [30]. However, short segments lacking this sheath, and thus, accessible to the chemical milieu surrounding these endings, are found at their distal ends, which are likely to be sensory specializations [30,32](Fig 3c). Signals of tissue damage and inflammation may not diffuse widely due to localized release or secretion, combined with limited diffusion capabilities of signaling molecules that are easily buffered (eg. protons), quickly degraded (eg. ATP), or large in size (eg. cytokines). This may explain the need for multiple closely spaced sensory dendrites. Therefore, we suggest that chemical sensitivity of polymodal nociceptors in *Drosophila* and mammals requires both free dendrites and closely spaced dendrites.

Conclusions

Polymodal nociceptors detect noxious signals associated with tissue damage and elicit protective responses. As such, these neurons are likely to be of great importance to the animal's survival. Indeed, many features of polymodal nociceptors are found in multiple organisms, suggesting evolutionary conservation. Specifically, a morphological feature found in polymodal nociceptors of vertebrates and invertebrates is a multi-dendritic arbor whose terminal dendrites are free of glial ensheathment. Recent findings from *Drosophila* and *C. elegans* demonstrate that generation of this multi-dendritic morphology depends on a complex developmental program. Furthermore, polymodal nociceptors throughout evolution depend on the same families of sensory channels, TRP and DEG/ENaC, for their function. The conserved association between specific functions and molecular sensors with specific morphology of dendrites and dendritic arbors suggests that the form of the dendritic arbor may contribute to the function of these neurons and molecular sensors. However, many questions need to be answered in order to validate this hypothesis (Box 1).

Similar contributions of form to function may explain the morphologies of diverse sensory neurons. Progress in imaging the morphology of individual cells within living tissues, as well as in advancements in functional imaging techniques and in the genetic labeling of specific neuronal classes should facilitate more detailed investigations of the underlying correlations between form and function in the various different subclasses of sensory neurons.

Outstanding questions

- Which particular features of the multi-dendritic arbor of polymodal nociceptors are important for which specific functions? One way to examine this question is to analyze sensory functions of mutants defective for specific morphological features.
- Are terminal dendrites of all multi-dendritic mechanosensors either embedded in or tethered to external rigid structures?
- Does activation of DEG/ENaC channels by mechanical stimuli require structural elements such as the large diameter microtubules found in *C. elegans* touch receptor neurons, a cilium, or alternatively, a multi-dendritic morphology?
- Are *C. elegans* polymodal nociceptors sensitive to chemical signals? If so, which signals, and what functional roles do such signals confer?
- Is a dense dendritic arbor required for efficient activation/sensitization by chemicals serving as signals of tissue damage?

- Some multi-dendritic arbors involve exceptionally fine processes (eg. <100 nm diameter in *C. elegans* PVD neurons [10]). Do the terminal branches of other nociceptors also contain such fine branches? To examine this question at a detailed level, better intracellular tracers, and/or high-resolution microscopy are needed.

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Glossary

Cilium	(plural cilia) A thin microtubule-based organelle. In invertebrates, sensory cilia often lie within a protected tube formed by glial cells. In <i>C. elegans</i> non-motile cilia sense the chemical or physical environment, via thin tube-like connections linking the glial channel to the exterior of the animal. Chemical and/or thermal signals can traverse these connections to bathe the cilia inside the channel.
DEG/ENaC channels	The DEGenerin/Epithelial Na ⁺ Channel gene family encodes for proteins with two transmembrane domain subunits that assemble as multimers (trimers) to form cation permeable ion channels. These ion channels have many functional roles, including in the regulation of cellular homeostasis and the sensation of mechanical stimuli or protons.
Dendritic arbor	a tree like organization of branched neuronal-processes responsible for receiving synaptic or sensory inputs; also called a “sensory arbor” in sensory neurons.
Encapsulated ending	a sensory ending (ie. a dendrite) that is fully wrapped by specialized protective glia
Free ending	a sensory ending (ie. a dendrite or part of a dendrite) that has no accompanying glial wrapping, also called a “bare” ending or a “naked” ending.
Hyperalgesia	(increased sensitivity to pain): sometimes a result of activation of nociceptor TRP channels, due to chemical signals resulting from inflammation and tissue damage.
Hypodermis	a single layer syncytium covering the nematode’s body and lying underneath the non-living cuticle. The hypodermal layer is much thinner where it extends between cuticle and bodywall muscles. The function of the hypodermis is analogous to that of the living skin or epidermis.
Nociceptor	a neuron that senses high threshold, noxious signals.
Polymodal nociceptor	a nociceptor that is sensitive to two or more sensory modalities, usually mechanical and thermal, and sometimes chemical.

Self-avoidance	a property of highly branched dendrites in certain neurons to develop evenly spaced arbors that never touch or cross neighboring dendrites from the same neuron
Tiling	a property of branched dendrites of some neuron classes to never touch or cross dendrites from neighboring neurons of the same modality, but instead cover the body with non- overlapping receptive fields.
TRP channels	Transient Receptor Potential genes encode for a diverse family of subunits, each comprised of six transmembrane domain subunits that form cation permeable ion channels. TRP channels have many roles in cellular homeostasis and in sensory transduction. Several subgroups (eg. TRPV, TRPA, and TRPM) can be activated by temperature changes and are thus called thermoTRPs.

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Figure 1. Organization and development of PVD and FLP arbors in *C.elegans*

Schematic diagrams of PVD (blue) and FLP (red) processes as they are seen at 5 different stages of development [late larval stage 2 (late L2) to late L4/ young adult]. Dashed lines (in black) indicate processes that appeared earlier in development but have retracted by this stage. All views are from the left aspect showing only the left side cells of each cell pair; anterior is to the left. For convenience, all stages are shown at constant size. A single axon emerges ventralward from the cell body (colored ball) before going rostrally within the ventral cord. The process(es) emerging laterally from the cell body elaborate into highly branched dendrites. Note that knowledge of FLP development is meager compared to that of PVD, but available data suggest that FLP dendrites undergo the same sequence of events, and are likely obey the same rules.

Figure 2. Proposed mechanism linking organization of PVD branches to mechanosensation in *C. elegans*

A. Schematic of an adult *C. elegans* midbody showing three ventral and three dorsal menorah-like structures growing out of the PVD primary dendrite (dark blue). Movement of a single menorah upon pressure application by a sharp needle is indicated (white lines indicate position of the central dorsal menorah before pressure application). Transverse cross-section on the left edge of the diagram indicates positions of the four muscle quadrants (green) and hypodermis (beige) in the bodywall. The cuticle and thin layer of hypodermis are peeled back in part of the diagram to reveal the PVD quaternary dendrites (but quaternary dendrites are really within the hypodermis). One dorsal menorah on the left has been numbered, to indicate the temporal stage of branch development [ie. primary branches appeared first (1), followed by secondary (2) etc.]. On the right of the diagram, the overlying structures are shown: the outer cuticle layer (grey) and cuticle annuli (grey lines).

B. PVD quaternary dendrite enmeshed within the thin hypodermal layer (beige) in a transmission electron microscopic (TEM) image [colors have been superimposed on the image for clarity: PVD, blue; M (bodywall muscle), green; H (hypodermis), yellow].

Adapted, with permission, from [10].

C. Enlarged schematic showing how stretching of affected processes may lead to local DEG/ENaC channel opening. Both the position and likely activation state of these channels are indicated (filled circle indicates fully open, filled ellipse partly open, and thin line is closed).

Figure 3. Multi-dendritic polymodal nociceptors and mechanosensors from different organisms

A. *Drosophila* DA-IV neurons. The skin of the fly third instar larva is tiled with dendritic arbors that cover large receptive fields; the many free endings of each cell show self-avoidance. Redrawn with permission, based on immunohistochemical images from [25].

B. Leech P-cell. Pressure receptors in leech skin have distinctive multi-branched arbors with very fine endings that show self-avoidance (adapted, with permission, based on dye-filling images in [37]). Their receptive fields cover large portions of the leech skin and are known to substantially overlap circumferentially (i.e. no tiling).

C. Penicillate neuron of human skin. Nociceptors form highly branched dendrites ensheathed by a Schwann cell and its processes, except for short free endings at their termini (gray process shown in inset) that insert themselves at the borders between epidermal cells (wiggly line extending from the ending) or by invagination into a subepidermal cell. Short terminal branches of the neuron run within peripheral branches of the Schwann cell, and anchor to the epidermal basal lamina (arrows). These neurons are unmyelinated and belong to the C-fiber neuron class. N, Schwann cell nucleus. Based on schematic diagram in [30].

D. Palisade neuron of mammalian fur. Mechanosensitive dendrites end in candelabra-like arbors. These arbors show self-avoidance, and perhaps tiling, and wrap around the base of a vibrissal hair follicle (indicated by *). A single protruding hair is indicated by an arrow. Adapted, with permission, from [60].

Table 1

Function and morphology of nociceptors discussed in this review

Organism	Cell type	Modalities	Multi-dendritic	Tiling ^c
<i>C. elegans</i>	PVD	Mechanical, thermal	Yes	Yes
	FLP	Mechanical, thermal	Yes	Yes
	ASH	Mechanical, chemical	No	NA
<i>Drosophila</i>	DA-IV	Mechanical, thermal, light, chemical (cytokines)	Yes	Yes
Mammals ^a	C-fibers	Mechanical, thermal, chemical	Yes	No
	A δ -fibers	Mechanical, thermal	Yes	?
<i>Hirudo medicinalis</i>	N- Cells	Mechanical, thermal, chemical	Yes ^b	No
	P-Cells	Mechanical (pressure)	Yes	No

^a Mammalian nociceptors are heterogeneous. Both C-fibers and A δ -fibers include multiple types of neurons having different functions, properties, and molecular markers

^b N-cells appear to be multi-dendritic, however, detailed analysis of their morphology is currently lacking

^c Abbreviations: NA, data not available.

Table 2

Mechanosensory neurons in the *C. elegans* hermaphrodite.

Cell name	Morphological features	Molecular sensor	Refs
ADE ^a	Cilium		[94]
ALM, AVM, PLM, PVM (TRNs)	Large diameter microtubules, ECM derived mantle, and periodic dense plaques.	MEC-4, MEC-10, and DEGT-1 (DEG/ENaC)	[8,23,58,69],
ASH	Cilium	OSM-9 and OCR-2 (TRP) ^b	[17,38,39]
CEP	Cilium	TRP	[66,94]
DVA	Unspecialized neurite	TRP	[95]
FLP	Cilium and multiple branched dendrites	MEC-10 (DEG/ENaC)	[12,17]
IL1	Cilium		[17]
OLQ	Cillum	TRPA-1 and OSM-9 (TRP)	[12,17,96]
PDE	Cilium		[94]
PVD	Multiple branched dendrites	MEC-10 and DEGT-1 (DEG/ENaC)	[8,10]

^a *C. elegans* neurons have three letter names indicating characteristics of their soma and/or processes. ADE- Anterior DEirid, AFD- Amphid Filamentous D, ALM- Anterior Lateral Microtubule-filled, AVM- Anterior Ventral Microtubule-filled, PLM- Posterior Lateral Microtubule-filled, PVM- Posterior Ventral Microtubule-filled, IL1- Inner Labial 1, OLQ- Outer Labial Quadrant, PDE-Posterior DEirid.

^b In ASH, the TRP subunits [OSM-9 (OSMotic avoidance abnormal) and OCR-2 (Osm-9 and Capcaisin receptor-Related)] subunits are needed for all sensory modalities, and thus, may function downstream of stimulus reception.