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Lessons from Worm Dendritic Patterning

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Abstract

The structural and functional properties of neurons have intrigued scientists since the pioneering work of Santiago Ramón y Cajal. Since then, emerging cutting-edge technologies, including light and electron microscopy, electrophysiology, biochemistry, optogenetics, and molecular biology, have dramatically increased our understanding of dendritic properties. This advancement was also facilitated by the establishment of different animal model organisms, from flies to mammals. Here we describe the emerging model system of a *Caenorhabditis elegans* polymodal neuron named PVD, whose dendritic tree follows a stereotypical structure characterized by repeating candelabra-like structural units. In the past decade, progress has been made in understanding PVD's functions, morphogenesis, regeneration, and aging, yet many questions still remain.

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INTRODUCTION

A prominent characteristic of neurons is their diverse and complex neurite architecture. Within a neuronal circuit, dendritic trees assemble synaptic contacts with other neurons (as in postsynaptic neurons) or serve as sensory devices that sample their environment directly (sensory neurons) (Bacon & Murphey 1984, Yang & Masland 1994). The process of dendritic branching is highly regulated and involves three steps: (*a*) neurite initiation, outgrowth, and guidance toward a target location; (*b*) branching with different degrees of complexity, depending on the cell type, and synapse formation on postsynaptic neurons; and (*c*) maintenance of the dendrite shape over long periods of time (Dong et al. 2015, Jan & Jan 2010, Portera-Cailliau et al. 2003, Urbanska et al. 2008). Most of the changes in dendritic architecture occur during development, while the adult stage is considered less plastic (Kolb & Whishaw 1998, Redila & Christie 2006, Urbanska et al. 2008, Wu & Cline 1998). Despite over 100 years of research, several fundamental questions in dendritic physiology remain. What determines the architectural identity of a dendrite? How do extrinsic and intrinsic branching mechanisms coexist? How do dendritic trees age and regenerate? What is the role of sensory experience in shaping dendritic trees? And, possibly the most fundamental question, to what extent and how does the structure itself determine the function of the neuron?

Elaborately arborized dendritic structures such as Purkinje cells of mammals and class III and IV dendritic arborization neurons of *Drosophila* have been extensively studied and offer

many insights (Corty et al. 2009, Fiala et al. 2002, Jan & Jan 2010, Urbanska et al. 2008), yet *Caenorhabditis elegans*, with its simple, invariant, and fully mapped nervous system (White et al. 1986) and stereotypic behavioral repertoire (Stephens et al. 2011, Swierczek et al. 2011), offers a unique system to study such dendrites.

Dendritic arborization in *C. elegans* is a young field that was initiated by the discovery of the complex dendritic trees of PVD and FLP neurons (Halevi et al. 2002, Tsalik et al. 2003). Their architecture is composed of multiple structural units resembling a candelabra (or menorah), propagating along the longitudinal axis from head to tail (Oren-Suissa et al. 2010, Smith et al. 2010) (**Figure 1*d***). In this review, we describe the molecular processes that govern the PVD's dendritic arborization during development, aging, and recovery from trauma and in relation to sexual dimorphism. In parallel, we relate its structural and molecular characteristics to the sensory functions it mediates. The review is organized into eight lessons that we have learned from recent studies.

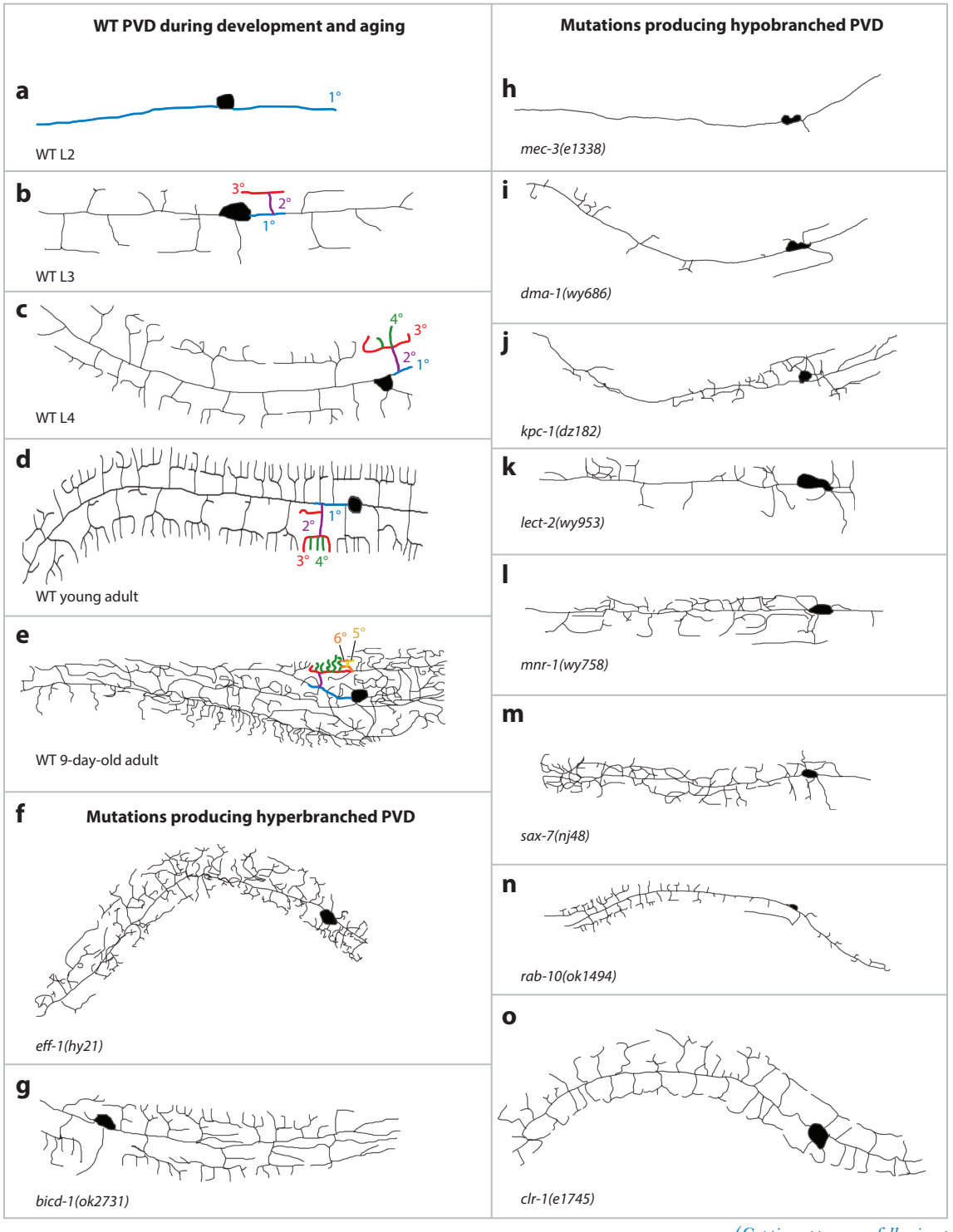
LESSON 1: PVD DENDRITIC ARBORIZATION IS NEARLY INVARIANT

Dendritic trees grow and retract, and their spatial and temporal coordination are thought to be required for the proper functioning of neurons and neuronal networks (McAllister 2000). Studies using *Drosophila melanogaster*, *Xenopus*, *C. elegans*, and rodents demonstrate that dendritic spatiotemporal coordination is achieved by following three principles. First, in the receptive field, the dendrite responds to attractive/repulsive signals to form a structure that covers a certain area. Second, in scaling, the receptive field increases its surface area to expand proportionally with the organism's growth. Third, in self-avoidance and tiling, neuronal branches of a receptive field do not overlap, creating full coverage of their receptive field (Corty et al. 2009, Dong et al. 2015, Kim et al. 2006, Lom & Cohen-Cory 1999, Parrish et al. 2007, Soba et al. 2007). While the original electron microscopy reconstructions of the PVD classified it as an interneuron of simple morphology (White et al. 1986), it in fact has a complex dendritic arborization pattern (Halevi et al. 2002, Oren-Suissa et al. 2010, Smith et al. 2010, Tsalik et al. 2003). The left and right cell bodies and primary branches of the PVD emerge postembryonically during larval stage 2 (L2) (**Figure 1*a***) and are derived from the ectodermal precursor cell V5 (Sulston & Horvitz 1977, White et al. 1986). As the worm grows and molts through L3 and L4, branches develop in an invariant fashion: (*a*) The primary branch extends toward the anterior and posterior parts of the worm below the seam cells; (*b*) secondary processes emerge orthogonally toward the dorsal and ventral areas; (*c*) tertiary branches propagate orthogonally from each secondary branch along the medial muscle border; and (*d*) orthogonal quaternary (terminal) branches propagate above the muscle, generating candelabra-like shapes that are distributed along the dorsal and ventral sides of the PVD primary process and cover the circumference of the worm (Oren-Suissa et al. 2010, Smith et al. 2010) (**Figure 1*b–d***). The full stereotypic branching pattern of the PVD appears at L4 and is maintained throughout early adulthood (Oren-Suissa et al. 2010, Smith et al. 2010) (**Figure 1*c,d***). Aging and various mutations can alter this architecture, causing excessive (hyper) or decreased (hypo) branching (**Figure 1*e–o***), as is described in the following sections (for a comprehensive list of mutants affecting PVD structure and function, see **Supplemental Table 1**). The next section describes the emerging model system of the PVD neuron for studying dendritic function.

Supplemental Material >

LESSON 2: FUNCTION OF DENDRITIC TREES MAY RELATE TO MORPHOLOGY

Nociceptors are neurons that detect noxious stimuli, including strong mechanical forces (e.g., harsh touch in *C. elegans*), toxic chemicals, and extreme temperatures. Understanding their underlying mechanisms can have beneficial clinical implications (Kuner & Flor 2017, Le Bars et al. 2001).



(*Caption appears on following page*)

Figure 1 (*Figure appears on preceding page*)

Reconstruction of PVD neuron morphogenesis during development and aging and for selected mutant backgrounds. (*a–d*) For wild-type (WT) PVD neurons, primary branches (*blue*) appear at larval stage 2 (L2), followed by the perpendicular appearance of secondary (*purple*) and tertiary (*red*) branches at L3 and quaternary branches (*green*) at L4. The result is repetitive candelabra-like structural units. Ectopic tertiary branches (*red*) elongate from a secondary stem of the candelabra. (*e*) In 9-day-old adult worms, the characteristic candelabra structures are hardly distinguished. Adult worms are characterized by multiple high-order ectopic branches [i.e., the fifth (*yellow*) and sixth (*orange*) branching orders]. (*f,g*) Examples of hyperbranched PVDs from L4 or young adult mutants are shown. (*h–o*) Examples of hypobranched PVD neurons in L4 or young adult mutants. Panels *a–d* and *f* adapted with permission from Oren-Suissa et al. (2010). Panel *e* adapted with permission from Kravtsov (2015). Panel *g* adapted with permission from Aguirre-Chen et al. (2011). Panel *h* adapted with permission from Tsalik et al. (2003). Panel *i* adapted with permission from Liu & Shen (2012). Panel *j* adapted with permission from Salzberg et al. (2014). Panel *k* adapted with permission from Zou et al. (2016). Panels *l* and *m* adapted with permission from Dong et al. (2013). Panel *n* adapted with permission from Zou et al. (2015). Panel *o* adapted with permission from Liu et al. (2016).

The PVD is defined as a polymodal nociceptor capable of detecting harsh touch (Way & Chalfie 1989), temperature reductions (Chatzigeorgiou et al. 2010), and body position (i.e., proprioceptive sensation) (Albeg et al. 2011). Despite extensive research, the exact contribution of the dendritic structure to the neuron's function remains elusive (Hausser & Mel 2003).

PVD Structure May Correlate with Its Mechanosensation States

Theoretical modeling suggests that changes in dendritic structure induce impaired signal propagation from the dendrites to the cell body and, consequently, a reduction in its response (Mainen & Sejnowski 1996, Vetter et al. 2001). In support of this claim, two mutants with PVD morphological defects also display reduced response to harsh touch: *mec-3* and *eff-1*. The mechanosensory function of the PVD was originally characterized (Way & Chalfie 1989) by the harsh-touch-insensitive *mec-3* LIM homeobox transcription factor mutant, which displays a complete loss of higher-order PVD branches (Tsalik et al. 2003) (**Figure 1*b***). Mutants of the cell fusion gene *eff-1* (epithelial fusion failure 1) (Mohler et al. 2002, Podbilewicz et al. 2006) show a disorganized, hyperbranched PVD phenotype (**Figure 1*f***) and also display a reduced response to harsh touch (Oren-Suissa et al. 2010). One proposed model suggests that the quaternary PVD branches serve as force-sensing devices, which bend and transmit external forces to the tertiary and primary branches (Hall & Treinin 2011). The quaternary branches express mechanosensory-transducing degenerins/epithelial sodium channels (DEGs/ENaCs) (e.g., MEC-10 and DEGT-1) (Chatzigeorgiou et al. 2010), which open to activate downstream interneurons and motoneurons to affect harsh-touch response. Interestingly, mutations in MEC-10 and DEGT-1 affect both the response to harsh touch (Chatzigeorgiou et al. 2010, Inberg & Podbilewicz 2018) and the morphological characteristics of the PVD (Inberg & Podbilewicz 2018). Recent results suggest that these two properties are also independently affected by mechanosensory experience via DEGs (Inberg & Podbilewicz 2018) (see the sidebar titled Sensory Experience Controls Dendritic Structure and Behavior via Degenerins).

An elegant study performed cell-specific activation by photostimulating channel rhodopsin-2 (ChR-2) expressed in the PVD, effectively bypassing DEG/ENaC sensory channel activity. This approach was combined with a candidate RNA interference–based gene silencing screen to identify genes that mediate the behavioral response to PVD activation (Husson et al. 2012). Interestingly, *mec-3* and *unc-86* mutants, which display severe hypobranching phenotypes, also display an impaired response to photostimulation. Another DEG/ENaC, named ASIC-1 (acid-sensitive ion channel 1), was found to be involved in extending the dynamic range of PVD activation under optogenetic activation. These results may be explained by reduced ChR-2 expression in the PVD or alternatively by a reduction in presynaptic functions, namely axonal changes.

SENSORY EXPERIENCE CONTROLS DENDRITIC STRUCTURE AND BEHAVIOR VIA DEGENERINS

Inberg & Podbilewicz (2018) show that sensory experience independently influences both the mechanosensory output of the PVD and its morphological structure. Worms that grew in isolation display reduced responses to harsh touch and altered dendritic architecture when compared with worms grown in a crowded environment. The two phenomena—behavior and structure—are unrelated, as isolated worms that respond to harsh touch are not morphologically different from isolated worms that do not. The experience-dependent behavioral and structural plasticities are mediated by the degenerins ASIC-1, MEC-10, and DEGT-1 that act as molecular devices that translate environmental signals into structural and functional changes. MEC-10 affects PVD morphology cell autonomously; its localization is affected in *degt-1* mutants and by sensory experience. This phenomenon represents a unique isolation-induced pathway of dendritic plasticity during the adult stage.

Nicotinic acetylcholine receptors (nAChRs), which are cation-permeable ion channels that enable fast excitation, were also found to affect the PVD's response to harsh touch (Cohen et al. 2014). Both nAChR-forming DEG-3 and DES-2 are highly expressed throughout PVD and FLP neurons (Halevi et al. 2002; Yassin et al. 2001, 2002). *des-2;deg-3* mutants show an abnormal morphological gradient in the anterior-posterior axis, with less anterior secondary branches, more self-avoidance defects between adjacent candelabras, and impaired mechanosensation. These nAChRs therefore represent another interesting case where mechanosensory channels affect the structural and functional phenotypes of the neuron (Cohen et al. 2014).

To summarize, more data are required to establish a causal link between the PVD's structure and its mechanosensory function. It is possible that sensory channels affect structure and function in parallel, yet disconnected, pathways.

Thermosensation Is Probably Not Affected by Dendritic Structure

Transient receptor potential 1 (TRPA-1) is a mechanosensory channel (Kindt et al. 2007); however, in the PVD it only senses dropping temperatures (Chatzigeorgiou et al. 2010). Several lines of evidence suggest that the PVD's dendritic structure is not involved in thermosensation: First, heterologous expression of TRPA-1 in human embryonic kidney cells and in the ALM unbranched neurons in *C. elegans* is sufficient to induce a response to cooling (Chatzigeorgiou et al. 2010). Second, TRPA-1 expression in the PVD is limited to the cell body, suggesting that it functions in the soma and not in the dendrites. Therefore, it is unlikely that the PVD's structure affects its thermal sensory modality.

It Is Unknown Whether Proprioceptive Functions of the PVD Relate to Dendritic Structure

Worms generate a periodic anterior-posterior sinusoidal waveform during movement. This locomotion is modulated by motor neurons (Von Stetina et al. 2006) and interneurons such as the DVA (Li et al. 2006). Intriguingly, the PVD generates calcium spikes during movement but not when immobile. Genetic ablation of the PVD decreases the bending angle of the worm's movement, a phenotype also apparent in the hypobranching mutant *mec-3* (Albeg et al. 2011). While these data suggest that the PVD may function as a proprioceptor, whether this relates specifically to its structural properties remains to be tested.

In summary, PVD is a polymodal neuron similar to somatosensory neurons found in mammals (Ebara et al. 2002, Tonomura et al. 2015) and insects (Corty et al. 2009, Parrish et al. 2007), yet its sensory functions do not display a direct correlation to its dendritic structure alone.

In the following sections, we review genes that are responsible for dendritic morphogenesis.

LESSON 3: DENDRITIC TREE CYTOSKELETAL STRUCTURE IS GENETICALLY DETERMINED

Dendritic branching is driven by a multitude of molecular components: secreted factors, neurotropic factors, cell adhesion molecules, synaptic scaffold proteins, signaling molecules, cytoskeleton modifiers, secretory pathway regulators, and transcription factors. These factors orchestrate to enable dendritic morphogenesis during development and mediate plasticity in adulthood (Arikkath 2012, Kim et al. 2006, Krivosheya et al. 2008, Lom & Cohen-Cory 1999, Meltzer et al. 2016, Parrish et al. 2006, Snider 1988, Warren et al. 2012, Yu & Malenka 2003).

Microtubules are tubular polymers that form part of the cytoskeleton. Their simultaneous assembly and disassembly, also termed dynamic instability, require energy obtained from GTP hydrolysis (Desai & Mitchison 1997). Microtubules are major structural elements of neurites, determining their rigidity, cargo transport, and shape. Hence, ordered microtubule dynamics may modulate the structure of dendritic trees. Kinesin/UNC-116 acts with the microtubule motor protein dynein to direct the anterior-posterior branching patterning of the PVD. The organization of the microtubules in the PVD is composed of plus-end-out orientation in the axon and posterior segments (Maniar et al. 2011, Taylor et al. 2015) and minus-end-out orientation in the anterior (Taylor et al. 2015). Bicaudal D (BicD in *Drosophila*, *bicd-1* in *C. elegans*, BicD1 and BicD2 in mammals) is an accessory factor of dynein and is required for messenger RNA transport (Bullock & Ish-Horowicz 2001, Bullock et al. 2006), nuclei positioning (Swan et al. 1999), and dendritic morphogenesis (Bianco et al. 2010). Missense and knockout mutations in *BICD2* have been linked to spinal muscular atrophy (Oates et al. 2013) and disrupted organization of the cerebral cortex and cerebellum (Jaarsma et al. 2014). In *Drosophila* larvae's dorsal ddaC neuron, a mutation in *BicD* shows reduced branching (Bianco et al. 2010). Since *bicd-1* acts cell autonomously and cooperatively with dynein, it may regulate some branching orders differently depending on their plus-minus microtubule orientation and the distance from the PVD cell body. Indeed, in *bicd-1* mutants, the anterior part of the PVD shows a decrease in the number of quaternary branches, but posteriorly to the cell body there is an increased number of tertiary ectopic branches. However, this phenotype appears only during adulthood (Aguirre-Chen et al. 2011) (**Figure 1*g***). Mutants in *dli-1*, a component of the cytoplasmic dynein, show similar phenotypes to that of *bicd-1* (Zhu et al. 2017).

Actin/*act-4* (Kueh & Mitchison 2009) is also involved in the assembly of higher-order PVD branches (Zou et al. 2018) and self-avoidance between branches (Liao et al. 2018).

Another genetically determined cell-autonomous regulator of the dendritic tree is *kpc-1*/furin, a proprotein convertase, which is an important activator of ventral closure and embryonic turning (Roebroek et al. 1998) and is associated with the induction of cell death in cortical neurons following injury (Yamada et al. 2018). Mutation in *kpc-1* induces disorganized and truncated arbors in the IL2 and PVD neurons (Salzberg et al. 2014, Schroeder et al. 2013) (**Figure 1*j***). Taken together, cytoskeleton-associated mechanisms affect the structural properties of the PVD from within.

LESSON 4: A COORDINATED MOLECULAR COMPLEX CONTROLS DENDRITIC TREE MORPHOGENESIS

The immediate environment surrounding the PVD includes the muscles and the epidermis (Oren-Suissa et al. 2010) (**Figure 2*a–d***). Their extrinsic signaling, combined with intrinsic

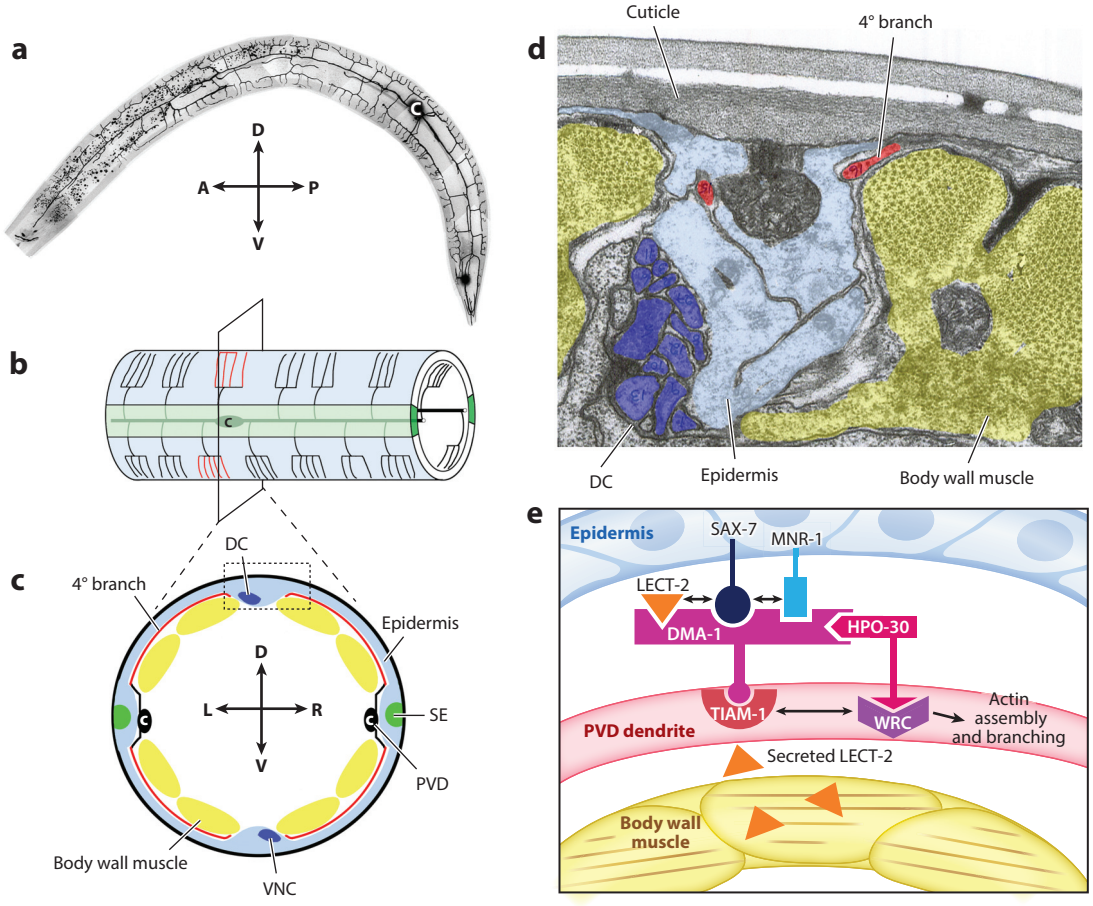


Figure 2

Epidermis and muscles direct PVD localization by multiple molecular components affecting neurite branching. (*a*) Full stereotypic PVD arborization pattern of a young adult (only left PVD shown). (*b*,*c*) Schematic description of the PVD's structure and anatomical positioning. Two wild-type PVD (and FLP) neurons grow between the epidermis (outer cylinder, *light blue*) and the body wall muscle cells (*yellow ovals*). The PVD is characterized by three orthogonal processes from the primary branch that form candelabra-like structures. Some candelabra have quaternary branches (*red lines*) that contact the edges of the DC and VNC (*dark blue*). (*c*) Transverse view of the adult hermaphrodite. (*d*) Micrograph of the ultrastructure of two FLP neurons' (which share a high structural similarity to the PVD) quaternary dendrite tips (*red*) joining the edge of the DC (*blue*). (*e*) Representation of the main known protein complex required for PVD dendrite arborization. Abbreviations: A, anterior; C, cell body; D, dorsal; DC, dorsal nerve cord; L, left; P, posterior; R, right; SE, seam cells; V, ventral; VNC, ventral nerve cord; WRC, WAVE regulatory complex. Panel *a* adapted with permission from A. Meledin (unpublished data). Panels *b–d* adapted with permission from Oren-Suissa et al. (2010). Panel *e* adapted with permission from Zou et al. (2016, 2018).

mechanisms, orchestrates to direct ordered dendritic arborization (Dong et al. 2015, Jan & Jan 2010, Wei et al. 2015). Here, we describe the best-characterized morphogenesis-guiding players and explain their localization patterns.

The Quad-Partite Guidance Complex of DMA-1/SAX-7/MNR-1/LECT-2

The primary guidance pathway for the developing PVD dendrite branches is a quad-partite complex (**Figure 2*e***) composed of (*a*) DMA-1, a neuronal leucine reach repeat extracellular domain

receptor acting cell autonomously from within the PVD, and three epidermally derived proteins: (*b*) sensory axon guidance-7 (SAX-7)/L1CAM, a member of the conserved immunoglobulin superfamily of cell adhesion molecules; (*c*) menorin-1 (MNR-1), a conserved type I transmembrane protein; and (*d*) the muscle-derived diffusible leukocyte cell–derived chemotaxin 2 homolog (LECT-2) (Diaz-Balzac et al. 2016, Dong et al. 2013, Salzberg et al. 2013, Zou et al. 2016). *dma-1*, *mnr-1*, and *sax-7* act in the same genetic pathway, and mutations in each factor cause a loss of tertiary and quaternary branches (**Figure 1*i*,*l*,*m***, respectively). *lect-2* mutants similarly display decreased tertiary and absent quaternary branches as well as disorganized secondary branches (**Figure 1*k***). LECT-2 enhances the formation of the DMA-1/SAX-7/MNR-1 complex (Diaz-Balzac et al. 2016, Zou et al. 2016) and is directed to the regions of tertiary and quaternary PVD branches by SAX-7 (Zou et al. 2016). Interestingly, while LECT-2 mediates quaternary branch growth as a muscle-derived cue, it directs secondary branches as a long-range cue from other tissues (Zou et al. 2016).

DMA-1 links the above-mentioned extrinsic factors with an intrinsic pathway affecting arborization through the claudin-like protein HPO-30 (Zou et al. 2018). DMA-1 and HPO-30 proteins form a receptor-associated signaling complex with their downstream partners (**Figure 2*e***): DMA-1 with RacGEF TIAM-1 and HPO-30 with WAVE regulatory complex (Chen et al. 2010, 2017; Zou et al. 2018). This intracellular complex modulates actin polymerization to enable complete dendritic branching (Zou et al. 2018).

Regulation of the Quad-Partite Complex Localization

The localization of DMA-1 to the PVD is regulated by several intrinsic factors, including RAB-10 GTPase and the exocyst complex, which transport and insert DMA-1 into the PVD membrane. RAB-10 mutants show a reduction in branch growth surrounding the PVD cell body (**Figure 1*n***) starting at L4, indicating that RAB-10 is temporally regulated to function only during the last steps of PVD assembly. Mechanistically, GTP-bound RAB-10 promotes dendritic growth through kinesin, localizing DMA-1 to the entire dendrite (Taylor et al. 2015, Zou et al. 2015). Another factor regulating DMA-1 is the conserved, eukaryotic inositol-requiring enzyme 1 (IRE-1), which is involved in the unfolded protein response of endoplasmic reticulum (UPR-ER) (Ron & Walter 2007). In *ire-1* mutants, DMA-1 protein is restricted to the PVD cell body, and a branching gradient appears around it. This function of *ire-1* in the PVD is independent of *xbp-1* (X-box binding protein-1), the best-known target of IRE-1, in the UPR-ER pathway (Salzberg et al. 2017, Wei et al. 2015).

SAX-7 localization is suggestively regulated by muscle sarcomere components. Specifically, the integrin PAT-2 and the extracellular proteoglycan UNC-52/Perlecan direct SAX-7 localization to dense parallel stripes between the muscle and the epidermis where quaternary PVD branches grow (Liang et al. 2015) (**Figure 2**).

A DMA-1-Independent Pathway Affecting PVD Branching

Another cue that affects dendrite structure independently from the *DMA-1/SAX-7/MNR-1* complex signaling pathway is the receptor tyrosine phosphatase CLR-1 protein, which is expressed in muscles and the hypodermis (Liu et al. 2016). *clr-1* mutants display a loss of quaternary branches (**Figure 1*o***), which can be rescued by hypodermal expression of CLR-1 containing its active phosphatase domain. Therefore, CLR-1 may dephosphorylate some unidentified factor rather than directly interacting with the PVD to affect its structure.

In summary, several signaling complexes, including intrinsic and extrinsic factors, pattern and work in unison to sculpt PVD architecture during development.

LESSON 5: DENDRITIC TILING, SELF-AVOIDANCE, AND COEXISTENCE

The spatial separation of an individual dendrite is maintained partly by self-avoidance, or enforcing repulsion between its own branches, while tiling, the effective separation between neighboring neurons, is mediated by partially distinct mechanisms (Cameron & Rao 2010, Corty et al. 2009, Grueber & Sagasti 2010, Jan & Jan 2010, Yip & Heiman 2016). The PVD's tertiary branches grow toward each other, touch shortly, and then quickly retract, forming a gap between adjacent candelabras. Furthermore, in *egl-46* mutant animals, which show a reduced number of candelabras, the tertiary branches increase in length so that the gap distance is maintained (Smith et al. 2012). Therefore, conserved self-avoidance principles act in *C. elegans* to shape distinct dendritic structural units.

In *Drosophila*, self-avoidance is maintained by surface proteins such as Turtle (Long et al. 2009), Flamingo (Matsubara et al. 2011), and Dscam (Hattori et al. 2008, Hughes et al. 2007, Matthews et al. 2007, Soba et al. 2007). In the PVD, the evolutionarily conserved UNC-6/Netrin axonal guidance protein (Mitchell et al. 1996, Serafini et al. 1994, Wadsworth et al. 1996) mediates self-avoidance by interaction with specific surface receptors such as UNC-5 and UNC-40 (Chan et al. 1996, Leonardo et al. 1997). Whereas both UNC-5 and UNC-40 act cell autonomously in the PVD, UNC-6 acts as a permissive extrinsic cue. One model suggests that UNC-40 localizes UNC-6 to one branch, where it interacts in *trans* with UNC-5 on another branch. This UNC-6-UNC-5 interaction triggers the branch repulsion required for self-avoidance (Smith et al. 2012).

lin-22, a homolog of *Drosophila* hairy/Enhancer of split transcriptional repressors, encodes a helix-loop-helix protein; during larval development it is required for patterning the epidermal mid-body and neuronal lineages. As a result, *lin-22* mutant worms have not one but five PVDs on each side. These five PVDs are shortened and do not cross, demonstrating that *C. elegans* ectopic PVD neurons are tiling with one another. Furthermore, *unc-6* mutants display PVD tiling defects between adjacent PVDs. Therefore, the self-avoidance factor UNC-6 is also required for isoneural tiling (Yip & Heiman 2016).

A recent paper discovered that *mig-14*/Wntless has a conserved role in PVD self-avoidance independent of the Wnt signaling pathway. *mig-14*/Wntless acts cell autonomously through the actin regulatory complex N-WASP (Wiskott-Aldrich Syndrome protein), which in turn mediates local F-actin concentrations found at the branch contact site (Liao et al. 2018). Taken together, conserved extrinsic and intrinsic factors mediate the preservation of receptive field separation at the candelabra and cellular levels of the PVD.

LESSON 6: FUSOGENS MEDIATE DENDRITIC REGENERATION AND SCULPTING

Sculpting of Dendritic Trees via EFF-1-Mediated Retraction and Auto-Fusion

The cell-cell fusion gene *eff-1*, which is involved in the morphogenesis of epithelial organs (Mohler et al. 2002, Podbilewicz et al. 2006), plays a major role in sculpting the PVD (Oren-Suissa et al. 2010). *eff-1* mutants show an increase in secondary branches and misguided quaternary branches that are directed medially toward the primary branch (retrograde/ectopic migration) (Oren-Suissa et al. 2010, Zhu et al. 2017) (**Figure 1*f***). In fact, this effect of EFF-1 on PVD structure gave rise to the PVD's utilization as a model for dendritic morphogenesis (Oren-Suissa et al. 2010). There are three suggested models for the nature of EFF-1's influence on the PVD; these models differ in the proposed location of EFF-1's function and in the direct/indirect nature of its contribution.

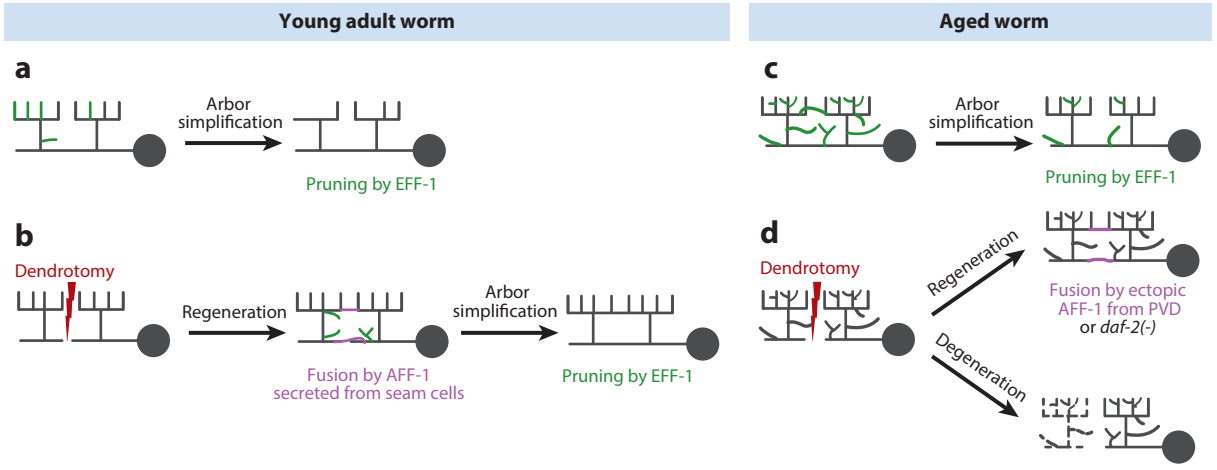


Figure 3

EFF-1 and AFF-1 proteins maintain dendritic structure and mediate dendrite regeneration by fusion, respectively. In young animals, (*a*) EFF-1 simplifies PVD structure by pruning, and (*b*) following injury, AFF-1, probably secreted from seam cells in extracellular vesicles, fuses two amputated PVD parts together, and EFF-1 eliminates ectopic branches formed around the injury site. In aged animals, (*c*) EFF-1 overexpression from the PVD simplifies age-associated hyperbranching, and (*d*) following dendrotomy, the dendrite usually undergoes degeneration, while overexpression of AFF-1 from the PVD or *daf-2(-)* background increases regeneration. Figure adapted with permission from Kravtsov et al. (2017).

The first model suggests that EFF-1 works cell autonomously and directly in the PVD (Oren-Suissa et al. 2010). EFF-1 expressed under a PVD promoter was shown to rescue the hyperbranching phenotype in *eff-1* mutants (Oren-Suissa et al. 2010), while overexpression of EFF-1 in the PVD increases the number of retractions and simplifies the overall structure of the PVD (Kravtsov et al. 2017, Oren-Suissa et al. 2010) (**Figure 3*a*,*c***). Based on time-lapse imaging, this pruning of the dendritic tree is the result of fission events or auto-fusion of branches forming loops (Oren-Suissa et al. 2010). In summary, this model supports a direct, cell-autonomous role for *eff-1* in simplifying the PVD's structure through retraction and fusion-related events.

In contrast, the second model supports a non-cell-autonomous, indirect function for EFF-1 in PVD morphogenesis (Zhu et al. 2017). In a conditional hypomorphic *eff-1* mutant, PVD-specific expression of EFF-1 does not rescue its dendritic phenotypes, whereas epithelial expression of EFF-1 does (Zhu et al. 2017). Intriguingly, SAX-7 localization is disturbed in *eff-1* animals, and its patch-like distribution coincides with hypodermal cells that failed to fuse. In turn, this unorganized distribution of SAX-7 partially overlaps with ectopic PVD branches, consistent with SAX-7's role in PVD morphogenesis. This model therefore supports an indirect, non-cell-autonomous role, whereby the *eff-1*-mediated fusion of epidermal cells affects the epidermal patterning of SAX-7 and, consequently, PVD branching.

The abovementioned studies used different promoters driving the expression of EFF-1 and different *eff-1* mutant strains, both of which may explain their discrepancies. A third alternative model is that epidermally derived EFF-1 acts non-cell-autonomously to mediate the direct phagocytosis of PVD fragments during maintenance and regeneration. This model is based on a new fission function of EFF-1 in sealing phagosomes responsible for cell fragment clearance; EFF-1 in the hypodermis is required for the engulfment of the distal fragment of the tail spike cell and the CEMVL neuron (Ghose et al. 2018). As described above, live imaging also demonstrated that EFF-1 induced the fission of PVD branches and probably the engulfment of dendritic

fragments by the hypodermis (Oren-Suissa et al. 2010). In summary, the fusion role of *eff-1* plays a key function in PVD dendritic arborization, although the precise mechanism is still debated. Below, we describe how anchor cell fusion failure-1 (AFF-1), the paralog of EFF-1, is involved in non-cell-autonomous regeneration of the PVD following injury.

Regeneration, Degeneration, and Dendritic Fusion

Neuronal degeneration and neurodegenerative diseases are common hallmarks of nerve injury (Fernandez-Gonzalez et al. 2002, Stoll et al. 2002). Damaged axons typically undergo beading, fragmentation, and clearance by a genetically regulated process termed Wallerian degeneration (Hilliard 2009, Stoll et al. 2002). The alternative response to trauma is axonal regeneration, which has been extensively studied in *C. elegans* and other systems (Ghosh-Roy & Chisholm 2010, Ghosh-Roy et al. 2010, Hafidi et al. 1995, Hilliard 2009, Shewan et al. 1995).

In *C. elegans*, axonal regeneration following laser-induced axotomy (severing of the axon) induces one of two consequences: Wallerian degeneration of the distal fragment, followed by complete regrowth from the remaining fragment proximal to the cell body (Hilliard 2009), or an alternative mechanism that has been characterized only in invertebrates, whereby the distal fragment is not degenerated but reconnected via fusion, reestablishing the original axonal tract (Hilliard 2009, Neumann et al. 2015).

The *C. elegans* PVD neuron presents a unique opportunity to also analyze the far-less-studied field of dendritic regeneration. The prevailing outcome following dendrotomy is reconnection via adjacent candelabra fusion or primary-primary branch merger, while degeneration occurs in 10–20% of young adult worms (Oren-Suissa et al. 2017).

Cell-cell fusion represents a mechanism for neuronal development, injury, and repair in both dendrites and axons (Giordano-Santini et al. 2016); however, data from different organisms suggest that dendritic and axonal regeneration mechanisms only partially overlap (Ghosh-Roy et al. 2010; Neumann et al. 2015; Oren-Suissa et al. 2010, 2017). In *C. elegans*, *eff-1* acts cell autonomously to mediate axonal regeneration via fusion (Ghosh-Roy et al. 2010, Neumann et al. 2015); however, it is not involved in regeneration of the PVD dendritic tree (Oren-Suissa et al. 2017). Instead, *eff-1* prunes excessive PVD dendrites as part of the homeostatic structure maintenance of branches and following injury (Oren-Suissa et al. 2010, 2017) (**Figure 3*a–c***).

Recent evidence suggests that following PVD dendrotomy, the fusion protein AFF-1 (Sapir et al. 2007) is responsible for reconnecting the severed branches (Oren-Suissa et al. 2017). *aff-1* worms have no morphological defects in the PVD; however, following dendrotomy, they exhibit increased degeneration and reconnect mainly via primary-primary branch fusion. Surprisingly, AFF-1 expression from epidermal seam cells but not the PVD is sufficient to restore PVD reconnection in *aff-1* background. Therefore, AFF-1 acts non-cell-autonomously from the epidermal seam cells to reconnect PVD segments (Oren-Suissa et al. 2017). The factors responding to PVD injury and inducing the release of vesicles coated with AFF-1 from the seam cells are as yet unknown. Taken together, studies of the PVD provide insights into dendrite regeneration following injury and provide a powerful tool to study morphological nerve responses to damage in vivo.

LESSON 7: FUSOGENS AND AGING PATHWAYS AFFECT PVD MAINTENANCE

Many neurodegenerative diseases are associated with aging (Yankner et al. 2008). Moreover, axons display age-associated morphological changes characterized by slower growth and retraction rates and recover less readily from injury (Bano et al. 2011, Verdu et al. 2000, Yankner et al. 2008). The most conserved pathway that controls aging and longevity in mammals, flies, and *C. elegans* is the

insulin/insulin growth factor-1 (IGF-1) receptor DAF-2 and its downstream effector DAF-16 (a FOXO transcription factor) (Kenyon 2010, Kenyon et al. 1993). Worms lacking *daf-2* live twice as long as wild types, are considered to stay healthy for longer (Kenyon 2010, Kenyon et al. 1993), and display delayed morphological changes and improved axonal regeneration (Pan et al. 2011, Tank et al. 2011, Toth et al. 2012). Little is known about how dendritic structure and regenerative capacity are affected during aging, and recent research employed the *C. elegans* PVD neuron as a model to answer these questions (E et al. 2018, Kravtsov et al. 2017).

Analysis of L4 to 10-day-old worms has demonstrated that the PVD structure is highly dynamic throughout aging (**Figure 1*c–e***): The total number of branches increases, high-order ectopic branches appear, and candelabras become more disorganized and lose their self-avoidance properties (**Figure 1*e***). This progressive dendritic remodeling is independent of the canonical insulin/IGF-1 receptor pathway; remarkably, overexpression of EFF-1 alone is sufficient to simplify the disorganized PVD morphology in aged worms (Kravtsov et al. 2017) (**Figure 3*c***).

A separate feature of aged PVD dendrites is the appearance of beads or bubble-like structures enriched in autophagosomes and fragmented microtubules along the dendrite (E et al. 2018) that likely represent an early stage of neuronal degeneration in other systems (Morsch et al. 2015, Pan et al. 2011). In contrast to arbor morphology, these changes are *daf-2* mediated. Interestingly, the loss of function of the *nlp-29* gene, encoding for an antimicrobial peptide, also delays this age-associated PVD degradation (E et al. 2018). Regarding PVD dendritic regeneration in aging, it was shown that aged worms exhibit reduced plasticity (growth/retraction rates) and a nearly complete loss of their regenerative capability (Kravtsov et al. 2017). This regenerative potential is restored by the ectopic expression of AFF-1. Remarkably, the regenerative potential of aged worms is also restored in *daf-2* mutants (**Figure 3*d***). In summary, the cell-cell fusion–mediating proteins AFF-1 and EFF-1 are also involved in rejuvenating the aged PVD.

LESSON 8: SEXUALLY DIMORPHIC DENDRITIC REMODELING

Dendritic remodeling has been shown to differ between the sexes. Sexually dimorphic pattering was observed during normal development (Goto et al. 2011), following injury (Pfister et al. 2013), or under chronic stress (Moench & Wellman 2017).

Like many invertebrates and vertebrates, most of *C. elegans*'s male and hermaphrodite neurons, the PVD included, are shared; however, some sex-specific neurons exist (White et al. 1986). The GABAergic motor neuron/interneuron DVB displays a male-specific progressive outgrowth posteriorly, which changes significantly during development and shows dramatic changes that are experience and activity dependent (Hart & Hobert 2018). Outgrowth is prompted by antagonistic activity of the conserved synaptic proteins NRX-1/neurexin and NLG-1/neuroligin, suggesting a novel role for these cell adhesion molecules in rewiring and plasticity.

PDB is a shared motor neuron located at the preanal ganglion. However, its processes are extensively grown in males, synaptically interacting with neurons of the male mating circuit (Emmons 2014). In addition, some sex-shared neurons, such as PHBs, are extensively dimorphically connected and engage in many more synaptic connections in the male compared with the hermaphrodite, yet they show no obvious morphological differences between the two sexes (Oren-Suissa et al. 2016). As for the PVD, no major differences were found in the dendrite arborization pattern that could be attributed solely to the sexual identity of the animals (S. Le Tho & B. Podbilewicz, unpublished data). However, aged males showed a significant increase in dendrite outgrowth compared with hermaphrodites (S. Le Tho & B. Podbilewicz, unpublished data). The male posterior nervous system is highly dense and arborized, complicating the morphological characterization of sex-shared neurons. The combination of cell-specific fluorescent reporters

with the full available reconstruction of the male nervous system by transmission election microscopy (Emmons 2018) will open up a new field of sexually dimorphic dendritic arborization.

SUMMARY AND FUTURE DIRECTIONS

Over the past decade, the PVD neuron has become an exciting system among animal models to study dendritic morphogenesis. Indeed, the effort has been fruitful, and different unique and widespread molecular mechanisms were discovered. The utilization of *C. elegans*, with its invariant nervous system, transparent body, advanced genetics, and simple behavioral outputs, supports the rise in popularity of the PVD neuron in the dendritic morphogenesis field. Given its polymodality, we predict that the PVD will also become a powerful model system to study relationships between dendritic structure and function. Together with the molecular mechanisms mediating its morphogenesis, aging, regeneration, and sensory functions, we expect it to provide new mechanisms and long sought-after answers in the future.

SUMMARY POINTS

1. The *C. elegans* polymodal sensory PVD neuron is stereotypically structured and provides a powerful model to study dendritic morphology.
2. The PVD's functions of thermosensation and mechanosensation are probably independent of its dendritic architecture.
3. Cytoskeletal components dynamically stabilize the PVD dendrites but also transport key molecules that guide its structure.
4. A quad-partite complex combines intrinsic (i.e., from the PVD) and extrinsic (i.e., from other tissues) components to guide the PVD branches during development.
5. PVD branches avoid each other by self-recognition and retraction, both on the same neuron and between adjacent neurons.
6. Two distinct fusogens are known to influence the PVD's structure: EFF-1 participates in the maintenance of the dendritic tree, while AFF-1 mediates dendritic regeneration.
7. The longevity-related DAF-2 pathway modulates the regenerative potential of the aged PVD. However, this pathway does not affect morphological changes of the PVD during aging.
8. Other neurons in *C. elegans* display sexual dimorphism, some varying in morphological characteristics and others showing differential synaptic connectivity.

DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

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Links the quad-partite component DMA-1 with HPO-30 to downstream cytoskeleton-related signaling pathways affecting morphogenesis.

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