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Assisted morphogenesis: glial control of dendrite shapes

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Abstract

Neurons display a myriad of dendritic architectures, reflecting their diverse roles in information processing and transduction in the nervous system. Recent findings suggest that neuronal signals may not account for all aspects of dendrite morphogenesis. Observations from *C. elegans* and other organisms suggest that glial cells can affect dendrite length and guidance, as well as localization and shapes of dendritic receptive structures, such as dendritic spines and sensory cilia. Thus, besides direct roles in controlling neuronal activity, glia contribute to neuron function by ensuring that neurons attain their proper shapes.

Introduction

The enormous diversity of dendritic shapes has been well documented [1]. This diversity is in no small part a result of each dendrite's unique task: to gather information from specific synaptic partners or from the environment, and to transmit this information to the axon. In mammals, dendritic arbors can be highly branched, and individual dendrite branches may possess numerous small protrusions termed dendritic spines, which represent postsynaptic terminals of excitatory synapses. The shapes of dendrites and their substructures can affect synaptic partner choice as well as the strength and efficacy of the connections that are made.

Intimately associated with neurons are glial cells, which comprise the most abundant cell type of the mammalian brain, and which, like neurons, exhibit dizzying morphological complexity and specialization [1-3]. Glia are well positioned to regulate dendritic morphology as they are not only in close proximity to neurons but also ensheath neuronal processes and synapses. Despite possible roles in controlling various aspects of nervous system function, *in vivo* studies of vertebrate glia and their roles in the nervous system have been complicated, primarily because the ablation or manipulation of glia often results in neuronal death [4,5]. By contrast, in the invertebrate nematode *Caenorhabditis elegans*, neurons survive following glia ablations, opening a unique *in vivo* arena in which to investigate the effects of glia on neuron function and shape [6*,7]. Like mammals, the dendrites of *C. elegans* neurons come in many shapes and sizes, from the single long extensions of amphid sensory neurons in the head of the animal [8], to the complex tiled branches of PVD and FLP mechanosensory neurons that cover the body [9*]. Associated with *C. elegans* neurons are 50 glial cells, which ensheath sensory endings, synapses, and neuron processes [10,11]. In this review, we describe recent findings

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that highlight the important roles of glia in dendritic morphogenesis, with a focus on recent studies of *C. elegans*.

Growing dendrites: anchors aweigh

The most prominent morphological features of neurons are their complex and highly stereotyped dendritic arbors [12]. Some of the signals controlling arbor shapes are neuron intrinsic. For example, the nuclear protein HAMLET is transiently expressed in external sensory neurons of *Drosophila* during the initial phases of dendrite outgrowth, and *hamlet* mutants display altered dendritic branching patterns [13]. In *C. elegans*, mutations that disrupt intrinsic activity of the transmembrane fusogen EFF-1 result in excessive and disorganized branching of PVD mechanosensory neuron dendrites, suggesting that EFF-1 may function to dictate membrane shape and curvature of the growing neurites [9*]. However, extrinsic signals seem to play important roles as well. External signals may be systemic [14], may emanate from other neurites, as in the case of activity-dependent dendritic shape determination [15] or dendritic tiling of *da* neurons of *Drosophila* [16,17], or may be provided by glia.

Glia have been implicated in directing process orientation in the developing vertebrate brain. Neurons generated by subventricular zone radial glia stem cells often contain a single process, resembling a dendrite [1,18], which is dynamically remodeled as neurons migrate to populate the brain. Neuronal migration is guided in part by the radial glia to which migrating neurons adhere and upon which they travel [19,20]. The dendrite-like processes that emanate from these migrating neurons are oriented along the radial glial tracks, suggesting specific adhesion. The basis of the adhesion is not well understood; however, astrotactin, a neuronal protein suggested to promote neuron-glia adhesion, is required for granule neuron migration and process adhesion in the cerebellum [21]. In the neocortex, recognition and adhesion of migrating neurons to radial glia requires integrins [22] and the gap junction proteins connexin 26 and connexin 43 [23].

Glia-derived cues are known to play important roles in axon guidance, affecting the shapes of axons by defining axonal extension paths [24]. Recent evidence suggests that these same glia-derived axon guidance cues can also act on dendrites [25]. For example, the extracellular matrix (ECM) protein Slit is expressed by specialized midline glia of the *Drosophila* central nervous system [26,27], and acts to repel axon growth cones that express the Slit receptor Robo [28, 29]. In *robo* mutants, the dendrites of some neurons inappropriately migrate towards or cross the midline [30], and proper guidance of these dendrites requires cell autonomous expression of Robo (Figure 1a,b; [30]). In *C. elegans*, ventral cephalic sheath (CEPsh) glia that ensheath the nerve ring, a dense neuropil analogous to the brain of higher organisms, express the chemotropic protein Netrin/UNC-6. In *unc-6* mutant animals [31] or in animals lacking CEPsh glia [7], axon paths are severely disrupted, demonstrating a role for these glial cells in axon guidance. RIA nerve ring neurons possess a single neurite whose proximal end is postsynaptic, resembling postsynaptic sites on dendrites. In *unc-6* mutants this neurite also exhibits severe guidance defects, and fails to navigate towards the CEPsh glia [32]. Thus, glia can contribute to dendrite guidance via the secretion of chemotropic factors.

Although dendrite tips may often need to be told where to go, this is not always the case. In *C. elegans*, most environmental signals are detected by neurons of the bilateral amphid sensilla. Each amphid consists of 12 neurons, each of which extends a single dendrite from the cell body to the nose-tip, a length of ~100 μm. Associated with these neurons is an amphid sheath (AMsh) glial cell, which also extends a process to the nose where it ensheaths the ciliated receptive endings of the dendrites [8]. Unlike some dendrites that elongate by growing a process out of a stationary cell body, time-lapse microscopy studies demonstrate that the dendrites of *C. elegans* amphid sensory neurons develop by first anchoring the presumptive dendritic tip to

the surrounding environment at the nose [33**]. Posterior migration of the cell body then stretches out a dendritic process (Figure 1c; [33**]). The length of the dendrite and glial processes are correlated: in mutant backgrounds where the dendrites are too short, the glial process is also truncated [33**]. At least one component of the dendritic-tip anchor, DYF-7, is expressed by the sensory neurons [33**], suggesting that anchoring is in part determined by the neurons themselves. However, a second anchor component, DEX-1, is supplied by non-neuronal hypodermal cells surrounding the dendrite tip, raising the possibility that a number of cell types may contribute to creating the anchor.

The DYF-7/DEX-1 anchor seems to be an example of a structurally unique ECM of diverse functions in different systems. DYF-7 is a secreted zona pellucida (ZP) domain protein localized near the tips of anchored sensory dendrites, while DEX-1 is a secreted zonadhesin (zonad) domain protein. ZP domains form the ECM surrounding vertebrate oocytes (the zona pellucida), while zonadhesin is a sperm protein required for fertilization [34*]. Both domains are also present in α-tectorin, a major component of the tectorial membrane, a highly organized proteinaceous ECM that anchors the ciliated outer hair cells of the inner ear [35]. Mutations in *dyf-7* and *dex-1* exhibit genetic interactions suggestive of physical binding. Furthermore, polymerization of DYF-7 may be required for sensory dendrite anchoring [33**], suggesting that proper matrix formation is required for attachment.

The observation that a single AMsh glial cell ensheaths all 12 amphid sensory neurons suggests that glia are also in a position to contribute to the common anchoring matrix. Indeed, AMsh glia express several ZP domain proteins as well as other predicted extracellular proteins that could potentially contribute to the ECM anchor [6*]. Furthermore, ablation in early development of the precursor cells of the AMsh glia results in unanchored, short dendrites (Bacaj and Shaham, unpublished results), but does not affect sensory neuron cell migration. Similarly, the dendrites of CEP sensory neurons, which are part of another *C. elegans* anterior sensory organ, are shortened when their glial precursors are ablated, or when genes affecting differentiation of the associated glia are mutated (Figure 1d; [7]). Strengthening the notion that glia contribute to the ECM required for dendrite anchoring is the observation that the ECM that tethers *Drosophila* mechanosensory neurons is, at least in part, secreted by glia-like cells associated with these neurons [36]. In *Drosophila* type I mechanosensory organs, the ciliated endings of sensory neuron dendrites are ensheathed by cells analogous to *C. elegans* glia. These glia-like cells produce the dendritic cap, a specialized ECM that covers the cilia tip and connects it to a stimulating structure, either a mechanosensory bristle or an attachment cell. One of the components of this ECM is NompA, a ZP domain protein made by the thecogen and scolopale support cells [36]. In the absence of NompA, sensory neuron dendrite endings fail to form connections to the dendritic cap, and as a result, animals exhibit mechanosensory defects [36].

The studies reviewed here suggest that sensory organ glia may produce local ECM to which dendrite endings attach. This ECM, in turn, plays a key role in determining dendrite length. However, components of this specialized ECM may have other functions besides process anchoring. Indeed, recent studies suggest the involvement of glia-secreted proteins in controlling the shapes of dendritic receptive structures as well.

Receptive ending shapes: a little help from my glia

All dendrites possess receptive structures that receive information, either from other neurons at synapses, or in the case of sensory neurons, from the environment. For example, in the mammalian brain, dendrites receive information at most excitatory synapses through specialized structures termed dendritic spines, which appear as small protrusions on the dendrite process. Dendritic spines can be remodeled by environmental experience [37], and

changes in spine shape are correlated with neuronal function [38]. Likewise, the shapes of sensory neuron dendritic endings are important, as mutations that affect sensory cilia morphology perturb the ability of a neuron to respond correctly to environmental stimuli [39]. These sensory receptive endings are also morphologically malleable. The dendritic receptive structures that receive information at synapses and those that receive environmental input share many similarities in function, shape and molecular components [40]. Intriguingly, both structures are frequently ensheathed by glia [40-42].

Studies of cultured purified mammalian retinal ganglion cell (RGC) neurons have been particularly informative in uncovering details of glia-neuron interactions during synapse formation, as these neurons form far fewer synapses when cultured *in vitro* in the absence of glia than in their presence [43]. A recent study suggests that physical contact between RGC neurons and astrocytic glia may allow these neurons to become competent for synapse formation. Glia-neuron contact reduces dendritic localization of the axonal protein neurexin [44], which reduces synapse formation when expressed in postsynaptic structures [45]. In *C. elegans*, Netrin/UNC-6 may play a similar role in excluding presynaptic elements from postsynaptic compartments [46]. Synapse formation between RGC neurons is further induced by secretion of the ECM molecule thrombospondin (TSP) from glia [47]. TSP interacts postsynaptically with the Ca^{2+} channel subunit α2δ-1 on neurons [48]. Interestingly, the AMsh glia of *C. elegans* also secrete a TSP-domain protein, called FIG-1, which is required for sensory neuron properties and function [6*]. Sensory neurons in *fig-1* mutants are no longer able to accumulate the membrane dye DiI, suggesting the speculative possibility that the synaptogenic effects of TSP on RGC neurons may reflect a role in setting up postsynaptic architecture.

Studies in *C. elegans* also provide evidence for roles of non-neuronal cells in determining the locations of synapses. The presynaptic HSN neurons form synapses onto the postsynaptic VC neuron to create part of the circuit controlling egg-laying behavior in the animal. The positions of these synapses is determined not by the neurons, but by guidepost epithelial cells [49]. These guidepost cells express the transmembrane, immunoglobulin superfamily protein SYG-2, which interacts with and localizes the SYG-1 immunoglobulin protein on the HSN neurons [49,50]. Synapses form where SYG-1 is localized [49]. Similarly, *C. elegans* CEPsh glia may affect the location of synapse formation between the presynaptic interneuron AIY and its postsynaptic partner RIA. The Netrin receptor DCC/UNC-40 is expressed in AIY and localizes near the site where the CEPsh glia contact the neuron and secrete Netrin/UNC-6 [32].

In addition to regulating the formation and localization of the receptive structures on dendrites, glia also affect the shapes of these structures. During development of the mammalian cerebellum, the extension of processes from Bergmann glia is intimately correlated with changes in Purkinje cell dendritic spine shapes [51], suggesting that glia might influence spine shape dynamics. One way they may do this is via ephrin-Eph signaling. The astrocytic glia that ensheath hippocampal excitatory synapses express ephrin A3, while the receptor EphA4 is expressed in neurons and localizes to dendritic spines [52]. When EphA4 is activated by adding exogenous ephrin A3, the dendritic spines retract [52]. By contrast, mice lacking either ligand or receptor tend to exhibit elongated dendritic spines (Figure 2a,b; [52,53*]). The analysis of EphA4 mutant mice suggests that the consequences of these spine shape abnormalities may include defects in hippocampus-dependent learning [53*].

Similar roles for glia in controlling receptive structure shapes are also seen in *C. elegans* sensory organs. Late-stage ablations of the AMsh glia result in changes in the morphology of the sensory endings of the ensheathed amphid neurons (Figure 2c,d; [6*]). These changes correlate with behavioral defects of the animals in response to specific environmental stimuli [6*]. The molecules contributed by the AMsh glia to maintain dendrite ending shape are not

yet known; however, the identification of a large number of glia-enriched mRNAs encoding secreted and transmembrane proteins by microarray analysis [6*] may provide candidates for mediating shape determination.

In addition to a maintenance role, the AMsh glia are also required for plasticity of sensory dendrite receptive endings. In response to environmental stressors, *C. elegans* enters a protective, developmentally-arrested stage termed dauer, in which the dendritic sensory endings of the AWC amphid neurons change shape [54]. This remodeling correlates with expansion and fusion of the two bilateral AMsh glia where they ensheath the AWC sensory endings [54]. By using mutations that specifically block glial fusion, we have shown that the changes in AWC shape are delimited by concomitant, dauer-dependent remodeling of glial shape (Procko and Shaham, submitted). Thus, sensory receptive ending plasticity in *C. elegans* depends on glial plasticity.

Conclusions

Dendrite length and guidance, as well as the formation, placement, and shapes of dendritic receptive structures can all be affected by glia, suggesting that these cells, once thought of as merely support cells, play key roles in shaping the nervous system. The implications of these studies are profound, as in all nervous systems, neuronal shape determines circuitry, and the shapes of receptive structures affect signal strength. Thus, exploration of glial roles in controlling neuron shape and activity is essential for understanding how the nervous system is put together and how it functions. A major unanswered question that must now be tackled is whether glial roles are permissive or regulatory. Are glia the sites of control, or a necessary background? Although the answer to this question is still unclear, and is likely to be complex, the advent of new model systems in which to study glia may help in tackling this important question. Studies of the nematode *C. elegans* may prove particularly useful in understanding gliadendrite interactions. *C. elegans* has a small, invariant number of neurons and glia, which have stereotyped shapes and connections. Importantly, *C. elegans* glia are not essential for neuronal survival. Furthermore, the facile genetics of *C. elegans* provides a powerful setting for gene discovery, which may prove useful for uncovering the molecular basis of glial actions in the nervous system. The conserved functional, morphological, and molecular features of mammalian and *C. elegans* glia [6*,7] suggest that this ‘simple’ nematode may be able to teach us something about the role of glia in the development and function of the most complex of organs: the human brain.

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** of outstanding interest

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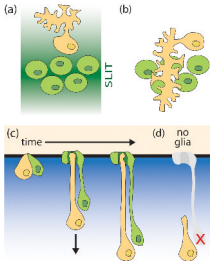

Figure 1.

Glia affect guidance and length of dendrite growth. **(a)** In *Drosophila*, midline glia (green) secrete the guidance molecule SLIT, shown as a dark green gradient in the extracellular environment. The dendrites of the RP2 motor neuron (orange) are repelled from the midline. The RP2 axon is not shown. **(b)** Same as (a), except in a SLIT receptor mutant background (*robo*). In these animals, the neurons no longer perceive SLIT (indicated by a loss of green shading). The RP2 dendrites inappropriately move towards and cross the midline [30]. **(c,d)** A model for glial involvement in dendrite extension of *C. elegans* sensory neurons. (c) The single, unbranched dendrite of a *C. elegans* amphid neuron (orange) extends a process via retrograde extension. The presumptive dendritic tip of the neuron is anchored to its local environment (black, horizontal line). The dendrite is then extended by posterior migration of the cell body (indicated by arrow). The direction of migration is likely driven by a gradient of a chemotropic factor (blue gradient). The neuron is associated with a glial cell (green), which extends a process that ensheaths the dendritic ending. The glial process likely develops by retrograde extension also [33**]. (d) When the amphid sheath glial precursor cell (Bacaj and Shaham, unpublished results) or the sheath glial precursor found in cephalic sensory structures [7] is ablated, the dendrite of the associated sensory neuron is too short.

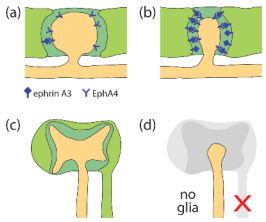

Figure 2.

Glia affect the shapes of dendritic receptive structures. **(a,b)** Mammalian astrocytic glia (light green) ensheath dendritic spines (orange protrusion) at excitatory synapses (a). For simplicity, the presynaptic specialization is not shown. An increase in ephrin A3/EphA4 signaling between the glia and dendritic spine results in spine retraction (b) [52,53*]. **(c,d)** The *C. elegans* amphid neuron AWC (orange) has a fan-shaped sensory cilium at its dendritic tip (c). The cilium is ensheathed by the amphid sheath glia (light green). When the glia is ablated late in development (d), the AWC cilium fails to maintain its proper shape [6*]. Extracellular matrix in (a)-(c) is colored dark green.