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Glia–neuron interactions in the nervous system of *Caenorhabditis elegans*

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A century and a half after first being described, glia are beginning to reveal their intricate and important roles in nervous system development and function. Recent studies in the nematode *Caenorhabditis elegans* suggest that this invertebrate will provide important insight into these roles. Studies of *C. elegans* have revealed a connection between glial ensheathment of neurons and tubulogenesis, have uncovered glial roles in neurite growth, navigation, and function, and have demonstrated roles for glia and glia-like cells in synapse formation and function. Given the conservation of basic anatomical, functional and molecular features of the nervous systems between *C. elegans* and vertebrates, these recent advances are likely to be informative in describing nervous system assembly and function in all organisms possessing a nervous system.

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Introduction

The nervous systems of animals are generally composed of two cell types: neurons, which propagate electrical currents and function as the signaling moieties of the nervous system, and glia, the functions of which are far less understood. The first anatomical studies of vertebrate nervous systems described glia as integral components of neural tissue [1], and it was recognized early on that glia outnumber neurons in the vertebrate brain. In human beings, for example, there are roughly five glial cells for every neuron [2,3]. It is remarkable, therefore, that so little is known about glia in comparison to their neuronal counterparts. The importance of glial cells to medicine is undisputed. Ninety five percent of brain malignancies are of glial character [4], and defects in glia are predisposing factors for several heritable brain diseases, including Alzheimer's disease [5]. Interestingly, the etiologies of many nervous system diseases are unknown. Given that glia outnumber neurons in the brain, it is very likely that many of these diseases will turn out to have a glial origin.

Although there might be historical reasons contributing to the preference for studying neurons over glia in the nervous system, there are also practical issues that have made glia particularly cumbersome to study. Glia are often referred to as neuronal support cells, and, indeed, it has been demonstrated in many experiments *in vivo* and *in vitro* that glia provide essential nutritive and growth signals for neurons [6]. Put simply, in the absence of glia, neurons die [7–9]. And herein lies perhaps the key reason for the poor understanding of glial cell function. Because removal of glia leads to neuronal death, it is generally difficult to study any glial effects on neurons other than the control of cell survival.

An opportunity for studying basic glial functions *in vivo* has been afforded by the recent finding that glia of the invertebrate *Caenorhabditis elegans* are not required for neuronal survival (T Bacaj, S Shaham, unpublished [10]). This observation, together with the outstanding genetic and molecular tools available for manipulating this soil nematode, has enabled the discovery of glial properties and functions that are likely to be conserved. Here, these advances are reviewed, and similarities to glial properties in vertebrates are highlighted.

Anatomy and development of *C. elegans* glia

Defining glia and their subtypes is a problematic endeavor. In vertebrates, some glia are identified by expression of the glial fibrillary acidic protein (GFAP), an intermediate filament protein [11,12]. Unfortunately, even among vertebrates, not all cells of glial character express GFAP [13], and thus this marker has limited utility. Three criteria, however, do seem to set glia apart from other basic cell types. First, glia are physically associated with neurons, and often ensheath them. Second, glia are not neurons themselves. They do not conduct fast currents, and lack neurotransmitter-laden vesicles. Third, and perhaps most telling, glia are lineally related to neurons. In vertebrates, both neurons and glia are derived from neuroectodermal tissues during development [14,15], as is the case in the fruit fly *Drosophila melanogaster* [16].

The adult *C. elegans* hermaphrodite contains 959 somatic cells, 302 of which are neurons, that have been characterized in detail with respect to position and shape using electron microscopy and fluorescent reporter transgenes [17]. The lineal history of all these cells has been traced

Glossary
Amphids: The primary sense organs of *C. elegans* located at the tip of its nose.
Dauer: An alternative, protective developmental state into which *C. elegans* can enter when encountering harsh environmental conditions.
Nerve ring: The *C. elegans* brain, a circular bundle of neurons in which there are many synapses.
Sheath glia: *C. elegans* glia that ensheath sensory neuron dendrites. They are generally associated with socket glia, which lie distally along the dendrite.
Socket glia: *C. elegans* glia that ensheath sensory neuron dendrites, and can often form an opening to the environment.

back to the zygote and is essentially invariant among individuals [18,19]. Applying the criteria for glia identification to the adult *C. elegans* hermaphrodite yields a list of 50 cells that show striking morphological similarities to glia of other organisms [10]. Twenty four of these cells are termed sheath glia (see glossary) [20]. These are associated with dendritic processes of sensory neurons that respond to a variety of sensory stimuli including temperature, odors, tastants, high osmolarity solutions, pheromones and touch. All sheath glia ensheath the modified dendritic endings of sensory neurons. These cells, thus, resemble glia associated with sensory structures in vertebrates, such as olfactory ensheathing glia and Müller glia in the eye.

The most studied sensory organs in *C. elegans* are the bilaterally symmetric amphids (see glossary), the largest sensory organs of the animal [20] (Figure 1). The tips of four of the 12 sensory neurons of each amphid organ are entirely embedded within the sheath glial cell, in a hand-in-glove configuration. The sheath glia ensheath the remaining eight dendritic endings to form a channel. This channel is contiguous with the socket glia (see glossary) channel that is exposed to the outside environment (Figure 1c). The 26 socket glia of the animal are associated with all sheath glia-containing sensory organs.

Four sheath glial cells, the CEP sheath glia, are bipolar, associating not only with the dendritic tips of sensory neurons but also sending large, sheet-like processes that envelop the nerve ring (see glossary) of *C. elegans* (Figure 1b). The nerve ring, a dense neuropil, is essentially the animal's brain, and contains the majority of synaptic connections. CEP sheath glia send a few slender processes into the nerve ring that terminate at specific synaptic sites [17]. Thus, these glia are anatomically similar to vertebrate astrocytes, and might similarly participate in synapse formation, synaptic modulation and formation of a permeability barrier around the nerve ring.

The six GLR cells of *C. elegans* can be considered glia-like, although they are mesodermally derived. These cells are connected by gap junctions to both motorneurons and muscle cells in the head of the animal [17]. Their roles in regulating motor responses, if any, are not known.

Little is known about the molecular basis of glial cell differentiation in *C. elegans*. However, the Zn-finger transcription factor LIN-26 seems to play an important early role in the decision between glial and neuronal cell fate. LIN-26 protein is expressed in all glial cells, and in *lin-26* mutants glia can adopt a neuronal fate [21–23]. Interestingly, *C. elegans* epithelial cells also express LIN-26 and are also transformed into neurons in *lin-26* mutants, highlighting the conserved lineal relationships between glia, neurons and epithelia.

Glial control of neurite extension and pathfinding

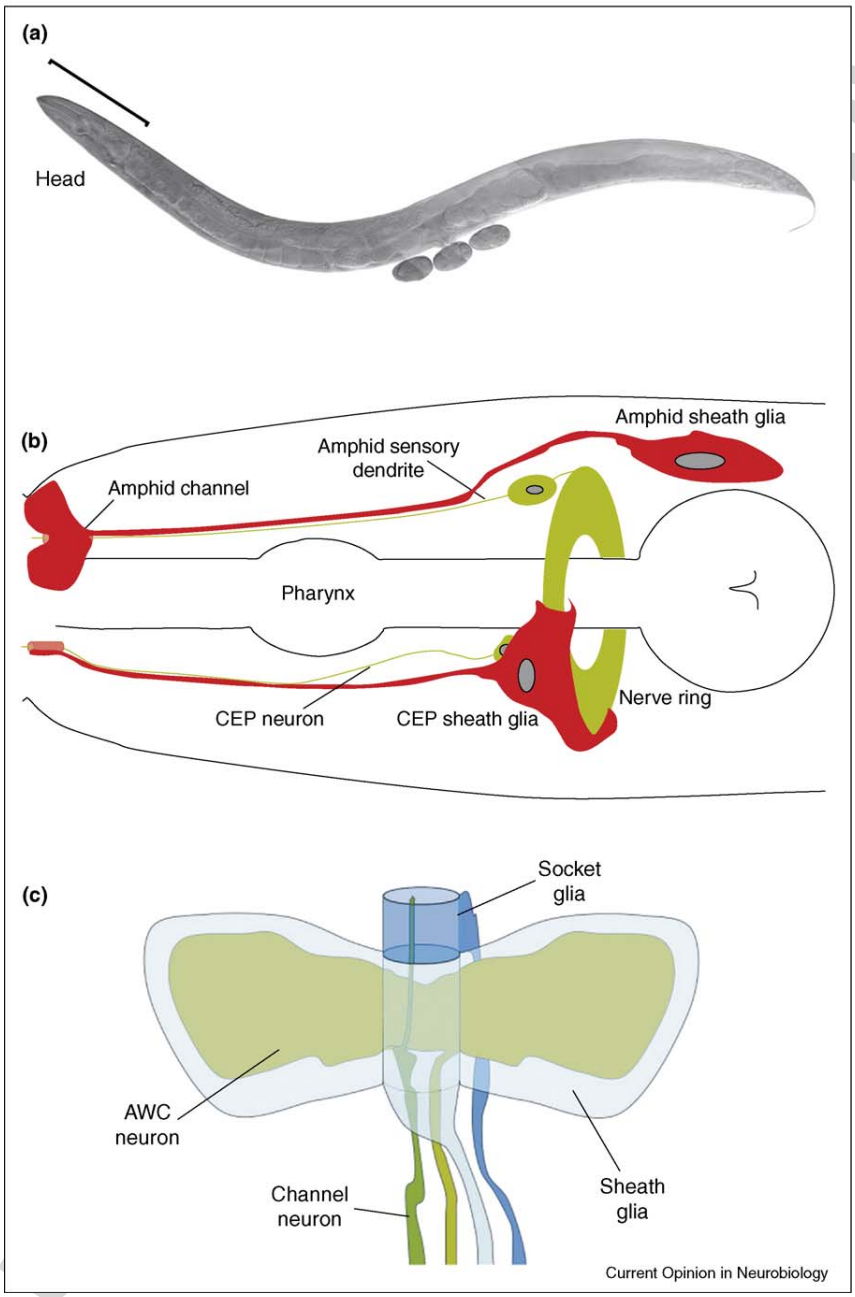
Initial studies aimed at deciphering glial functions in *C. elegans* involved targeted ablation of glial cells using genetic strategies or using a laser microbeam to investigate their possible roles (T Bacaj and S Shaham, unpublished; [24,25]). Remarkably, these experiments demonstrated that unlike vertebrate and fruitfly glia, *C. elegans* glia are not required for neuronal survival. Nonetheless, glia-less animals manifested obvious and specific defects in neuronal development, structure and function. For example, ablation of the precursor of the amphid sheath glial cell resulted in failure of sensory dendrites to extend to the tip of the nose. This remarkable observation strongly supports a role for amphid sheath glia in regulating dendrite extension. Similar roles in directing process outgrowth have been suggested for radial glia in the developing vertebrate brain and in *Drosophila*. However, specific roles in dendritogenesis have not been previously described.

The effects of the amphid sheath glial cell on dendrite extension are probably not confined to this sensory organ alone. Sulston *et al.* [18] reported studies of a few animals in which precursors of sheath glia of other sensory organs were ablated. These authors found that neuronal processes associated with the ablated sheath glia failed to extend to the tip of the nose, although their precise fate was not determined.

In the same set of ablation studies, Sulston *et al.* [18] demonstrated an important role for the socket glia of sensory structures in directing dendrite association with specific sensory organs. Ablation of precursors of socket glia of one sensory organ led dendrites and sheath glia of that organ to infiltrate a different sensory organ. Thus, dendrites normally associated with one socket glia were now ensheathed by a different socket glial cell. This remarkable effect suggests that socket glia are not equivalent, and that a glial code employing long range signals could play important roles in the association of dendrites and socket glia. Neither the physical nor the molecular basis of this code, nor the nature of the long-range signals attracting dendrites to socket cells, are known.

In addition to directing dendrite extension and pathfinding, glia might also play roles in axon guidance in

Figure 1



Organization of glia in *C. elegans*. **(a)** Image of an adult *C. elegans* hermaphrodite and three laid embryos. Bar depicts the head region that is represented in the schematic in (b), and is 140 μm long. **(b)** A schematic of the head region of *C. elegans* showing two glial cell types, amphid and CEP sheath glia. Both glial types are associated with dendritic tips. The CEP sheath glia also ensheath the nerve ring, the animal's brain. **(c)** A schematic of the amphid sensory organ at the tip of the *C. elegans* nose. Two glial cells, the sheath and socket glia, form a channel that surrounds eight ciliated sensory neurons. One such channel neuron is shown. The AWC neuron, in addition to three other amphid neurons, does not project through the channel, but is embedded within the sheath glial cell. The processes of neurons and glia fasciculate after leaving the sensory compartment.

C. elegans. The two ventral CEP sheath glia express the netrin protein UNC-6 during embryogenesis around the time that axons begin to form the nerve ring [26]. These observations suggest that CEP sheath glia might help to guide axons into the nerve ring and promote synapse formation. Animals carrying mutations in the *unc-6* gene do not display profound defects in nerve ring assembly, however, suggesting that additional signals driving nerve ring formation must act redundantly with UNC-6.

Glial functions at the synapse

Completion of axonal or dendritic outgrowth must be accompanied by the formation of specific synapses between neurons and their target cells. Synapses in the nervous system can be broadly classified according to their pre- and post- synaptic components: neuronal synapses between neurons; effector synapses between a presynaptic neuron and a postsynaptic non-neuronal cell, such as a muscle or a gland cell; and sensory synapses between the environment, which serves as the presynaptic signaling moiety, and a postsynaptic neuron. In vertebrates, glia are tightly associated with all three synaptic classes [27]. In *C. elegans*, glia are mostly present at sensory synapses, but are also found at neuronal synapses. For example, the *C. elegans* CEP sheath glia that ensheath the nerve ring send projections that contact several specific neuronal synapses within the nerve ring. The roles of CEP sheath glia at synaptic sites are not known; however, the morphological similarities with vertebrate synapses suggest that they have both developmental and functional activities at these sites.

An interesting example of specific epithelial cells directing neuronal synapse formation has been recently described in *C. elegans*. These cells, although morphologically distinct from *C. elegans* glia, are lineally related to neurons, and thus, could resemble glia. During larval development, the HSN and VC neurons synapse onto each other next to a primary vulval epithelial cell. Studies of the formation of these synapses revealed that their location is determined by transient expression on primary vulval epithelial cells of an Immunoglobulin (Ig) domain-containing protein called SYG-2, similar to *Drosophila* Sticks and Stones and vertebrate Nephrin proteins [28]. SYG-2 expression enables the HSN neurons to initiate the building of presynaptic structures near vulval epithelial cells. HSN neurons recognize the vulval epithelial cells by expressing the SYG-1 Ig-domain protein, which is related to *Drosophila* IrreC and mammalian NEPH1 proteins [29]. SYG-1 and SYG-2 have been shown to interact in cell aggregation assays. Once the HSN presynaptic site has been formed, the VC neuron, which grows in close proximity, completes the synapse by forming a postsynaptic site. These results suggest that non-neuronal cells play important roles in determining synaptic assembly and specificity in *C. elegans*. Mutations in the *syg-1* and *syg-2* genes do not grossly affect animal behavior and nervous system function, suggesting that they are not absolutely required for the formation of all synapses, and might, therefore, represent two of many components that determine synapse location and assembly.

Glia also play important roles at *C. elegans* sensory synapses. In vertebrates, glutamatergic excitatory postsynaptic sites are generally present on dendritic elaborations called spines. Spines are highly malleable in shape and size. Where examined, most spines are tightly associated with the processes of astrocytes or other glia [30–33]. In *C. elegans*, the AWC sensory neuron contains at its tip an elaborate sensory modification containing receptors and signaling molecules that mediate olfaction [34,35] (Figure 1c). This dendritic modification thus represents a receptive ending similar to a dendritic spine. Indeed, the shape of the AWC receptive ending is also highly malleable. For example, during starvation and entry into the dauer stage of development (see glossary), the surface area and volume of the AWC endings increase dramatically [36]. Interestingly, animals in which the precursor of the amphid sheath glial cell has been ablated fail to develop a proper receptive ending on the AWC dendrite (T. Bacaj, S. Shaham, unpublished). These animals are also severely defective in many sensory functions transduced by neurons of the amphid. Ablation of the glia after amphid formation has been completed seems to prevent further growth of the AWC ending even in dauer animals. These results suggest that amphid sheath glia play a key role in the development and maintenance of AWC receptive ending morphology, and suggest, by analogy, that glia at excitatory vertebrate CNS synapses play a similar role. The results also support an important role for glia in regulating neuronal function. Interestingly, in the murine hippocampus some neurons express ephrin A3, and their associated astrocytes express the ephA4 receptor, suggesting that they might communicate [37]. Indeed, mice lacking the ephA4 receptor display abnormalities in spine length, supporting the notion that glia could regulate spine morphology, shape and perhaps function.

A link between glial ensheathment of neurons and tubulogenesis

Although glial roles in synaptic development and function have become increasingly evident, their ability to ensheath neurons and influence neuronal conduction has long been recognized. Although *C. elegans* glia do not form myelin, they do ensheath neurons, forming channels through which dendrites are threaded. Examination by electron microscopy (EM) of serially sectioned developing embryos revealed that amphid channel formation occurs through an intermediate similar to that observed during myelin formation. Specifically, the amphid sheath glia send a sheet-like process that wraps around neurons of the amphid to initiate channel

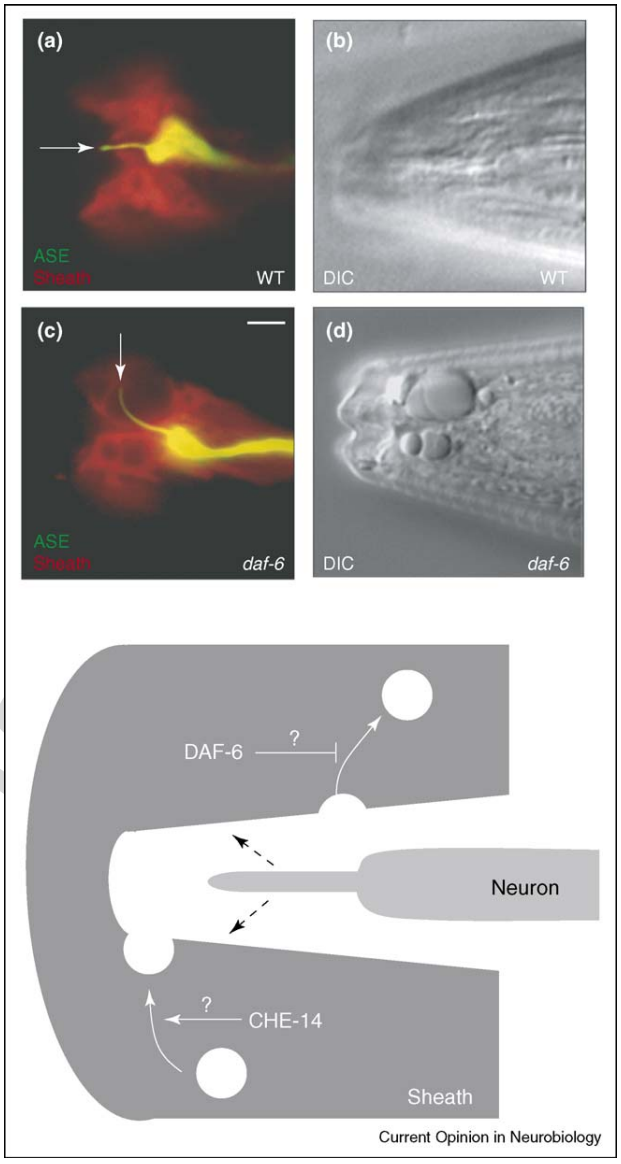
formation (M Heiman, J Sulston, N Thomson, S Shaham, unpublished). Thus, understanding amphid channel formation in *C. elegans* could reveal common principles governing neuronal ensheathment.

Mutations in the *daf-6* gene result in sensory deficits and defects in the exposure of amphid sensory neurons to the environment [38,39], suggesting a primary defect in the amphid sheath glia channel. Indeed, *daf-6* function is required within amphid sheath glia to regulate environmental access of neurons [40,41••]. A careful examination of *daf-6* mutants using electron microscopy and fluorescent reporters expressed in amphid neurons and glia revealed that the channel surrounding the sensory neurons was indeed defective. The channel failed to open, and contained numerous herniations filled with extracellular matrix material [41••] (Figure 2).

DAF-6 defines a previously uncharacterized subfamily of Patched-related proteins. *Drosophila* and mammalian Patched are 12-transmembrane proteins that possess a sterol-binding domain, and that bind the secreted cholesterol-modified protein Hedgehog. DAF-6 protein functions early during channel formation, and is expressed in amphid socket and sheath glia, localizing to the cell membrane of the amphid channel. Interestingly, whereas mutations in conserved residues of the DAF-6 sterol-binding domain only weakly affect its localization and function, a point mutation in the first extracellular loop of DAF-6 enables proper localization to the cell membrane, but fails to rescue *daf-6* mutants [41••]. These observations suggest that DAF-6 binds to an extracellular ligand involved in regulating channel morphogenesis. Remarkably, mutants in which amphid neuron dendritic endings are absent or abnormal display amphid sheath glia channel abnormalities. Furthermore, these mutants fail to properly localize DAF-6 [41••]. Thus, it is possible that a ligand for DAF-6 is secreted by sensory neuron endings (Figure 2). Regardless of the exact molecular mechanisms at play, these experiments strongly suggest that *C. elegans* sensory neurons play an active role in determining the properties of their glial sheath. Similar roles for neuronal proteins in controlling the extent of axonal myelination in vertebrates have been documented.

In addition to expression in amphid sheath glia, DAF-6 protein is also expressed in all other tubular structures of *C. elegans*, including the vulva, rectum, excretory system and intestine. Although *daf-6* mutants do not exhibit defects at these other sites, double mutants between *daf-6* and *che-14*, another sterol-sensing domain-encoding gene similar to *Drosophila Dispatched* [39,42], exhibit synthetic tubulogenesis defects at all sites of *daf-6* expression [41••]. These results support the idea that the processes of neuronal ensheathment and tubulogenesis are related. Vertebrate proteins related to DAF-6 exist,

Figure 2



The *daf-6* gene provides a possible molecular link between ensheathment and tubulogenesis in *C. elegans*. **(a)** A wild type animal expressing reporter proteins in the amphid sheath glia (red) and the ASE channel neuron (green). Tip of nose is to the left. Arrow indicates neuronal cilium exiting channel. **(b)** A differential interference contrast (DIC) image of the animal in (a). **(c)** A *daf-6* mutant animal expressing same reporters as in (a). Note that the neuron is not exposed to the outside (arrow), that the channel is deformed, and the presence of large vacuoles within the sheath glial cell (asterisks). **(d)** A DIC image of the animal in (c). **(e)** A model for channel formation and neuronal ensheathment by *C. elegans* glia. Based on their sequences, DAF-6 and CHE-14 proteins might participate in endo- and exocytosis in glia, perhaps regulating membrane addition to growing lumenal surfaces. The shape and extent of membrane growth is regulated by a signal from the ensheathed neurons, which also regulate DAF-6 localization. Adapted with permission from [41••]. Scale bars, 5 μm.

and are expressed in the brain. These might participate in aspects of neuronal ensheathment as well.

Conclusions

Recent studies in the nematode *C. elegans* have shown that this organism has much to offer in deciphering the basic functions of glial cells in the nervous system. Unlike other model organisms that have been examined, *C. elegans* does not require glia to promote neuronal survival, enabling the effects of glial removal on neuronal function to be studied in detail *in vivo*. Recent studies have demonstrated key roles for *C. elegans* glia in neuronal development, morphogenesis and function. The combination of genetic studies of *C. elegans* glia with *in vitro* and *in vivo* work in other organisms promises to push our understanding of these important cells to new depths.

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References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

1. Virchow R: **Ueber das granulierte Ansehen der Wandungen der Gehirnventrikel**. *Allge Z Psychiatr* 1846, **3**:424-450 [Translation of title: On the granular appearance of tissue surrounding the cerebral ventricles].
2. Bass NH, Hess HH, Pope A, Thalheimer C: **Quantitative cytoarchitectonic distribution of neurons, glia, and DNa in rat cerebral cortex**. *J Comp Neurol* 1971, **143**:481-490.
3. Cajal RS: *Histologie du système nerveux de l'homme et des vertébres*. (1909) N Swanson and L Swanson, English translation. Oxford University Press;1995. [Translation of title: Histology of the nervous system of man and vertebrates]
4. Wechsler-Reya R, Scott MP: **The developmental biology of brain tumors**. *Annu Rev Neurosci* 2001, **24**:385-428.
5. Mauch DH, Nagler K, Schumacher S, Goritz C, Muller EC, Otto A, Pfrieger FW: **CNS synaptogenesis promoted by glia-derived cholesterol**. *Science* 2001, **294**:1354-1357.
6. Meyer-Franke A, Kaplan MR, Pfrieger FW, Barres BA: **Characterization of the signaling interactions that promote the survival and growth of developing retinal ganglion cells in culture**. *Neuron* 1995, **15**:805-819.
7. Hosoya T, Takizawa K, Nitta K, Hotta Y: **glial cells missing: a binary switch between neuronal and glial determination in *Drosophila***. *Cell* 1995, **82**:1025-1036.
8. Jones BW, Fetter RD, Tear G, Goodman CS: **glial cells missing: a genetic switch that controls glial versus neuronal fate**. *Cell* 1995, **82**:1013-1023.
9. Ullian EM, Sapperstein SK, Christopherson KS, Barres BA: **Control of synapse number by glia**. *Science* 2001, **291**:657-661.
10. Shaham S: **Glia-neuron interactions in nervous system function and development**. *Curr Top Dev Biol* 2005, **69**:39-66.
11. Eng L, Gerstl B, Vanderhaeghen J: **A study of proteins in old multiple sclerosis plaques**. *Trans Am Soc Neurochem* 1970, **1**:42.
12. Eng LF, Vanderhaeghen JJ, Bignami A, Gerstl B: **An acidic protein isolated from fibrous astrocytes**. *Brain Res* 1971, **28**:351-354.
13. Dahl D, Crosby CJ, Sethi JS, Bignami A: **Glial fibrillary acidic (GFA) protein in vertebrates: immunofluorescence and immunoblotting study with monoclonal and polyclonal antibodies**. *J Comp Neurol* 1985, **239**:75-88.
14. Doetsch F: **The glial identity of neural stem cells**. *Nat Neurosci* 2003, **6**:1127-1134.
15. Alvarez-Buylla A, Seri B, Doetsch F: **Identification of neural stem cells in the adult vertebrate brain**. *Brain Res Bull* 2002, **57**:751-758.
16. Jones BW: **Glial cell development in the *Drosophila* embryo**. *Bioessays* 2001, **23**:877-887.
17. White JG, Southgate E, Thomson JN, Brenner S: **The structure of the nervous system of the nematode *Caenorhabditis elegans***. *Phil Trans R Soc Lond B* 1986, **314**:1-340.
18. Sulston JE, Schierenberg E, White JG, Thomson JN: **The embryonic cell lineage of the nematode *Caenorhabditis elegans***. *Dev Biol* 1983, **100**:64-119.
19. Sulston JE, Horvitz HR: **Post-embryonic cell lineages of the nematode *Caenorhabditis elegans***. *Dev Biol* 1977, **56**:110-156.
20. Ward S, Thomson N, White JG, Brenner S: **Electron microscopical reconstruction of the anterior sensory anatomy of the nematode *Caenorhabditis elegans***. *J Comp Neurol* 1975, **160**:313-337.
21. Labouesse M, Hartwieg E, Horvitz HR: **The *Caenorhabditis elegans* LIN-26 protein is required to specify and/or maintain all non-neuronal ectodermal cell fates**. *Development* 1996, **122**:2579-2588.
22. Labouesse M, Sookhareea S, Horvitz HR: **The *Caenorhabditis elegans* gene *lin-26* is required to specify the fates of hypodermal cells and encodes a presumptive zinc-finger transcription factor**. *Development* 1994, **120**:2359-2368.
23. Dufourcq P, Chanal P, Vicaire S, Camut E, Quintin S, den Boer BG, Bosher JM, Labouesse M: ***lir-2, lir-1* and *lin-26* encode a new class of zinc-finger proteins and are organized in two overlapping operons both in *Caenorhabditis elegans* and in *Caenorhabditis briggsae***. *Genetics* 1999, **152**:221-235.
24. Hedgecock EM, Culotti JG, Thomson JN, Perkins LA: **Axonal guidance mutants of *Caenorhabditis elegans* identified by filling sensory neurons with fluorescein dyes**. *Dev Biol* 1985, **111**:158-170.
25. Vowels JJ, Thomas JH: **Multiple chemosensory defects in *daf-11* and *daf-21* mutants of *Caenorhabditis elegans***. *Genetics* 1994, **138**:303-316.
26. Wadsworth WG, Bhatt H, Hedgecock EM: **Neuroglia and pioneer neurons express UNC-6 to provide global and local netrin cues for guiding migrations in *C. elegans***. *Neuron* 1996, **16**:35-46.
27. Auld DS, Robitaille R: **Glial cells and neurotransmission: an inclusive view of synaptic function**. *Neuron* 2003, **40**:389-400.
28. Shen K, Fetter RD, Bargmann CI: **Synaptic specificity is generated by the synaptic guidepost protein SYG-2 and its receptor, SYG-1**. *Cell* 2004, **116**:869-881.
29. Shen K, Bargmann CI: **The immunoglobulin superfamily protein SYG-1 determines the location of specific synapses in *C. elegans***. *Cell* 2003, **112**:619-630.
30. Ventura R, Harris KM: **Three-dimensional relationships between hippocampal synapses and astrocytes**. *J Neurosci* 1999, **19**:6897-6906.
31. Wolff JR: **The morphological organization of cortical neuroglia**. In *Handbook of electroencephalography and clinical neurophysiology*, vol2A. Edited by Remond A. Elsevier; 1976.
32. Spacek J: **Three-dimensional analysis of dendritic spines. III. Glial sheath**. *Anat Embryol (Berl)* 1985, **171**:245-252.

33. Peters A, Palay SL, Webster HD: **The neuroglial cells**. *The Fine Structure of the Nervous System*. Oxford University Press; 1991:273-311.

34. Troemel ER, Chou JH, Dwyer ND, Colbert HA, Bargmann CI: **Divergent seven transmembrane receptors are candidate chemosensory receptors in *C. elegans***. *Cell* 1995, **83**:207-218.

35. Troemel ER: **Chemosensory signaling in *C. elegans***. *Bioessays* 1999, **21**:1011-1020.

36. Albert PS, Riddle DL: **Developmental alterations in sensory neuroanatomy of the *Caenorhabditis elegans* dauer larva**. *J Comp Neurol* 1983, **219**:461-481.

37. Murai KK, Nguyen LN, Irie F, Yamaguchi Y, Pasquale EB: **Control of hippocampal dendritic spine morphology through ephrin-A3/EphA4 signaling**. *Nat Neurosci* 2003, **6**:153-160.

38. Albert PS, Brown SJ, Riddle DL: **Sensory control of dauer larva formation in *Caenorhabditis elegans***. *J Comp Neurol* 1981, **198**:435-451.

39. Perkins LA, Hedgecock EM, Thomson JN, Culotti JG: **Mutant sensory cilia in the nematode *Caenorhabditis elegans***. *Dev Biol* 1986, **117**:456-487.

40. Herman RK: **Mosaic analysis of two genes that affect nervous system structure in *Caenorhabditis elegans***. *Genetics* 1987, **116**:377-388.

41. •• Perens EA, Shaham S: ***C. elegans daf-6* encodes a patched-related protein required for lumen formation**. *Dev Cell* 2005, **8**:893-906.
Although glia are known to wrap around neurons, similarities between glial ensheathments and tubes have not been reported. The authors demonstrate morphological and molecular similarities between glial ensheathment and tubulogenesis, suggesting that basic aspects of these two processes are related.

42. Michaux G, Gansmuller A, Hindelang C, Labouesse M: **CHE-14, a protein with a sterol-sensing domain, is required for apical sorting in *C. elegans* ectodermal epithelial cells**. *Curr Biol* 2000, **10**:1098-1107.