is an opportunity for an in-depth analysis of nuclear organization. The small nuclear size and central chromocenter, which contains all of the subcentromeric DNA, suggests that all chromosomes converge in the nuclear center and radiate out toward the periphery, much like a round flower head (Figure 1D). Preliminary data from the gene-specific FISH experiments already suggest that chromosome territories may be arranged in radial segments, but a comprehensive analysis of chromosome positioning would address this question further (Bolzer et al., 2005). Uncovering the spatial relationships between chromosome territories and coregulated genes in this context may shed additional light on the adaptation of form to function in biology (Kosak et al., 2007).

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Neurite Extension: Starting at the Finish Line

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The outgrowth of axons and dendrites from neuronal cell bodies to their appropriate targets is the canonical means of creating new processes. Heiman and Shaham (2009) now show that neuronal processes can also be made by anchoring dendrite tips at their target locations while the cell body pulls away, a process termed retrograde extension.

The intricacy of wiring billions of axonal cables into a functioning nervous system has been appreciated since the days of Ramón y Cajal. In the last two decades tremendous progress has been made in identifying the classes of molecules that guide the growth of neuronal processes during development over long distances to their precise termination points (Dickson, 2002; Tessier-Lavigne and Goodman, 1996). Despite diversity in these modes of guidance—from the "towing" of sensory axons by migrating lateral line primordium cells in zebrafish (Gilmour et al., 2004) to the snaking of commissural axons through a minefield of attractive and repulsive cues at the ventral midline (reviewed in Dickson, 2002)—it has always been the neuronal process that travels to the target location. But is this the only way for a neuronal process to reach its target? According to new work by Heiman and Shaham (2009), the answer is no.

Using the nematode *Caenorhabditis elegans* as a model system, Heiman and Shaham now show that the sensory processes of amphid neurons reach their target location via a previously unreported mode of outgrowth that the authors call "retrograde extension." Amphid neurons are a class of sensory neurons in *C. elegans* with a cell body in the head of the animal and a sensory dendritic process that extends toward the anterior all the way to the tip of the animal's nose (Ward et al., 1975). By visualizing the development of single amphid neurons during embryogenesis in vivo, the authors make a surprising discovery; rather than sending out a sensory process that extends toward the tip of the nose, the cell bodies of amphid neurons start out at the tip of the nose and migrate away toward the posterior, leaving behind a sensory process (Figure 1). Thus, the choice of target location is achieved not by ending up at the destination but rather by starting there. Amazingly, this process was suggested a quarter of a century ago in a landmark paper by Sulston et al. (1983) based on analysis of electron micrographs.

The process is akin to a spider letting itself down by a thread. But just as the tip of a spider's thread needs to be anchored, the same holds true for sensory processes of the amphid neurons. The authors find two worm mutants, *dex-1* and *dyf-7*, in which the migration of the neuronal cell bodies appears

to be normal, but the neurons lack a sensory process because the tips of these stubby processes keep moving with the migrating cell bodies (Figure 1) (Heiman and Shaham, 2009). These two genes encode components of the extracellular matrix and are required for anchoring the sensory processes at the tip of the nose. Using temperature-sensitive alleles of both mutants, the authors performed temperature shift experiments, which suggest that anchoring is only required during development when the amphid neuron cell bodies are migrating.

DEX-1 resembles the sperm protein zonadhesin, whereas DYF-7 contains a zona pellucida (ZP) domain that is found in proteins that coat vertebrate oocytes. Zonadhesin and ZP proteins work in a ligand-receptor fashion in the interaction between sperm and egg. DEX-1 and DYF-7 act cooperatively to form the extracellular matrix. In this sense, the function of DEX-1 and DYF-7 is similar to α-tectorin, a component of the tectorial membrane of the vertebrate inner ear that is required for anchoring sensory hair cells (Legan et al., 1997). Interestingly, α-tectorin has features of both DEX-1 and DYF-7 in that it has both von Willebrand factor domains and a ZP domain. Surprisingly, when the authors fuse DEX-1 and DYF-7 to create a fusion protein similar to α-tectorin, it is still functional and able to completely rescue the anchoring defect observed in double mutant worms deficient in both DEX-1 and DYF-7. Thus, the use of these proteins in sensory organs appears to be evolutionarily conserved, regardless of whether the functional domains are in two different proteins or whether they are encoded within the same polypeptide.

The study raises a number of questions, some of which can be addressed in the immediate future. For example, there are 12 amphid neurons on each side of the animal. One interesting finding that the authors report is that in alleles of *dex-1* and *dyf-7* that have low penetrance, failure in anchoring of a sensory process of one amphid neuron correlates with the failure in anchoring of other sensory processes on the same side. Thus, the anchoring of sensory processes of amphid neurons on the same side, which are tightly bundled together, is highly coordinated. In the case of classic axon guidance, there is often a pioneering axon, which is subsequently used by other axons as a track to follow (Tessier-Lavigne and Goodman, 1996). Is there a pioneering sensory process within an amphid bundle that is anchored first? Or is each sensory process anchored independently? Fortunately, the molecular tools needed to address this issue are available. First, the authors have shown that expression in amphid neurons of a membrane-bound (nonsecretable) form of DYF-7 is functional. Second, there are well-characterized cell-specific promoters for many of the amphid neurons. Thus, expression of the membrane-bound form of DYF-7 in individual neurons should allow one to address whether there is a pioneering sensory process in the amphid bundle.

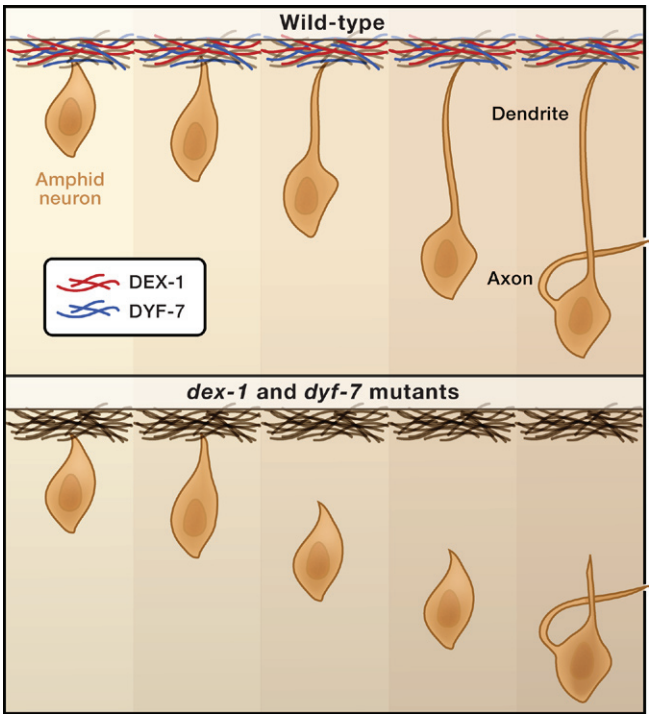

Figure 1. Dendrite Extension in Amphid Neurons of the Worm
During development, amphid neurons in the nematode *Caenorhabditis elegans* anchor their dendritic tips to the extracellular matrix prior to their cell bodies pulling away. The end result of this process is production of a long dendrite with precise targeting. In the absence of the extracellular matrix components DEX-1 or DYF-7, the dendrite tip fails to attach to the matrix, resulting in the failure of dendrite extension.

How widespread is retrograde extension? And is there a reason why it might be favored over other classical modes of neurite extension and targeting? There is at least one example in the vertebrate nervous system that might hold some clues. The granule cells in the cerebellum have T-shaped axons. During development, rather than extending a single axon, which then bifurcates, the granule cells do something unusual. The granule cells first grow out two processes in opposite directions such that they are parallel to the surface of the brain (and hence form the parallel fibers) (Komuro et al., 2001). The cell body then drops down radially, leaving behind a single neuronal process that connects the cell body to the bifurcated axon. This last step in the development of the granule cell axon is highly reminiscent of the sensory dendrite extension described by Heiman and Shaham. Perhaps the bifurcation of the granule cell axons in completely opposite directions within the confines of a densely packed cerebellum does not lend itself to instruction by attractive and repulsive guidance cues, which is why the granule cells have adopted a retrograde mode of extension. But what about the amphid sensory neurons?

Tips of 4 out of the 12 amphid sensory processes are embedded within thin fan-shaped glial cells called the amphid sheath cells. The tips of the remaining eight processes are threaded through a pore formed by socket glia and then exposed to the external environment (reviewed in Shaham, 2006). Both types of targeting events require extreme precision. Thus, one possibility is that retrograde extension achieves greater precision than is possible with classical targeting strategies.

Regardless of the reasons for targeting via retrograde extension, it will be interesting to determine the molecular mechanisms that underlie this process. By identifying key components of the dendrite anchoring machinery, Heiman and Shaham have shown that looking for these mechanisms in the tiny nematode is a fruitful endeavor.

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Ubiquitin Connects with Planar Cell Polarity

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Planar cell polarity (PCP) regulates the orientation of cells in epithelia and of mesenchymal cells during gastrulation. In this issue, Narimatsu et al. (2009) report that the Smurf E3 ubiquitin ligases are required for localized protein degradation of a core PCP factor to generate cellular asymmetry.

Establishment of cellular polarity is an important feature of organ development and function. Epithelial apical-basolateral polarity allows tissues to perform vectorial functions, like the transport of fluid or directed secretion of specialized components. In addition, epithelial tissues acquire a second polarity axis within the epithelial plane, referred to as planar cell polarity (PCP). PCP was discovered in the fruit fly *Drosophila* and much of what we know about PCP comes from studies in flies (Seifert and Mlodzik, 2007; Strutt, 2003). In vertebrates, processes requiring PCP signaling include skin and body hair orientation, polarization of sensory epithelia in the inner ear, and the directed movement and intercalation of mesenchymal cells during gastrulation (Wang and Nathans, 2007). How individual cells coordinate their orientation over hundreds of cell diameters is a fascinating biological problem. Although much progress has been made, the molecular mechanisms that establish PCP are still far from being understood.

In this issue of *Cell*, the labs of Attisano and Wrana provide an elegant analysis of Smurf1 and 2 in the mouse, demonstrating that these E3 ubiquitin ligases are critical to the establishment of PCP mediated by the Wnt receptor Frizzled (Fz) (Narimatsu et al., 2009). The authors show that loss-of-function mutations in the *Smurf1* and *Smurf2* genes of mice cause PCP defects during convergence and extension in gastrulation and misalignment of sensory cells in the cochlea. These phenotypes are surprising given that the Smurf ligases were originally linked to the regulation of signaling by the receptors for transforming growth factor β and bone morphogenetic protein. At the molecular level, the Smurfs are recruited via Dishevelled (Dvl), a downstream effector of Frizzled receptors, to core PCP protein complexes that include the polarity protein Par6. This interaction leads to a Smurf- and Dvl2-dependent degradation of Prickle (Pk1). Strikingly, in the *Smurf* mouse mutants, the characteristic asymmetric subcellular localization of Prickle1 is lost in cochlear hair cells and the neuroepithelium, indicating that Smurf-dependent localized degradation of PCP components plays a critical role during the establishment of PCP.

Evidence for an antagonistic relationship between the Dishevelled (Dsh; Dvl in mammals) and Prickle proteins within the Frizzled-Van Gogh (Vang) core PCP group has been suggested by prior work. A negative effect of *Drosophila* Prickle on Dsh localization has been documented (Jenny et al., 2005; Tree et al., 2002), whereas a negative effect of Dsh/Dvl on Prickle has been suggested but not yet shown. In the current study, Narimatsu and colleagues provide support for the hypothesis that Dishevelled antagonizes Prickle and, importantly, add mechanistic insight into how the Frizzled and Vang complexes promote their mutually exclusive asymmetric subcellular localizations (Figure 1).

In *Drosophila*, prior to the initiation of PCP signaling, all core PCP factors of the Frizzled-Vang group colocalize in a ring at the apical cortex of epithelial cells (Seifert and Mlodzik, 2007; Strutt, 2003). Although not yet shown, it is very likely that this is also the case in vertebrates. The molecular interactions among the Frizzled-Vang group then lead to the stable formation of two complexes at opposing ends of each cell, along the respective axis of