these fibers act as an innate monitor for epithelial barrier compromise? Furthermore, whether there are distinct neural populations that respond to epithelial-derived cytokines other than TSLP is yet unknown. Answering these questions will be crucial to our evolving understanding of the pathogenesis of atopic disease and other inflammatory cutaneous disorders.

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SAX-7 and Menorin Light the Path for Dendrite Morphogenesis

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Environmental and cellular cues pattern dendritic growth and direct dendrites to their targets. However, little is known about the signals regulating interactions with the surrounding substrate. Dong et al. and Salzberg et al. now identify a tripartite ligand-receptor complex that conveys cues from the substrate necessary for the patterning of complex dendrites in *C. elegans*.

The ability of the nervous system to receive and process information from the external world depends on the development of neurons with specific dendritic and axonal wiring patterns. The precise spatial patterning of dendritic arbors requires highly regulated molecular signaling, and intracellular pathways for dendritogenesis have been intensively studied over the last several decades in numerous model organisms (Jan and Jan, 2010; Parrish et al., 2007). However, dendrites in vivo grow within a constantly changing milieu of neural and nonneural tissue, necessitating extensive extracellular communication between dendrites and their often dynamic substrates. It seems unlikely that these substrates only provide structural support to mature arbors, yet the degree to which the patterns of molecules expressed by the substrate might instruct dendritic morphology during development, and the nature of these cues is poorly understood. In this issue of *Cell*, Dong et al. (2013) and Salzberg et al. (2013)—utilizing as a model the highly stereotyped PVD somatosensory neurons in *C. elegans*—identify a mechanism of dendrite-substrate interaction essential for complex dendritic morphogenesis (Figure 1). The authors report the identification of a tripartite receptor-ligand complex that operates between body wall hypodermal cells and the developing neuronal dendrites. These reports are exciting as they reveal how a highly localized patterning cue in nearby cells can direct dendrite growth with remarkable precision.

Through visualization of PVD morphology, both research groups carried out screens for genes that are required for dendrite morphogenesis and focused their attention on mutants with a particularly striking loss and disorientation of higher-order dendrite branches (Figure 1). These mutations mapped to a previously uncharacterized gene, which is given the name *menorin* or *mnr-1* (named after the menorah-like dendrites of PVD neurons), and to the gene *sax*-7,

which encodes a Neuroglian/L1-CAM homolog of the immunoglobulin superfamily. *mnr-1* encodes a member of the Fam151 family of proteins that are conserved from simple eukaryotes to higher vertebrates but whose functions are unknown. Based on its expression in the hypodermis and the ability of hypodermal, but not neural, expression of *mnr-1* to rescue mutant phenotypes, MNR-1 appeared to be a cue for arborization provided by adjacent hypodermal cells. Of note, whereas *mnr-1* mutants have defective PVD and FLP (the only other neurons with extensively branched dendrites in worms) morphology, other neurons in the worm nervous system appear to be unaffected, suggesting that MNR-1 may be one of a suite of substrate→dendrite cues that specifically promotes complex branching, with cues specifying other dendritic types awaiting identification.

Disruption of SAX-7 leads to very similar phenotypes as loss of MNR-1 function, and double mutant analysis suggests that the two act in the same pathway. However, in contrast to the widespread localization of MNR-1, SAX-7 protein forms a precise subcellular pattern in the hypodermis along which tertiary dendritic branches grow, leading to the interesting hypothesis that SAX-7 localization may provide an instructive cue for dendrite growth and, together with MNR-1, a preferred substrate for PVD dendrites. Both groups test this idea with an elegant approach, ectopically expressing SAX-7 in cells that are not normal substrates for PVD dendrites, such as motor neurons and other sensory neurons, as well as a population of egg-shaped epithelial "seam cells." The characteristic positions and shapes of these cells provide a very powerful assay to test for instructive patterning. Remarkably, PVD dendrites target and follow any discrete areas ectopically expressing SAX-7 and MNR-1, providing strong support for the preferred substrate model (Figure 1). Both papers also point to an essential role for extracellular fibronectin (FnIII) domains in SAX-7 function. Prior studies indicated a critical function of the extracellular immunoglobulin domains of SAX-7 in neuronal adhesiveness (Pocock et al., 2008). Little has been known about FnIII; however, there is in vitro evidence of a role for the FnIII domains of L1 in neurite outgrowth and homomultimerization (Appel et al., 1995; Silletti et al., 2000). Understanding how the functions of SAX-7 are diversified during neuronal morphogenesis through the use of different extracellular domains is an intriguing question for future research.

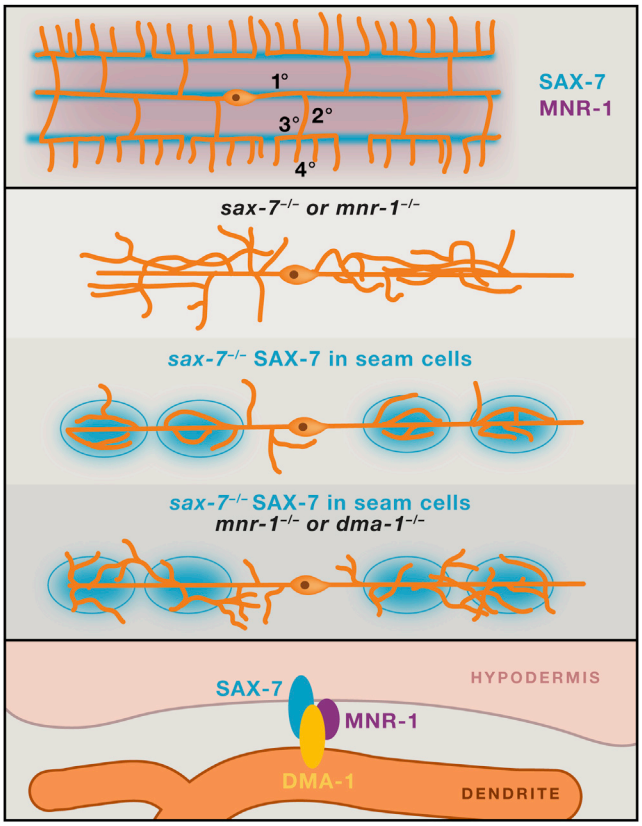

Figure 1. The Tripartite Complex Instructs Dendritic Patterning of PVD Neurons

Top: MNR-1 (purple) is broadly distributed in the hypodermis, whereas SAX-7 (blue) is enriched along sublateral stripes in the hypodermis, colocalizing with 3° PVD dendrites. Middle: the PVD dendrite becomes disorganized in *sax-7* or *mnr-1* mutant animals. Ectopic expression of SAX-7 in seam cells in a *sax-7* mutant background instructed PVD dendrites to be restricted in and around the seam cells, which required *mnr-1* or *dma-1*. Bottom: model of the SAX-7/MNR-1/DMA-1 tripartite complex. See text for details.

How is the growth signal passed from the hypodermis to the dendrite? Both papers convincingly demonstrate through genetic and biochemical evidence that MNR-1 forms a complex with SAX-7 in the hypodermis, acting on dendrite growth through the recently identified neuronal leucine-rich repeat containing transmembrane protein DMA-1 (Liu and Shen, 2012) expressed in PVD neurons (Figure 1). Strikingly, loss of DMA-1 abolishes the SAX-7 and MNR-1 gain-of-function phenotypes. Thus, it seems that the high local concentration of SAX-7 and MNR-1 activates DMA-1, possibly leading to tighter adhesion of neurites to the hypodermis and signaling events that recruit cytoskeletal components necessary for promoting stabilization and branching of tertiary dendrites at specific locations.

Together, these papers make a very strong case for a preferred molecular substrate that instructs dendritic arbor branching and stabilization. Although one might argue that PVD neurons show an extreme form of regularity not often observed in other dendritic arbors, similarly localized cues might act in diverse contexts to generate local stereotypy in branching or growth. It will be important to dissect the mechanisms leading to dendrite growth, branching, or retraction in response to these extrinsic signals. Interestingly, the papers also show that loss of MNR-1 function leads to a number of additional patterning defects, including loss of self-avoidance and menorah tiling. Such defects could reflect a broad requirement for substrate interactions for several different patterning events. Given this new role for SAX-7, MNR-1, and DMA-1 in worms and the recurring conservation of mechanisms of dendrite morphogenesis in invertebrates and vertebrates, it will be interesting to study the expression and function of

vertebrate homologs and Fam151 family members. Once again, studies of the worm nervous system have uncovered a new path for a growing field.

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Remembrance of Cilia Past

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The primary cilium is thought to be disassembled prior to mitosis, freeing the centrosomes to participate in the mitotic spindle. In this issue, Paridaen et al. demonstrate that a remnant of the ciliary membrane remains attached to the mother centriole and is asymmetrically inherited in the developing neocortex.

Information about the state of a cell in one generation can be transmitted through cell division to the next generation, maintaining a form of cellular memory. These "memories" ultimately have a molecular basis, and asymmetric segregation of these molecular manifestations of cellular memory is an important part of asymmetric cell division. Such divisions are typical of stem cells, in which one cell retains the stem cell fate and the other differentiates into another cell type. The best-known examples of cellular memory mechanisms involve chromosomes, with their epigenetic markings that control how they are expressed. But in this issue, Paridaen et al. (2013) describe a cytoplasmic instantiation of cellular memory involving the centrosome and primary cilium.

"Cilium" is Latin for eyelash, and the primary cilium is a single, nonmotile eyelash-like structure that grows from the older of the two centrioles within a centrosome. The primary cilium was identified most clearly by electron microscopists in the 1950s and 60s, but its function was unknown, and in one of the great disappearing acts of 20th century cell biology, it fell from favor as a topic of study. However, the primary cilium has come back into vogue recently, as a result of genetic studies in mouse and humans that showed that it is an essential sensor for mechanical and chemical signals from the extracellular environment and is a signaling platform for several important signaling pathways (Garcia-Gonzalo and Reiter, 2012).

If the primary cilium is so important as a signaling hub, controlling which cells make a cilium and when they make it would be critical. In most animal cells, the primary cilium is disassembled prior to mitosis and is assembled again in G1 following division, and this cilium cycle is tied to the centriole cycle. Centrioles duplicate once per cell cycle (Nigg and Stearns, 2011) by a semiconservative mechanism that is superficially like that of DNA replication. In G1, each cell has a pair of centrioles—one newer, which was formed in the previous cell cycle, and one older, which was formed in some earlier cycle. The convention is to refer to the older as the mother centriole and the younger as the daughter. The mother centriole has specialized appendages at its distal end that allow it to interact with the plasma membrane and form a cilium. Depending on the cell type, the requirements for cilium formation are presence of a mother centriole with appendages, G1 cell-cycle stage, and, for maximum extent of ciliogenesis, a driver of quiescence such as serum starvation or contact inhibition. In a cycling cell, the centrioles duplicate at the entry into S phase such that two new daughter centrioles grow, each tightly apposed to one of the original centrioles. So, at this stage, there is an old mother and a new mother centriole, each with a daughter centriole. In most cells, the cilium is disassembled in S phase, and the two centriole pairs are free to associate with the mitotic spindle and then segregate to the two products of division (Figure 1).