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Development of Dendritic Form and Function

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Abstract

The nervous system is populated by numerous types of neurons, each bearing a dendritic arbor with a characteristic morphology. These type-specific features influence many aspects of a neuron's function, including the number and identity of presynaptic inputs and how inputs are integrated to determine firing properties. Here, we review the mechanisms that regulate the construction of cell type–specific dendrite patterns during development. We focus on four aspects of dendrite patterning that are particularly important in determining the function of the mature neuron: (*a*) dendrite shape, including branching pattern and geometry of the arbor; (*b*) dendritic arbor size; (*c*) targeting of dendrites to particular locations; and (*d*) subdivision of dendrites into compartments with unique electrical properties or synaptic inputs.

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INTRODUCTION

Of all the features that distinguish different types of neurons from each other, perhaps the most obvious and striking are their dendrites (**Figure 1**). Across the enormous diversity of neuronal types, dendritic arbors vary markedly in their shape—that is, in the geometry of the territory they cover and how their branches fill that territory. Arbors also vary in size and, therefore, in the number and types of inputs they receive. Furthermore, dendrites grow in cell type–specific locations relative to the cell body, and within an arbor dendrites may be specialized to receive input from certain synapses or have certain electrical properties. Together, these features shape each cell's dendritic arbor into an arrangement that is characteristic among individuals of a single cell class.

The arrangement of dendrites has important implications for neural information processing in two broad ways (London & Häusser 2005, Spruston 2008). First, the placement and density of dendrites determine the number, position, and types of synapses a neuron will have. Second, the electrical properties of dendrites, combined with the location of particular inputs, enable computations that shape circuit function. The relationship between dendrite form and function suggests that each neuron type has adapted its dendritic structures for its unique role and that the diversity of dendritic morphologies in the nervous system is necessary to fulfill a wide range of computational needs. By elucidating the developmental mechanisms that coordinate the patterning and wiring of dendritic structures, we can learn more about what dendrites do and how their dendritic fields organize into functional circuits. This knowledge also provides a basis for understanding how dendritic defects cause circuit dysfunctions.

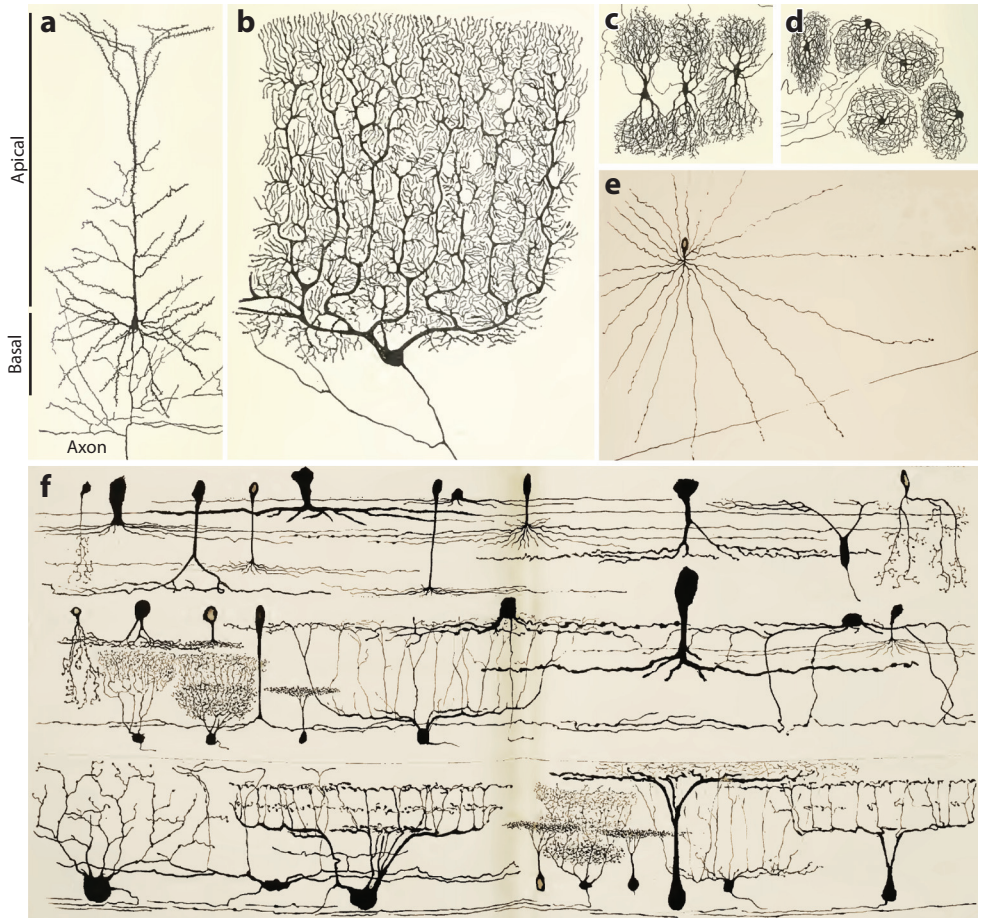


Figure 1

Diversity of dendrite morphology captured by Ramón y Cajal. (*a–e*) Gallery of drawings by Ramón y Cajal, depicting the characteristic dendritic arbors of different cell types throughout the brain. Arbors vary in their geometry and branching patterns. (*a*) Cortical pyramidal cell (rabbit) with apical and basal dendrites and axon. (*b*) Cerebellar Purkinje cell (human). (*c*) Neurons of the dorsal column nuclei (human). (*d*) Neurons of the inferior olive (human). (*e*) Retinal amacrine cell (green lizard). (*f*) Ramón y Cajal illustration of cell types found in lizard retina. Drawings depict two cell classes: the amacrine cells (*top row*) and retinal ganglion cells (*bottom row*; *middle row* contains some of each), as seen in transverse sections. Even within a single cell class, the variation in dendrite size and shape is remarkable. Ramón y Cajal used drawings such as these to enumerate and classify the cell types that populate various nervous tissues. Panels *a–d* from Ramón y Cajal (1909); panels *e* and *f* from Ramón y Cajal (1893).

In this review, we discuss progress in uncovering cellular strategies and molecular mechanisms that generate dendritic diversity. Guided by the Darwinian assumption that developmental rules evolve to serve adult functions, we organize our review around the idea that dendrites—to use a colloquial phrase—know what they want to be when they grow up. Broadly, they want to be able to perform the functions required of the cell and the circuit in which they are located. To accomplish this, they acquire appropriate shapes, sizes, locations, and compartmental organization. To organize the review, we assign the examples we discuss to one of these four categories, a

somewhat arbitrary distinction. Nevertheless, this framework allows us to highlight recent cellular and molecular findings that reveal organizational principles of cell type–specific dendrite patterning. To illustrate these emerging principles, we draw examples from a variety of species (mouse, chick, frog, worm, fly, and leech), systems (visual, mechanosensory, olfactory, and others), and molecular mediators (neurotransmitters, transcription factors, attractants, and repellents). Our coverage, therefore, is broad rather than deep. We refer the reader to other recent reviews in which individual mechanisms or topics are treated in greater depth (Baier 2013, Hong & Luo 2014, Jan & Jan 2010, Puram & Bonni 2013, Zipursky & Grueber 2013).

Before proceeding to review mechanisms that specify dendritic form, we begin with a brief overview of the general trajectory of dendrite development.

A DENDRITE IS BORN

The life of a dendrite begins when a newly born neuron polarizes its cytoskeleton and organelles to define nascent neurites as either axon or dendrite (for a review, see Cheng & Poo 2012). Once specified as a dendrite, the neurite grows and branches using cell biological mechanisms that are specialized for building the dendritic frame. Two of the most important mechanisms are microtubule-directed transport and organelle localization. In contrast to the uniformly plus end–directed microtubule organization in axons, dendrites contain both plus- and minus-end microtubules (Baas et al. 1988). Mixed microtubule polarity facilitates assembly of highly branched arbors, which are characteristically formed by dendrites (for a review, see Conde & Cáceres 2009). Organelles such as ribosomes, the secretory endoplasmic reticulum, and the Golgi complex are trafficked by minus end–directed transport and are thus enriched in dendrites, where they contribute to branch initiation and differentiation. The endoplasmic reticulum exhibits zones of structural complexity in dendrites that spatially correlate with both insertion of proteins into the plasma membrane and branch formation (Cui-Wang et al. 2012). The Golgi complex influences branching through discrete and mobile structures called Golgi outposts, which regulate post-Golgi trafficking and facilitate microtubule nucleation at nascent branch points (Horton et al. 2005, Ori-McKenney et al. 2012, Ye et al. 2007). An active area of research is to understand how these cellular machineries are controlled in different cell types to build their characteristic arbors.

Cellular and transcriptional mechanisms specify a general shape and size but are unlikely to determine the number and position of all dendritic branches in any mature arbor. Dendrite morphogenesis occurs in a highly dynamic fashion with overproduction of branches that either stabilize and form synapses or retract. Whether a transient branch will survive to become part of the mature dendritic arbor depends on many factors, including cell-extrinsic cues, contact with a permissive substrate, formation of synapses, and the activity of those synapses (Cline & Haas 2008, Yuste & Bonhoeffer 2004). The cues and signaling pathways that influence dendrite arbor growth and remodeling remain a subject of active investigation. In this review we consider how such cues act together with intrinsic factors particular to each cell type to generate the unique dendritic arborization patterns that define a neuron's form and function.

DENDRITES WANT TO BE THE RIGHT SHAPE

Why Does Shape Matter?

The shape of a neuron's dendritic tree determines its function by influencing how synaptic information is received and integrated. This relationship is perhaps seen most clearly in neurons of the somatosensory and visual systems, where the shape of the dendritic arbor is the primary

determinant of the shape of the receptive field. The arbor territory defines the region of the world from which a neuron receives input, either directly from sensory receptors or indirectly via synapses (Peichl & Wässle 1983). A second aspect of shape, the arbor's branching pattern, determines the density with which a neuron samples this field. Complex dendrites with high branch number and branching frequency can capture inputs from numerous presynaptic partners, whereas simple arbors sample more sparsely. Features such as dendrite diameter, distance from the soma, and the number of branch points that must be crossed to reach the soma also determine function by influencing the probability that an excitatory postsynaptic potential (EPSP) produced at a given synapse will contribute to the firing of the neuron. Furthermore, nonlinear effects on synaptic efficacy arise from having multiple inputs on the same dendritic branch (London & Häusser 2005, Spruston 2008). Undoubtedly, additional ways exist in which features such as branch length, orientation, distribution, and complexity impact processing and transmission of incoming information, but the precise effects remain to be determined.

Although it is easy to see in principle that changing arbor shape should change function, it has been harder to demonstrate that particular shapes underlie particular neuronal functions. In theoretical studies, however, certain arbor shapes have been identified that are well suited for certain physiological properties. For example, shape can influence whether a pyramidal cell fires tonically or in bursts (van Elburg & van Ooyen 2010). Certain shapes can also make a neuron better at linear summation of EPSPs, as one might see in a sensory neuron, or at distinguishing the temporal order of EPSPs, as would be expected of a coincidence detector in a circuit that learns (Stiefel & Sejnowski 2007). Whether these shape parameters are common is unclear, although these studies cite several cases in which neurons have both the predicted shape and physiology. One striking example of function following form is the wedge-shaped arbor formed by dendrites of J-RGCs, a type of retinal ganglion cell (RGC) found in mouse (Kim et al. 2008). The asymmetric distribution of branches along the dorsoventral axis tunes neurons to respond selectively to upward motion. We do not know exactly how dendrite shape imparts direction selectivity to these cells' light responses, but we do know that shape is important because of a subset of J-RGCs that are less asymmetric are also less directionally selective.

How do neurons develop their unique shapes? Although the extraordinary variety of dendrite shapes has been known since the time of Ramón y Cajal (1893, 1909) (**Figure 1**), we are just beginning to understand how cell type–specific shapes emerge. In the past, a key impediment was that one could seldom prospectively identify which developing neurons in a mixed population would acquire arbors of particular morphologies. Now we are in the age of molecular markers for specific neuronal cell types, which provide genetic tools for monitoring and manipulating many aspects of their development, including dendrite patterning. These cell type–specific markers underlie many of the advances we will discuss here and throughout the review.

Genetic Control of Dendrite Shape

As with many features that define a neuron's structure and function, the basic plan of the dendritic arbor shape is specified by intrinsic transcriptional mechanisms. Gene regulatory pathways that endow neurons with particular cell fates also endow them with cell-intrinsic effectors that regulate the propensity for dendritic branching as well as receptors that specify responsiveness to extrinsic growth-promoting or -inhibiting cues. A key model for the study of dendrite shape is the dendritic arborization (da) sensory neuron system responsible for somatosensation in *Drosophila melanogaster* larvae (**Figure 2**). Four classes of da neurons bear dendrites that innervate the epidermis and axons that extend into the ventral nerve cord. The classes differ in their dendritic morphology and in the sensory modality they detect (Grueber et al. 2002, Hwang et al. 2007, Jan & Jan 2010, Yan et al.

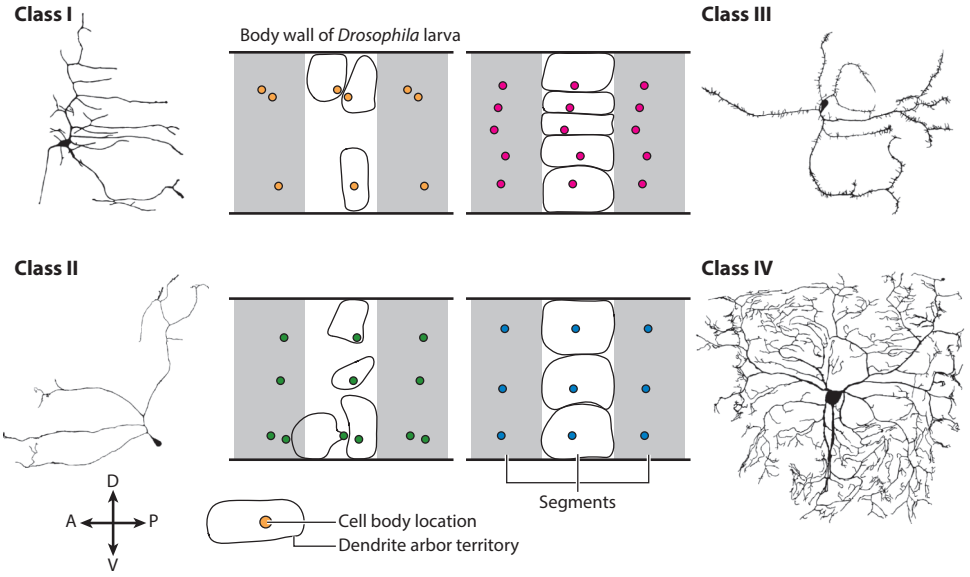


Figure 2

Drosophila dendritic arborization (da) neurons. Four classes of mechanosensory da neurons cover the *Drosophila* larval body wall with their dendrites. The characteristic morphology of individual class I–IV neurons and their arrangement in the body wall are depicted. The larval body has a segmental anatomy, and each da neuron class shows typical cell body locations (*colored circles*) and dendritic territories that are repeated across segments (*alternating gray and white stripes*). Anteroposterior (A, P) and dorsoventral (D, V) body axes are indicated (*crossed arrows*). Class I cells have the simplest anatomy; neither they nor class II cells cover the body wall completely with their dendrites. Class III and IV cells have more complex branching patterns. Their dendrites tile the body wall to make complete, cell type–specific sensory maps. The nonoverlapping territories occupied by each cell are established by homotypic repulsion. The four classes exhibit dendrite self-avoidance, as branches rarely cross each other. Schematic modified from Grueber & Sagasti (2010) and Jan & Jan (2010). Cells traced from images provided by D. Tracey and S. Mauthner.

2013). Because da classes have stereotyped dendrite structures that are identifiable across animals, this system permits forward genetic screens to uncover mechanisms of dendrite patterning and morphological diversity. For example, in an RNA interference (RNAi) screen for transcriptional factors controlling dendrite morphogenesis of the class I da neurons, more than 70 genes were identified that regulate multiple aspects of arbor development, including dendrite branching and maintenance as well as field size and coverage (Parrish et al. 2006). These and other screens have led to insights into transcriptional control of dendrite shape.

First, selector genes expressed by single da classes specify their morphology. *abrupt* and *knot* encode transcription factors exclusively expressed in class I and IV da neurons, respectively, and when misexpressed they are sufficient to induce class-specific features. Abrupt specifies the simple dendritic arbor typical of class I da neurons by limiting dendritic branch outgrowth (Li et al. 2004, Sugimura et al. 2004). Knot endows class IV neurons with an expansive and highly branched morphology by promoting microtubule-dependent dendritic branching (Jinushi-Nakao et al. 2007). Abrupt and Knot induce their disparate effects by activating distinct target genes and also by producing different expression levels of common target genes. For example, Teneurin-m (*ten-m*) is a common gene target, but it is expressed at higher levels in class I than in class IV cells. *Ten-m* encodes a homophilic cell adhesion molecule that is also expressed in a gradient in the epidermis.

Growing class I dendrites respond more robustly to this gradient because of their high *ten-m* expression, orienting their terminal branches to form a comb-like arbor shape (Hattori et al. 2013).

Second, some transcription factors control dendrite morphology in multiple da types through different expression levels. The homeobox transcription factor *cut* is expressed at increasing levels in class II, IV, and III, and overexpression of *cut* in a class II cell transforms its arbor to a class IV morphology (Grueber et al. 2003a). Cut levels specify distinct morphologies by providing an increasing abundance of proteins that direct branch morphogenesis and stabilization (Iyer et al. 2013, Sulkowski et al. 2011). Cut also leads to formation of the actin-rich dendritic spikes typical of class III da neurons by elevating levels of effectors such as Fascin, an actin-bundling protein (Nagel et al. 2012).

Finally, combinatorial expression of transcription factors can specify dendrite shape. Useful model systems for such studies have included class III and IV da neurons as well as *Caenorhabditis elegans* mechanoreceptors (Jinushi-Nakao et al. 2007, Smith et al. 2013). Further studies on the combinatorial actions of transcription factors in these systems could lead to new insights into the integration of transcriptional networks that control type-specific dendritic patterning.

In contrast to the situation in flies and worms, little is known about type-specific transcriptional control of mammalian dendritic structures. One fruitful approach has been to study mammalian homologs of invertebrate transcription factors. The mammalian genes *Cux1* and *Cux2* are conserved Cut homologs that can functionally substitute for Cut in *Drosophila* (Grueber et al. 2003a). They promote dendritic but not axonal branching of layer II–III cortical pyramidal neurons (Cubelos et al. 2010). Functioning nonredundantly, Cux1 and Cux2 selectively promote basal and apical dendritic branching, respectively (Cubelos et al. 2014). Thus, mammalian *Cux* genes play roles in generating the characteristic dendrite pattern of pyramidal cells. Whether they do so for other mammalian neurons remains to be seen.

Interactions with Local Cues

Although transcriptional mechanisms are clearly important for determining a neuron's overall dendrite shape, they do not specify the location of individual branches. Growing neurons interact extensively with cues in their environment that promote dendrite growth, branching, or retraction. Thus, the fine structure of a neuron's dendritic arbor arises from the interplay between intrinsic and extrinsic mechanisms.

Before we discuss extrinsic cues that influence dendrite growth, let us consider briefly what these signals might accomplish from the perspective of the developing neuron. How much does it matter for neuronal function whether each fine dendritic tip is positioned in exactly the right place? To address this question, theoreticians have examined the spatial statistics of dendritic structure across many cell types and species, looking for commonalities. The assumption is that common patterns must have been selected through evolution for some important function. These studies have found that, at least for the cell types in their data sets, individual dendritic branches are distributed stochastically; their locations cannot be predicted. However, the overall distribution of branches through the arbor territory can be predicted, being well described by a Gaussian function. This distribution reduces the chance of arbor clumping and therefore promotes efficient sampling of the receptive field (Snider et al. 2010, Wen et al. 2009). Indeed, the arbors analyzed in these studies not only maximize the chances of encountering presynaptic axons but also maximize the number of different presynaptic axons that may be encountered. Moreover, dendrites achieve this maximal sampling using close to the minimum possible dendrite length (Cuntz et al. 2012, Wen et al. 2009). These findings suggest that the precise location of any one branch is less important

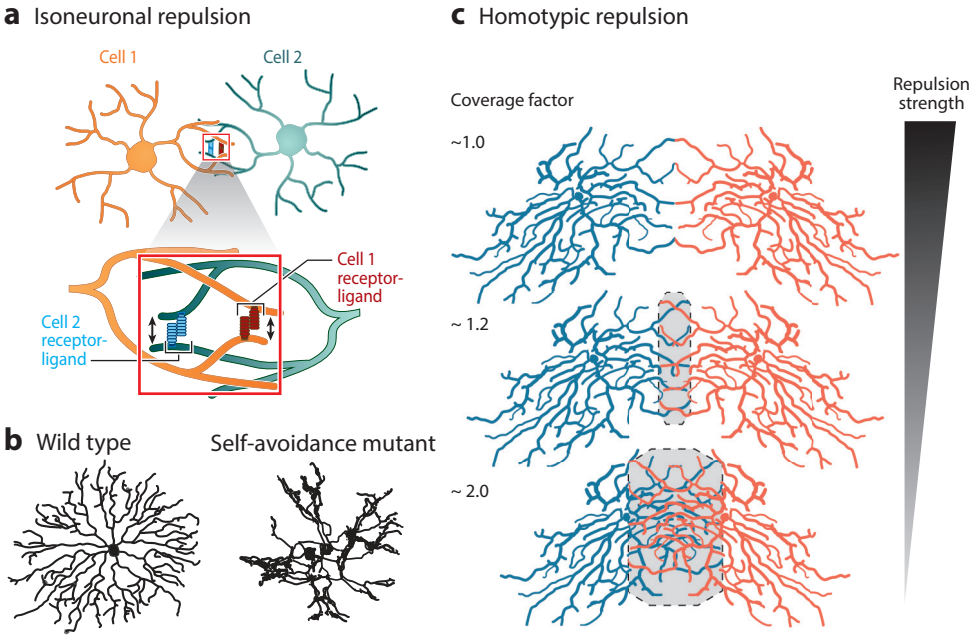


Figure 3

Repulsive dendrite patterning by self-avoidance and homotypic repulsion. (*a*) In self-avoidance, dendrites originating from the same neuron recognize and avoid each other. Receptor-ligand interactions underlying self-avoidance are depicted in the inset. Cell 1 dendrites interact only with other dendrites from Cell 1, and the same is true for Cell 2. Thus, dendrites from Cell 1 can cross dendrites from Cell 2, but Cell 1 dendrites cannot cross each other. (*b*) Self-avoidance promotes efficient dendritic coverage of the receptive field; when molecular cues underlying self-avoidance are eliminated, dendrites fill space inefficiently. (*c*) In homotypic repulsion, dendrites originating from a different neuron of the same type recognize and avoid each other. Strong repulsion leads to perfect tiling (*top*), in which each cell covers a unique territory. In this case, each point in the neuropil is covered by one cell, for a coverage factor of one. Weaker repulsion leads to increasingly large zones of overlap (dashed-outlined regions). Homotypic repulsion can therefore produce a range of different coverage factors.

than the overall distribution of branches. Thus, the key developmental mechanisms are those that ensure dendrites sample their entire territory evenly and efficiently. Much progress has been made recently in identifying these mechanisms.

Dendrite self-avoidance for optimal spacing and coverage. One strategy to prevent dendrite clumping and maximize coverage of the arborization field is to sample the location of sibling dendrites. Dendrite self-avoidance accomplishes this task through a contact-mediated mechanism in which sibling branches belonging to the same neuron selectively repel each other (a process termed isoneuronal repulsion), but they freely overlap with those of neighboring (heteroneuronal) neurons (**Figure 3*a***). Through competitive interactions and mutual retraction, sibling dendrites fill the available space and form a nonoverlapping territory (Zipursky & Grueber 2013). This mechanism promotes efficient sampling of each neuron's receptive field (**Figure 3*b***).

Molecules known to regulate self-avoidance include repulsive ligand-receptor pairs that signal in *trans* between dendrites of the same cell. Such signaling occurs in starburst amacrine cells of vertebrate retina (**Figure 4**), where transmembrane Sema6A and its PlexA2 receptor mediate

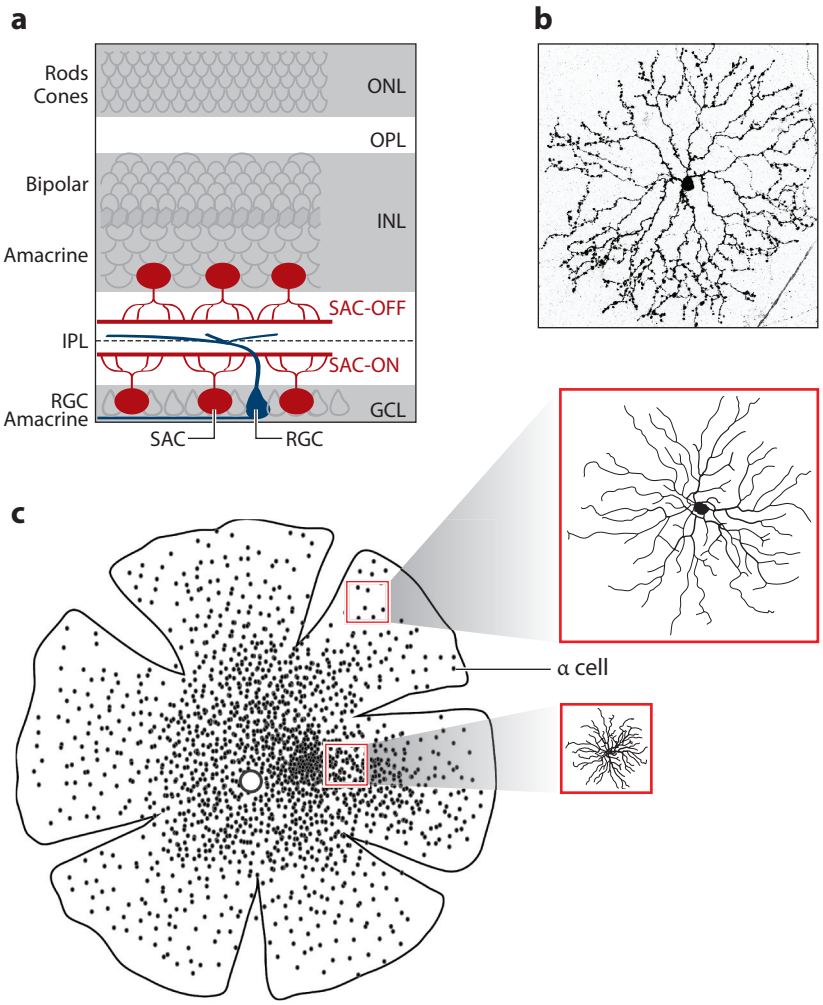


Figure 4

Vertebrate retina. (*a*) Schematic depicting vertebrate retina in cross section. Neurons reside in three cellular layers: the outer nuclear layer (ONL), inner nuclear layer (INL), and ganglion cell layer (GCL). These are separated by two synaptic layers, the outer and inner plexiform layers (OPL, IPL). Cell types residing in each layer are indicated on the left. Retinal ganglion cells (RGCs) and amacrine cells, in particular the subtype known as the starburst amacrine cell (SAC), are highlighted. RGCs and amacrines project dendrites into the IPL, where they receive synapses from bipolar cell axons (*not shown*). Most amacrine cells have no axon; instead they use their dendrites both to make and receive synapses. Each type of ganglion and amacrine cell projects dendrites to particular IPL sublayers. This is illustrated by the SACs, which come in two varieties: one responding to light ON and the other to light OFF. Both target unique IPL sublaminae. (*b*) Photomicrograph of a starburst neuron from mouse retina, showing its characteristic radial dendritic pattern. This *en face* view is orthogonal to the cross section diagrammed in (*a*). (*c*) Retinal neurons vary in cell density and dendrite size across the visual field. Illustration depicts a flat-mounted cat retina; dots indicate density of a single RGC type, the α cell (Peichl 1991). Highest-density region defines the area centralis, a retinal zone specialized for high-acuity vision. Single cell tracings on the right show that dendrite size varies as the inverse of cell density, such that dendrites are smallest in the high-acuity zone. Despite size differences, α cells have a characteristic dendrite shape regardless of their retinal location. This pattern is typical of many retinal neuron types.

isoneuronal repulsion (Sun et al. 2013). In *C. elegans*, spacing between dendritic subfields of the PVD neuron is established by contact-repulsion mediated by Unc6/Netrin, a diffusible ligand anchored to the membrane surface by its Unc40/DCC receptor, and Unc5 receptors on apposing sibling dendrites (Smith et al. 2012). A similar mechanism has been proposed for Slit-Robo2–mediated spacing of cerebellar Purkinje dendrites (Gibson et al. 2014).

Simple ligand-receptor pairs may be sufficient for self-avoidance of cells whose arbors do not overlap with other neurons of the same class, such as the two PVD neurons in *C. elegans* that separately innervate the left and right body walls. But in some cases, neurons that exhibit self-avoidance share territory with their homotypic neighbors. A striking example is the retinal starburst amacrine cells (**Figure 4*b***) that form a highly overlapping array in which dendrites of one starburst cell encounter dendrites of 30–40 neighboring starburst cells. Moreover, the starburst cells form inhibitory synapses with each other to sharpen the tuning of the direction-selective RGCs that they innervate. In such an arrangement, a dendrite must discriminate between sibling dendrites, which they repel, and dendrites of their neighbors, with which they interact freely (**Figure 3*a***). This remarkable feat requires that self-avoidance be accompanied by a mechanism for self/nonself discrimination.

Two sets of genes have been identified that mediate both self-avoidance and self/nonself discrimination: *Dscam1* in *Drosophila*, which encodes a set of immunoglobulin superfamily adhesion molecules, and a cluster of *protocadherin* (*Pcdh*) genes in mice, which encode a set of cadherin superfamily adhesion molecules (**Figure 5**). Evidence to support these roles comes primarily from genetic analyses. In *Drosophila*, *Dscam1* mediates contact-dependent repulsion of sibling neurites to pattern dendritic fields of da neurons and segregate axonal branch projections of mushroom body neurons (reviewed by Zipursky & Grueber 2013). Similarly in mice, the γ subcluster of Pcdh proteins (Pcdhγ) mediates self-avoidance to pattern retinal starburst cells and cerebellar Purkinje cells (Lefebvre et al. 2012). In *Dscam1*- or *Pcdhg*-null mutants, sibling branches overlap, resulting in dramatic changes to arbor shape and incomplete dendritic field coverage (**Figure 3*b***). Isoform diversity is not necessary for self-avoidance, as any single and arbitrarily chosen isoform is sufficient. However, diversity is critical for dendrites whose fields overlap those of other neurons in order to distinguish and repel only those neurites arising from the same neuron. If neurons express the same isoform, their dendrites recognize each other as self and avoid one another. Expression of distinct Dscam or Pcdh cell-surface identities between neighboring neurons is central to the self-avoidance model: Dendrites repel self (sibling) neurites through homophilic Dscam/Pcdhg interactions. Nonself overlap occurs because dendrites are unlikely to encounter neurites expressing the same Dscam/Pcdh signature unless they emanate from the same neuron.

Although *Dscam*s and *Pcdh*s are unrelated genes, they share three exceptional molecular features that underlie self/nonself discrimination. First, they have complex genomic organizations that generate large numbers of isoforms (**Figure 5*a***). *Drosophila Dscam1* encodes more than 38,000 transmembrane molecules through alternative splicing of three large cassettes of alternate exons that encode variable ectodomains (Schmucker et al. 2000), a splicing pattern notably absent from their vertebrate orthologs (Barlow et al. 2002). The mouse *Pcdh* cluster encodes 58 transmembrane molecules, divided into α, β, and γ subclusters, with promoter choice leading to expression of specific members of each subcluster (**Figure 5*b***) (Kohmura et al. 1998, Wu & Maniatis 1999). Like Dscam1s, clustered Pcdh isoforms present distinct cell surface identities but implement common signals through shared intracellular sequences. To date, little is known in either system about the signaling pathways that transform self-recognition events between dendrites into repulsion.

The second feature underlying self/nonself discrimination is random combinatorial expression of Dscam1 and Pcdh isoforms (**Figure 5*b***). This has been demonstrated for both molecules in studies of gene expression by dissociated single neurons (Kaneko et al. 2006, Neves et al. 2004).

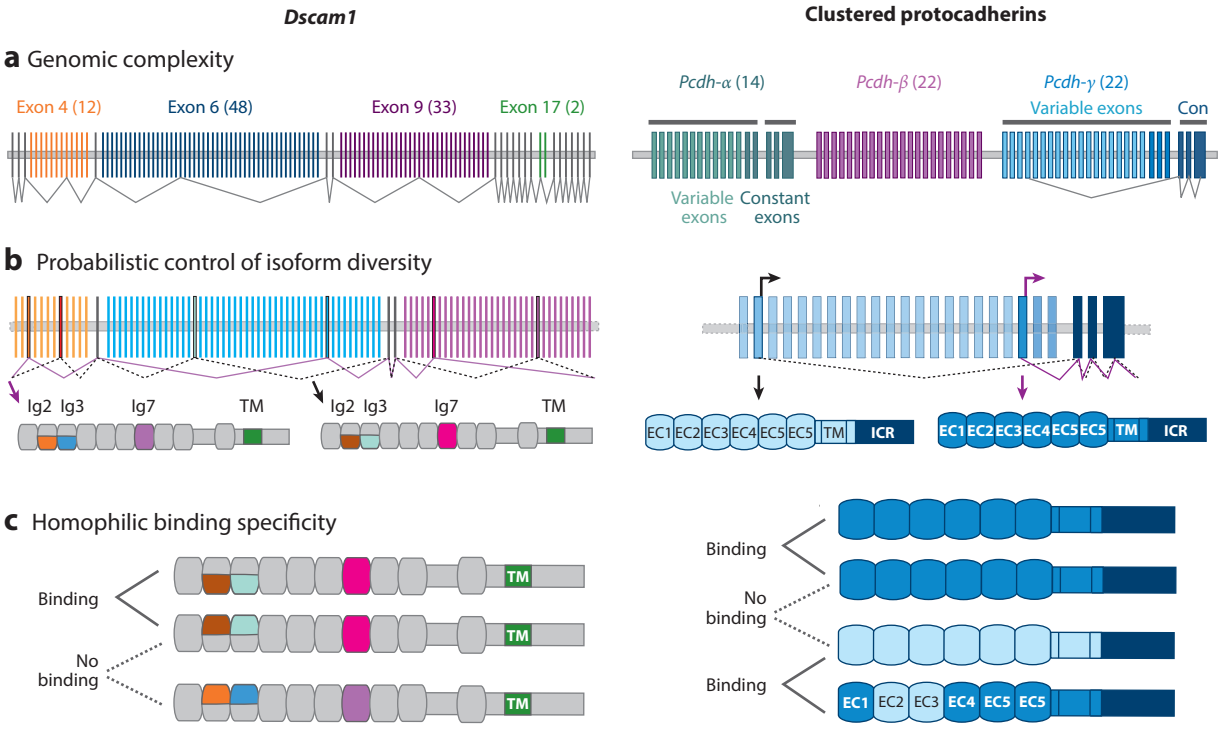


Figure 5

Fly Dscam1 and vertebrate clustered protocadherins (Pcdhs) share molecular strategies for dendrite self-avoidance. (*a*, *left*) The *Dscam1* gene locus contains three large cassettes of alternate exons (exon variant number in parentheses). Exon 17 provides two alternate exons that encode transmembrane domains. (*Right*) Clustered *Pcdh*s include three separate α, β, and γ subclusters and encode 14, 22, and 22 isoforms, respectively. *Pcdh-α* and *Pcdh-γ* comprise alternate variable exons that encode the extracellular and a portion of the intracellular sequences, and three constant exons (Con) that encode a shared intracellular region. (*b*) Isoform diversity of Dscam1 or Pcdhs among single neurons is stochastic. Dscam1 isoform expression is controlled at the splicing level, by probabilistic inclusion of alternate exons that contribute to three variable immunoglobulin (Ig) ectodomains. Choice of *Pcdh* variant expression is regulated at the level of individual promoters that precede each variable exon. Pcdhγ proteins have six cadherin repeats (EC 1–6) encoded by variable extracellular sequences and a common intracellular region (ICR). (*c*) Homophilic binding of Dscam1 isoforms is determined by pairing of variable Ig domains. Homophilic pairing of Pcdh isoforms is determined by EC2 and EC3 repeats. Abbreviation: TM, transmembrane domain.

Moreover, introducing a splice reporter into the *Dscam1* locus showed that each neuron expresses multiple splice variants and that alternate exon selection was random from cell to cell regardless of type, lineage, and animal (Miura et al. 2013). For Pcdhs, expression of each variable exon is controlled by its upstream promoter (Tasic et al. 2002, Toyoda et al. 2014, Wang et al. 2002a). Together, these findings support a model in which selection of alternative exons (*Dscam1*s) or promoters (*Pcdh*s) is stochastic, making it likely that individual neurons express unique sets of isoforms on their cell surface.

Finally, homophilic adhesion between isoform combinations provides the recognition specificity for self/nonself discrimination (**Figure 5*c***). Dscam1 binding specificity is determined by three variable ectodomains, which must match in *trans* for binding to occur (Sawaya et al. 2008, Wojtowicz et al. 2007). Pcdh homophilic specificity is determined by the cadherin consensus motifs EC2 and EC3. Although the number of Pcdh isoforms is far smaller than the number

of Dscam1 isoforms, *cis* tetramerization of Pcdhs appears to expand diversity of homophilic cell surface signatures by several orders of magnitude. In cell-based assays, all four Pcdh isoforms must match in *trans* for maximal binding to occur (Schreiner & Weiner 2010, Thu et al. 2014).

Although Dscam1s and Pcdhs are widely expressed throughout the nervous system (Kohmura et al. 1998, Schmucker et al. 2000, Wang et al. 2002b), their roles in self-avoidance and self-/nonself-recognition have only been demonstrated for a limited set of cell types. These neurons share a planar dendritic morphology, and it has been argued that self-avoidance can only be achieved when dendrites are constrained to grow along a two-dimensional (2D) surface (Han et al. 2012, Kim et al. 2012). However, the theoretical studies cited above suggest that most neurons want their dendrites to efficiently and maximally sample their territory. Purkinje cells, which use Pcdhgs and Slit/Robo for self-avoidance (Gibson et al. 2014, Lefebvre et al. 2012), first elaborate in a three-dimensional (3D) space and become planar with refinement (Kaneko et al. 2011). Moreover, loss of self-avoidance in starburst cells leads to formation of autapses (Kostadinov & Sanes 2015), which is clearly dysfunctional. Thus, we suspect that self-avoidance and self-/nonself-discrimination will turn out to be common, though not universal, properties of dendritic arbors.

Substrate-derived cues and anchors. Growing dendrites also interact with nonneuronal cells and extracellular matrix (ECM). Molecular cues positioned in these substrates can pattern dendrite growth to ensure that arbors fill their space appropriately. Two examples from *C. elegans* demonstrate this type of mechanism. PVD mechanosensory neurons innervate the body wall with elaborate menorah-shaped dendritic arbors. Molecular cues located in the skin elicit branch formation at designated points to generate the characteristic PVD morphology. The key cue is a signaling complex formed by MNR-1, a Fam151 homolog, and SAX-7, an L1-CAM homolog. PVD detects this cue using DMA-1, a leucine-rich repeat (LRR)–family transmembrane protein that acts as a receptor for the MNR-1/SAX-7 complex (Dong et al. 2013, Salzberg et al. 2013). When PVD dendritic arbors are disorganized, animals show reduced sensitivity to the mechanical pressure stimuli normally detected by PVD (Oren-Suissa et al. 2010). Thus, efficient receptive field coverage mediated by this and other signaling pathways is important for neural function. Patterning cues located in the ECM are also critical for the positioning of amphid sensory neuron dendrites. Instead of using a long-range guidance cue for growth, developing amphid dendrites first form a stationary anchor in the ECM at the nose tip and extend by retrograde migration of the cell body (Heiman & Shaham 2009). These examples illustrate that the distribution of dendrites within an arbor is likely determined by the combined influence of molecular landmarks in the growth substrate together with dendro-dendritic interactions, such as those underlying self-avoidance.

Dendritic Pruning and Remodeling

The final touches to dendrite shape are applied by pruning. Neurons eliminate excess dendritic branches and spines to form a mature arbor pattern that remains largely stable once the animal reaches adulthood. Many factors can determine which dendrites will be pruned; they vary depending on the cell type in question, but broadly speaking, they are driven by either genetically determined or competition-based mechanisms.

In genetically determined pruning, branches are eliminated at stereotyped places and developmental times. A useful system to study this process is *Drosophila* metamorphosis, when most neurons, including class IV da neurons, are dramatically remodeled in response to the hormone ecdysone. Although ecdysone signaling does not occur in vertebrates, downstream

cellular mechanisms such as neurite severing, fragmentation, and phagocytic clearance of neurite debris likely occur in all pruned dendrites (Han et al. 2014, Williams & Truman 2005). At least one molecular mechanism, the local activation of caspase, is also required for elimination of dendritic branches and spines in mammalian neurons (Ertürk et al. 2014, Kuo et al. 2006). To ensure the correct branches get removed, the activity of caspases and other pruning effectors, such as calpains, must be spatially constrained. Compartmentalized calcium signaling and the ubiquitin-proteosome system are potential regulators that exert spatial and temporal control over branch elimination (Ertürk et al. 2014, Kanamori et al. 2013, Kuo et al. 2006).

Competition-based pruning results from differential levels of neural activity or trophic factors, eliminating weakly connected or poorly supported dendritic branches and strengthening those in areas receiving stronger synaptic inputs. This adaptive process is central to the maturation of sensory circuits, in which pruning sculpts receptive fields to match the strength of particular inputs. In mouse barrel cortex, for instance, dendrites of layer IV stellate neurons that initially occupy multiple barrel domains are pruned and then reorient their growth toward the center of a single barrel. Activity-dependent signals transduced through *N*-methyl-D-aspartate (NMDA)-type glutamate receptors are critical for this dendrite arbor remodeling (Espinosa et al. 2009). In the visual system, neural activity promotes stabilization of more active dendrites and pruning of weaker ones, using mechanisms that require NMDA receptors and/or local rises in calcium (Engert et al. 2002, Lohmann et al. 2002, Sin et al. 2002; for a review, see Cline & Haas 2008).

Transducing changes in neural activity into changes in dendritic structures occurs through several mechanisms. At earlier stages of dendrite morphogenesis, calcium influx stimulates dendrite elaboration through activation of calcium/calmodulin-dependent kinase (CaMK) IV and transcriptional regulators such as CREB, NeuroD, and CREST (for a review, see Puram & Bonni 2013). Later, during pruning and remodeling, different transcription factors are engaged. For instance, pruning of barrel cortex stellate cells requires NMDA receptor–mediated activation of an Abrupt homolog, BTBD3 (Matsui et al. 2013). Activity also acts locally at the site of neurotransmission to regulate dendritic remodeling through transcription-independent mechanisms. Local calcium elevation sends a signal to regulate branch dynamics through CaMKs and Rho GTPases. Whether this signaling ultimately leads to branch stabilization or removal may depend on the activation of specific CaMK effectors (for reviews see Cline & Haas 2008, Lohmann & Wong 2005, Puram & Bonni 2013). Undoubtedly, future studies aimed at identifying calcium-dependent signaling pathways will help us understand how intrinsic and extrinsic signals are integrated during remodeling to define dendrite shape.

DENDRITES WANT TO BE THE RIGHT SIZE

Why Does Size Matter?

Dendrite size—the area or volume occupied by a neuron's dendritic arbor—has a profound influence on neuronal function. The bigger a dendritic tree, the more synapses it can receive and the more presynaptic cells and synapses it can sample. These two parameters impact the logic of circuit wiring and, hence, the computations that a circuit can perform.

Among the fundamental circuit properties determined by dendrite size, we highlight three of the most important here. First, just as the shape of a dendritic arbor is intimately related to the shape of the receptive field center, so too is arbor size linked to receptive field size (Peichl & Wässle 1983). Second, dendrite size is important for building individual receptive fields into maps that represent the physical world. In sensory systems, different types of neurons encode distinct features of a stimulus, and individual cells of each type are repeated across the structure to encode

those features at distinct map locations. Accomplishing map formation according to this strategy requires precise control of dendrite size. Take, as an example, the class III and IV *Drosophila* da mechanosensory neurons, which encode distinct tactile modalities (Hwang et al. 2007, Yan et al. 2013). An individual cell's arbors must be large enough so that collectively the members of that class cover the entire skin surface (**Figure 2**). To do otherwise would create blind spots. However, dendrites must not be so large that the receptive fields of individual cells oversample the target space. The definition of oversampling varies across different neural structures and is determined by the computational requirements of downstream neurons: Some circuits may be wired so as to require that receptive fields (and hence dendrites) overlap extensively, whereas others, such as the da neurons (**Figure 2**), represent unique slivers of the map. The general principle is that dendrites can be neither too big nor too small if members of a single cell class are to accurately sample a presynaptic target zone for the purpose of building a map.

Finally, dendrite size must be matched to the size and density of presynaptic terminals. This matching establishes the degree of convergence or divergence among the elements of each neural circuit. If a dendrite is large enough to receive many presynaptic inputs, information will be pooled and averaged. If dendrites are small relative to presynaptic arbors, the input from single neurons will be transmitted to multiple postsynaptic cells, creating parallel channels. By modulating dendrite size and the degree of information pooling, neurons can achieve significant changes in circuit function. A particularly striking example of this comes from the retinas of higher mammals (**Figure 4*c***): In the center of the visual field, retinal circuits are specialized for acuity and precise object discrimination, whereas in the periphery, circuits are specialized for sensitivity, so that animals can detect salient stimuli. (These gradients are also present in mouse retina but are much less striking; e.g., Bleckert et al. 2014, Hong et al. 2011) To implement these distinct functions, individual RGCs of a single cell type have small dendrites when they are located in the visual field center but large dendrites when they are located in the periphery (Kolb & Marshak 2003, Peichl 1991). Large dendrites permit pooling and averaging of information from many photoreceptors, which increases sensitivity and reduces noise at the cost of lost acuity. By contrast, small dendrites boost acuity at the cost of sensitivity. Thus, neurons employ developmental mechanisms to match the size of their dendrites to the size and number of presynaptic inputs, according to the computational needs of the circuit.

Here, in reviewing the many developmental strategies that establish dendrite size, we focus on the two that have been studied most intensively: competitive dendro-dendritic interactions and size-regulating signals from afferents.

Homotypic Repulsion

Some neurons set their dendrite size according to a simple developmental rule: Grow until you touch a neighbor, then stop. This rule is referred to as homotypic repulsion, because the stop signal operates specifically between dendrites of neurons belonging to the same functional type. In some cases, the stop signal is relatively weak and permits some overlap between neighboring dendritic fields. In other cases, the stop signal is absolute, producing sharp borders between the territories of individual cells. This latter case creates the phenomenon known as tiling, whereby each cell claims its unique territory through competitive interactions. The degree of dendrite overlap is described numerically using a coverage factor, which is defined as the average number of cells that cover a single point in space with their dendrites. Perfect tiling creates a coverage factor of one, whereas weaker repulsion produces coverage factors greater than one (**Figure 3*c***). A cell type that uses homotypic repulsion will never have a coverage factor less than one, which makes this mechanism advantageous for avoiding the blind-spot problem faced by many sensory neurons.

Indeed, most known examples of homotypic repulsion come from vertebrate and invertebrate sensory systems (for a review, see Grueber & Sagasti 2010). Here, we describe how this patterning works, its consequences for circuit assembly, and the molecular mechanisms that implement it.

Invertebrate mechanoreceptor dendrites. In *Drosophila* larvae, class III da neurons act as light-touch sensors (Yan et al. 2013), whereas class IV neurons act as nociceptors (Hwang et al. 2007). These two mechanoreceptor types tile the body wall with their dendrites, generating separate maps of the body for each modality (**Figure 2**) (Grueber et al. 2002). Ablation of cells or dendrites induces neighboring arbors of the same class to invade the vacated territory, whereas supernumerary cells generated through genetic manipulation of cell fate tile with their homotypic neighbors (Grueber et al. 2003b, Sugimura et al. 2003). These data demonstrate that the tiling pattern is generated through cell type–specific dendro-dendritic repulsion (Grueber et al. 2002, 2003b). The increased or decreased dendritic area resulting from these manipulations might be expected to influence modality-specific maps. This notion has not been tested in *Drosophila* but is supported by work in other mechanosensory systems. In the leech, which has much in common with *Drosophila*, ablation of nociceptive neurons causes the receptive fields of remaining nociceptive neighbors to expand, but the fields of neighboring touch-sensitive neurons do not (Blackshaw et al. 1982). Likewise, zebrafish trigeminal sensory neurons can expand their receptive fields to encompass the entire head when homotypic neighbors are removed (Sagasti et al. 2005). Thus, by implementing the grow-until-you-touch-a-homotypic-neighbor rule, mechanoreceptors encoding different stimulus features generate complete, independent representations of the skin surface.

Vertebrate retina. The retina comprises multiple cell types that are specialized to encode distinct features of the visual scene (**Figure 3**). The physiological requirements of dendrite size and coverage are similar to invertebrate mechanosensory systems, but the retina requires ~100 cell types to represent independent maps of the physical world. Dendrites of some RGCs, cone bipolar cells, narrow-field amacrine cells, and bipolar axons tile the retinal surface (Dacey 1993; Helmstaedter et al. 2013; Vaney 1994; Wässle et al. 1981, 2009).

Three lines of evidence indicate that homotypic repulsion operates in retinal dendrite patterning. First, RGC cell types with small dendrites are more numerous than cell types with large dendrites. Moreover, as discussed earlier, intraretinal variations in dendrite size are paralleled by differences in cell number (Bleckert et al. 2014, Kolb & Marshak 2003, Peichl 1991) (**Figure 4*c***). The inverse correlation between cell density and dendrite size is consistent with a grow-until-you-touch-a-homotypic-neighbor model. Second, live imaging of developing RGCs shows that dendrites make selective-repulsive contacts with homotypic neighbors. Because this phenomenon is not limited to cells that tile, homotypic repulsion could be a general mechanism for establishing dendrite size and coverage factors (**Figure 4*c***) (Lohmann & Wong 2001). Third, RGC ablation studies suggest that cell removal also removes an inhibitory cue for dendrite growth. When a small patch of retina is denuded of RGCs, neighboring RGC dendrites orient their growth into the vacated territory (Eysel et al. 1985, Perry & Linden 1982). Together, these data demonstrate that homotypic repulsion contributes to setting the receptive field size and overlap of retinal neurons.

Additional factors must also influence retinal dendrite size, because in the RGC ablation experiments, neighboring RGCs were incapable of completely filling the vacated area with their dendrites. Moreover, in mice in which most RGCs have been genetically eliminated, dendrite size and shape in the remaining RGCs are relatively normal (Lin et al. 2004). Lack of invasion by neighboring dendrites may reflect the elimination of positive factors for dendritic growth or the intrinsic limits of RGC outgrowth. Either way, it is clear that homotypic repulsion cooperates with currently unidentified mechanisms to determine retinal dendrite size. Homotypic repulsion

appears best suited for making fine size adjustments, perhaps to fill small holes in coverage or to adjust dendrite overlap so that the population can achieve its appropriate spatial sampling rate.

Retinal mosaics. For those retinal neurons that do not tile, the task of building a complete and uniform map of the visual scene requires additional patterning mechanisms. One of these mechanisms is the retinal mosaic. Every type of retinal neuron forms a mosaic pattern, whereby individual cells are more evenly spaced relative to each other than would be expected by chance (Wässle & Riemann 1978). The even distribution of cell bodies across the retinal surface ensures that each map location is adequately sampled and processed. Because patterning of mosaics and dendrite size share a similar purpose, it is not surprising that homotypic dendrite repulsion plays a key role in both.

The defining feature of a retinal mosaic is an exclusion zone, a region around each cell in which another neuron of the same type is rarely found. By locally repelling each other, developing neurons form these exclusion zones, which in turn impart regular spacing on the entire neuronal array (Galli-Resta et al. 1997, 1999). Each retinal cell type makes an independent mosaic; a cell of type A is distributed nonrandomly with respect to other A cells but randomly with respect to cells of types B, C, and D. Thus, the forces that create exclusion zones act in a homotypic manner (Rockhill et al. 2000). Studies of two retinal interneurons, the horizontal cell and the starburst amacrine cell, have provided key insights into the cellular mechanisms responsible for exclusion zones. In both cell types, neurons remain randomly spaced until their nascent dendritic arbors contact those of their homotypic neighbors (Galli-Resta et al. 2002, Huckfeldt et al. 2009, Poché et al. 2008). Therefore, neurons may use their dendrites to detect and avoid their neighbors. Indeed, time-lapse imaging of mouse retinal explants has shown that dendrites of horizontal cells exhibit homotypic repulsion and tiling during the early postnatal period when they are forming mosaics; laser ablation of one cell induces dendrite growth and soma repositioning of neighbors (Huckfeldt et al. 2009). These results suggest that the function of tiling and homotypic dendrite repulsion in this system is to carve out a space that defines the mosaic exclusion zone.

Molecular mechanisms of homotypic repulsion. The central molecular players in homotypic repulsion are believed to be cell surface molecules that accomplish cell type–specific dendro-dendritic recognition. In the *Drosophila* mechanoreceptor system, in which only two cell types tile, this is a straightforward molecular problem. But in the vertebrate retina, where dozens of cell types perform homotypic dendritic tiling in the inner plexiform layer (IPL) while coexisting with dendrites of heterotypic neighbors, the molecular recognition problem is complex.

Recently, a few homotypic recognition cues involved in tiling and mosaic formation have been identified. First, in mouse retina, two cell surface molecules called MEGF10 and MEGF11 act as homotypic recognition cues for starburst amacrine and horizontal cell mosaic formation. In the absence of the genes encoding these molecules, the loss of homotypic short-range repulsion results in a random distribution of starburst and horizontal cell bodies (Kay et al. 2012). Given the close link between mosaics and dendrite repulsion, one might expect these molecules to mediate the interactions among horizontal cell dendrites described by Huckfeldt et al. (2009). However, this has yet to be demonstrated. Mosaic arrangements also require a molecular mechanism to balance dendritic repulsion and attraction. In the absence of mammalian Dscams (encoded by two simple genes, unlike in flies), this balance is lost, leading to excess dendritic attraction that degrades mosaics after they have formed (Fuerst et al. 2008).

The second insight comes from studies of axon tiling in the *Drosophila* visual system. There, the L1 neuron tiles its axons using an alternative splice form of Dscam2 as the homotypic recognition cue. Unlike the stochastic alternative splicing of Dscam1, alternative splicing of Dscam2 is a

reliable marker of specific cell types, including L1 (Lah et al. 2014). This raises an intriguing possibility: RNAs that are widely expressed may undergo cell type–specific splicing to create the molecular diversity required for homotypic recognition.

Some neurons employ a second mechanism that spatially restricts dendrites to facilitate homotypic interactions. As discussed in the section on self-avoidance, one strategy is to force dendrites to occupy a 2D plane, which *Drosophila* da neurons accomplish using an integrin-dependent signaling pathway comprising *tricornered*, *furry*, and the TORC2 complex. By promoting dendrite attachment to the basement membrane, this pathway is required for proper dendrite repulsion, in the context of both tiling and self-avoidance. When the pathway is compromised, dendrites dodge contact in the third dimension, which in turn prevents homotypic repulsion/tiling mechanisms from limiting dendrite size (Han et al. 2012, Kim et al. 2012). Similar mechanisms may be involved in tiling of retinal neurons whose dendrites are confined to a single layer of the IPL (**Figure 4**). However, cells need not be confined to a 2D plane to exhibit tiling. Brain astrocytes tile despite having 3D arbor territories. Perhaps this is because they possess numerous fine branches that act as barriers to intrusions from homotypic neighbors (Bushong et al. 2002, Ogata & Kosaka 2002). Similarly, horizontal cell dendrites in neonatal retina densely innervate a 3D column of tissue that blocks neighboring dendrites from entering (Huckfeldt et al. 2009). Thus, molecular mechanisms that influence tiling by limiting dendrites to a single plane may not be relevant to all instances of homotypic repulsion.

Tiling without homotypic repulsion. The establishment of dendrite territories can also arise through signals secreted by heterotypic neighbors or nonneuronal cells. In the *Drosophila* embryonic nerve cord, motor neurons that innervate specific muscles tile their dendrites to produce maps of the muscle field. Dendrites target particular mediolateral domains based on midline-derived patterning cues such as Slit and Netrin that define the axes of the embryo (Brierley et al. 2009, Kim et al. 2009, Landgraf et al. 2003, Mauss et al. 2009). In this case, a motor map is generated through cues extrinsic to the circuit itself. This hard-wiring mechanism for generating receptive field size is less flexible than a homotypic repulsion-based mechanism, but it may gain robustness by taking advantage of patterning signals that are being used for other developmental purposes. Whether similar mechanisms operate in other systems has yet to be determined. The retina uses positionally varying cues to pattern cell types along the dorsoventral and anteroposterior axes (Schulte & Bumsted-O'Brien 2008); some of these cues could be repurposed to establish regional differences in dendrite size at a later stage of development, but whether this occurs is not known.

Afferent-Derived Cues for Dendrite Size

Presynaptic inputs provide a critical source of signals that regulate dendrite size. In some cases, inputs act locally to promote growth. Severing of afferents to the nucleus laminaris (NL) of the chick auditory brainstem leads to NL neurons with smaller dendrites. Because NL neurons have a bipolar morphology, with separate dendritic tufts receiving input from either the ipsilateral or contralateral ear, one can sever only a single input and observe size changes specifically in the denervated dendrites (Deitch & Rubel 1984). In other cases, afferents appear to restrain dendritic growth. Unilateral removal of the auditory organ in crickets causes postsynaptic partners to sprout dendrites across the midline to receive input from the intact contralateral auditory organ (Hoy et al. 1985). As these examples illustrate, presynaptic partners can provide different kinds of signals that either restrict or promote elaboration of the dendritic arbor. By matching the receptive field of a postsynaptic cell, or the collective receptive fields of a group of cells, to the density of presynaptic elements, these signals can set the extent of convergence or divergence of information in a circuit.

These mechanisms may also have a role in ensuring that dendritic coverage remains constant as an animal grows, a phenomenon known as dendrite scaling. Here we consider the nature of the signals that pass between axons and dendrites to set dendrite size.

Neurotransmission. Why do arbors change size when afferents are ablated? In some systems, loss of neural activity is responsible for the changes. In chick auditory brainstem, removal of the cochlea or spike suppression by tetrodotoxin (TTX) causes site-specific dendrite shrinkage in the NL similar to that observed after afferent ablation (Wang & Rubel 2012). As the NL is two synapses upstream from the cochlea, these manipulations do not directly remove afferents but instead reduce their activity. Conversely, increases in activity promote NL dendrite growth. If one of the NL inputs is stimulated with an electrode, the dendritic tuft innervated by the stimulated pathway grows while the other shrinks (Sorensen & Rubel 2011). Strikingly, most of these effects are detectable within hours and, upon TTX withdrawal, are reversible on a similar time scale, suggesting that dendrite size can be exquisitely sensitive to presynaptic activity during development (Wang & Rubel 2012).

Manipulating activity using electrodes or TTX can affect both excitatory and inhibitory neurotransmission. Which is more important for determining dendrite size? In the optic tectum of *Xenopus*, where retinal afferents are glutamatergic, manipulations of glutamate signaling primarily affect the number and local density of dendritic branches, which are features of dendrite shape (see section above on Dendritic Pruning and Remodeling). Effects on dendritic arbor area are minimal (reviewed by Cline & Haas 2008). By contrast, when inhibitory drive onto tectal cells is reduced by single-cell expression of a dominant-negative GABA-A receptor subunit, arbor area increases markedly (Shen et al. 2009). These findings, which are consistent with results from chick and mammalian brainstem (Sanes & Chokshi 1992, Sorensen & Rubel 2006), suggest that in these systems, excitation and inhibition act on distinct processes: Excitation influences dendrite shape, whereas inhibition influences dendritic field size. The mechanism by which inhibition restricts size is not known, but one possibility is that the receptive field surround, in which inhibition dominates, is important for sculpting the receptive field center. If the surround is weak, dendrites may be permitted to grow and thereby expand the zone where excitatory inputs are received, i.e., the receptive field center (**Figure 6*a***).

Not every dendritic arbor responds to neurotransmission in this way. A *Drosophila* larval motor neuron shows the opposite response; its arbor grows larger upon loss of excitatory cholinergic input and shrinks when excitation is increased (**Figure 6*b***). This dendritic behavior is termed structural homeostasis: The cell uses dendrite size changes to eliminate or capture new synaptic inputs to compensate for those that have been experimentally eliminated or added (Tripodi et al. 2008). Other neurons are less sensitive to neural activity manipulations. In mouse retina, when bipolar cell inputs to RGCs are genetically silenced, RGC arbor size and branching are unaffected (Kerschensteiner et al. 2009). Thus, the role of activity on dendrite size varies across different circuits and systems.

Molecular cues from afferents. To communicate with postsynaptic dendrites, afferents use a variety of protein signals in addition to neurotransmitters. The neurotrophin family of molecules regulates dendrite elaboration in a variety of cell types, influencing both shape and size (Liu et al. 2009, Lom & Cohen-Cory 1999, McAllister et al. 1995). Although in some cases neurotrophins may originate from sources other than afferents, the mouse cerebellum provides a clear example of size regulation by presynaptic neurotrophin. There, parallel fiber afferents onto Purkinje cells secrete Neurotrophin-3, which signals through TrkC receptors on Purkinje cells to promote expansion of Purkinje arbor territories. Among neighboring Purkinje cells, those with less TrkC

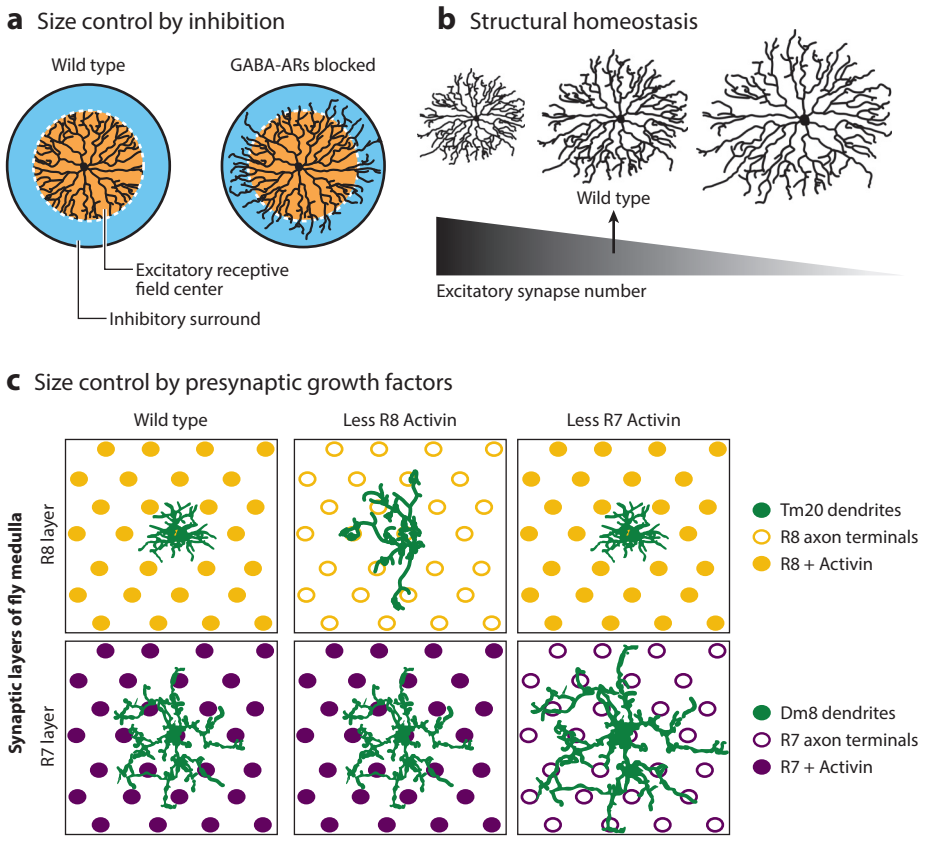


Figure 6

Strategies for afferent control of dendrite size. (*a*) Inhibitory synaptic transmission restrains dendrite size in some neurons. A neuron's dendritic arbor is depicted together with its excitatory receptive field center (+) and inhibitory surround (−). Normally the dendritic territory corresponds to the receptive field center (*left*). Loss of inhibition [for example, through genetic blockade of GABA-A receptors (GABA-ARs) in *Xenopus* tectal neurons; Shen et al. 2009] causes dendrite territory to expand. One possible mechanism is that relief of inhibition in the surround permits dendrites to invade that area (*right*). (*b*) Neurons capable of structural homeostasis change their dendrite size in response to strengthening or weakening of excitatory input. This was illustrated in embryonic *Drosophila* motor neurons by experimentally manipulating the number of cholinergic synapses (Tripodi et al. 2008). When input is weak, neurons grow larger arbors, presumably in an effort to contact more presynaptic partners. The opposite occurs when input is strong. (*c*) Afferents provide growth factors for dendrite size control. In the *Drosophila* visual brain, R7 and R8 photoreceptor axons form regularly spaced arrays in separate layers of the medulla. In wild-type flies (*left*), Tm20 neurons ramify dendrites in the R8 layer, contacting only a single photoreceptor, whereas Dm8 neurons contact several presynaptic partners in the R7 layer. When R8 neurons are made to secrete less Activin (*center*), dendrites of Tm20 (but not Dm8) become larger and receive more photoreceptor synapses. Dm8 (but not Tm20) does the same when R7 Activin secretion is inhibited (*right*).

activity have smaller arbors, suggesting that cells compete for presynaptic neurotrophin (Joo et al. 2014).

Signals from afferents presumably serve to coordinate the growth of axons and dendrites to establish or maintain receptive fields. Two *Drosophila* sensory systems have served as key models to understand the molecules involved and the cellular mechanisms by which they coordinate growth.

First, mechanosensory da neurons initially establish receptive fields while the larva is still growing; to maintain those receptive fields, they must expand their dendrites to match the growth of the skin surface. This expansion is accomplished by a mechanism called dendrite scaling. Because dendritic arbor sizes are usually established before brains have reached their adult volume, dendrite scaling is likely a universally important mechanism for circuit assembly. In da neurons, dendritic scaling is triggered via signals transmitted from the skin to the neuron (Parrish et al. 2009). The details of the signaling system have yet to be worked out, but one component is a developmental change in dendrite-substrate adhesion (Jiang et al. 2014). Thus, one way for dendrites and afferents to coordinate their growth is by clinging tightly to each other.

The second example of afferent size control comes from the *Drosophila* visual system, where R7 and R8 photoreceptors project to the brain visual structure known as the medulla. Postsynaptic partners include a medulla projection neuron called Tm20, which makes one-to-one connections with R8, and an interneuron called Dm8, which receives input from ~16 R7 cells (**Figure 6*c***) (Ting et al. 2014). Activin, a TGFβ superfamily ligand secreted by R7 and R8 afferents, regulates each cell's receptive field size. When Activin or its receptor is deleted, the dendritic arbors of Dm8 and Tm20 expand and synapse with more photoreceptors. The signal is transmitted in a circuit-specific manner because R7-specific Activin knockdown or cell ablation affects only Dm8, whereas equivalent experiments targeting R8 affect only Tm20 (**Figure 6*c***). Moreover, increasing the activity of this receptor-ligand system at the R7-Dm8 synapse decreases Dm8 arbor size, suggesting that this system could be tuned to generate a variety of coverage factors (Ting et al. 2014). Given that TGFβ superfamily molecules are implicated in dendrite growth in the mammalian nervous system (Osório et al. 2013), it will be interesting to see if their mechanism of action and the outcome for receptive field size is similar to what has been described in *Drosophila*.

DENDRITES WANT TO BE IN THE RIGHT PLACE

Why Does Location Matter?

Dendrites of the appropriate shape and size will do a neuron no good if they are not in position to receive presynaptic inputs. Thus, many types of neurons grow their dendrites in a targeted fashion to meet the axon terminals of their presynaptic partners. In the visual system of vertebrates and invertebrates, neurons target their dendrites to particular layers within stratified neuropil regions in the retina and brain (**Figure 3*b***) (reviewed in Baier 2013, Sanes & Zipursky 2010). Similarly, in olfactory systems, second-order neurons (known as projection neurons in insects and mitral/tufted cells in vertebrates) send dendrites to single glomeruli, neuropil structures located in the antennal lobe (insect) or olfactory bulb (vertebrate). This targeting choice is critical, because each glomerulus is innervated by axons of olfactory sensory neurons that carry one type of chemosensory information (reviewed by Imai et al. 2010). Targeted dendrite growth therefore helps ensure synapse specificity by limiting possible presynaptic partners to those that project axons to the same location. When neighboring neurons receive different presynaptic inputs, they transmit different types of information to downstream neurons. In this way, dendrite and axon targeting are part of a developmental strategy that creates parallel channels of information flow through a circuit.

Dendrite Targeting Is Determined Genetically

Dendrite targeting is closely intertwined with cell-type identity. In the *Drosophila* olfactory system, the timing of a projection neuron's birth specifies its cell fate, including the specific glomeruli it

will innervate. This occurs through expression of POU domain transcription factors (Jefferis et al. 2001, Komiyama et al. 2003). A similar principle operates in the vertebrate retina, where subtypes of RGCs and amacrine cells—identified by their physiological light responses, neurotransmitter phenotypes, or gene expression profiles—have stereotyped dendritic projections to IPL sublayers (**Figure 4*a***) (Famiglietti & Kolb 1976, Siegert et al. 2009, Wässle 2004). RGC and amacrine subtype fate choices, including laminar-targeting decisions, are correlated with and likely specified by birthdate (Cherry et al. 2009, De la Huerta et al. 2012, Osterhout et al. 2014, Voinescu et al. 2009). A few transcription factors controlling laminar choice have been identified, but none of these alter IPL stratification without changing other aspects of cell fate, such as neurotransmitter type (Cherry et al. 2011, Kay et al. 2011). Because choice of presynaptic partner is such a crucial determinant of neuronal function, it is not surprising that mechanisms for specifying it are hard-wired as part of a neuron's fate decision.

Although hard-wired connectivity of some cell types can be modified or refined with experience, neural activity has little effect on targeted dendrite growth in the olfactory system. *Drosophila* projection neuron dendrites (Jefferis et al. 2004, Zhu & Luo 2004) and vertebrate mitral/tufted cells (Malun & Brunjes 1996) initially innervate multiple glomeruli before pruning to target a single glomerulus. This pruning falls into the genetically determined category, as manipulation of afferent activity does not alter it (Devaud et al. 2003, Lin et al. 2000). Neural activity can affect some aspects of RGC dendrite refinement (Bodnarenko et al. 1995, Okawa et al. 2014, Tian & Copenhagen 2003), but for the most part, IPL sublaminar targeting is not altered by manipulating neural activity (Kerschensteiner et al. 2009; for a review, see Kay & Sanes 2013). Therefore, to understand dendrite targeting in these and other cell types throughout the brain, we need to understand genetically determined mechanisms linking cell fate and arbor morphology. These mechanisms include receptors for guidance cues present in the environment, adhesion molecules that join dendrites with presynaptic partners, and repulsive cues that exclude neighboring dendrites from encroaching on the target zone.

Cues That Guide Dendrites to Their Target Zone

To target an appropriate location, some growing dendrites use positional cues for navigation to the right general area. The best-known example occurs in cortical pyramidal neurons, which use Sema3A as an attractant to guide their apical dendrites in the right direction (Polleux et al. 2000) (for a review see Cheng & Poo 2012). Directional guidance is also critical for dendrite placement in visual and olfactory systems. In vertebrate retina, the IPL first emerges when dendrites of the earliest-born amacrine cells join to form a neuropil that divides the neuronal population into a presumptive inner nuclear layer (INL) and ganglion cell layer (GCL) (Godinho et al. 2005). At this stage of development, RGCs and amacrine cells are multipolar and use transient filopodia to sample their environment for cues that define the location of the nascent IPL. Dendrites oriented toward the IPL are preferentially stabilized, whereas others are eliminated, leading to an arbor biased toward the IPL (Choi et al. 2010, Godinho et al. 2005, Hinds & Hinds 1978). These findings suggest that cues promoting dendrite stabilization are present in the IPL. The identity of the cue(s) is unknown, but one receptor may be the atypical cadherin FAT3, which is expressed by amacrine cells and is required for polarization of their dendrites toward the IPL (Deans et al. 2011). Loss of FAT3 in mice causes errors consistent with a failure of newborn amacrine cells to recognize the location of the IPL. Complementary repulsive signals, including Sema5A and Sema5B, are expressed in the INL and signal through PlexinA1 and PlexinA3 receptors on amacrine and RGC dendrites. These repulsive cues also contribute to the IPL-oriented growth of dendrites, likely by suppressing growth and/or promoting removal of exuberant branches. Loss of either the ligands

or the receptors causes formation of ectopic IPLs in the middle of the INL that are similar to those seen in *Fat3* mutants (Matsuoka et al. 2011a).

In the *Drosophila* antennal lobe, the site of the olfactory glomeruli, a pair of repulsive guidance cues, Wnt5 and Sema2A/2B, are expressed in opposite gradients that define the lobe's dorsolateral-ventromedial axis. These gradients provide positional information to projection neuron dendrites, thereby allowing each cell to restrict its dendrites to the region of the antennal lobe where its eventual glomerular target is located (Komiyama et al. 2007, Sweeney et al. 2011, Wu et al. 2014). Together, these examples suggest that positional cues—within the retina, the antennal lobe, and elsewhere—orient dendrites to guide them to the right place.

Cues That Determine Fine-Grained Specificity

Once they have reached the right general area, dendrites achieve highly specific targeting by eliminating branches that are mislocalized and elaborating those that have found the correct target. How this targeting is accomplished varies among experimental systems, but some general principles have emerged.

Selective cell-cell adhesion. In neonatal retina, the IPL first forms as a narrow gap between the INL and GCL. With subsequent waves of neurogenesis, arbor growth, and synapse formation, the neuropil expands and adds new sublayers containing targeted projections of amacrine, bipolar, and RGC neurites (Drenhaus et al. 2003, Godinho et al. 2005, Kay et al. 2004, Mumm et al. 2006). Therefore, the process of laminar targeting is tightly coupled to the formation and expansion of the IPL. Although the cellular mechanisms underlying these processes remain unknown, one appealing idea is that IPL sublayer formation is driven by self-assembly (Baier 2013, Sanes & Zipursky 2010): As young neurons project their arbors into the IPL, cells fated to costratify adhere to each other and elaborate together. This model is attractive in several ways. First, dendrites of cells that project to the same sublayer would not only guide each other to that layer, they would create the layer through their adhesive interactions. Second, dendrites would be immediately matched with their presynaptic partners, because they would express the same selective adhesion cues.

Several results are consistent with this model, though none yet proves it. In chick retina, RGCs and amacrine cells that project to specific IPL sublayers express immunoglobulin (Ig)-superfamily cell adhesion molecules of the Sidekick, Dscam, and Contactin families. Each of these molecules mediates homophilic interactions, but does not bind to other molecules of these three families. Misexpression of Sidekick-1, Sidekick-2, Dscam, DscamL, or Contactin-2 is sufficient to drive neurons to project their dendrites to the laminae characteristic of the misexpressed molecule. Moreover, knockdown of these genes degrades sublaminar-targeting accuracy (Yamagata & Sanes 2008, 2012; Yamagata et al. 2002). These studies are consistent with the idea that selective adhesion underlies self-assembly of IPL sublayers and thereby controls precise dendrite targeting to those layers.

Selective adhesion also plays a key role in dendrite targeting of projection neurons in the *Drosophila* antennal lobe. Projection neuron dendrites organize themselves into a rough glomerular map prior to arrival of afferent axons (Jefferis et al. 2004). A subset of projection neurons expresses the LRR protein Capricious (Caps), which mediates dendro-dendritic interactions for selective innervation of glomeruli by Caps-positive dendrites. Deletion of Caps results in mistargeting of mutant dendrites to Caps-negative glomeruli. Similarly, misexpressing Caps causes dendrites to target Caps-positive glomeruli (Hong et al. 2009). These experiments suggest that selective adhesion among dendrites can sort them into groups that share a glomerular target, a mechanism that is, in principle, similar to the self-assembly of IPL sublaminae in the vertebrate retina.

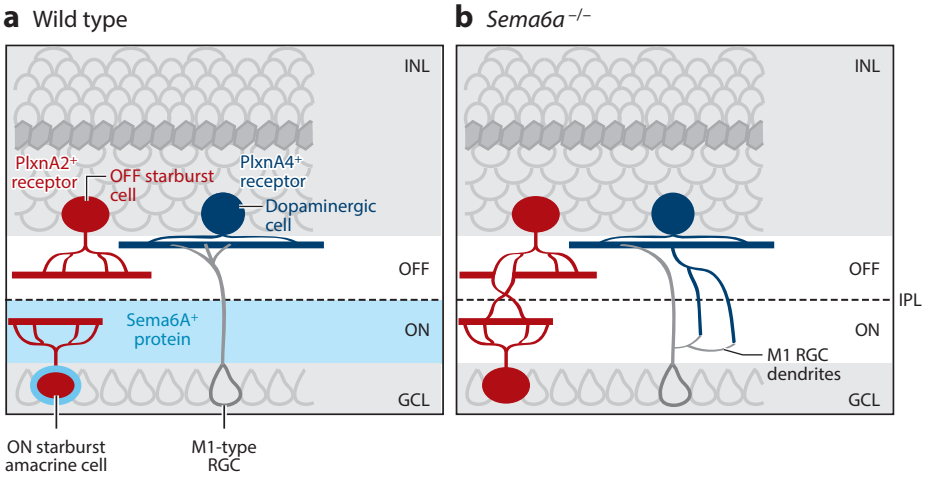


Figure 7

Retinal dendrite targeting controlled by Sema6A repulsion. (*a*) The inner plexiform layer (IPL) is divided into ON and OFF regions, corresponding to the projection patterns of neurons that respond best to light increments or decrements, respectively. Sema6A protein is broadly expressed on the arbors of neurons that project to the ON IPL, including ON starburst amacrine cells. The Sema6A receptors PlxnA2 and PlxnA4 are expressed by starbursts and by dopaminergic amacrine cells, respectively, as indicated at left. M1-type retinal ganglion cells (RGCs) are synaptic partners of dopaminergic amacrines and costratify with them in the OFF IPL, but they do not express any of these molecules. (*b*) In Sema6A mutants, OFF starburst dendrites inappropriately cross over to the ON starburst sublayer, whereas dopaminergic dendrites misproject throughout the ON IPL. M1 RGC dendrites follow the dopaminergic arbors to their incorrect location, unmasking an attractive cue between these synaptic partners. Abbreviations: GCL, ganglion cell layer; INL, inner nuclear layer.

Repulsive cues. Dendrite targeting results from a balance of attractive and repulsive cues. In vertebrate retina, one repulsive cue is the transmembrane semaphorin Sema6A. This molecule is expressed by a broad subset of RGCs and amacrine cells that project to the inner half of the IPL, the so-called ON portion, which contains arbors of neurons that respond to light increments (**Figure 7**). Two Sema6A receptors, PlexinA2 and PlexinA4, are expressed in distinct subsets of amacrine cells that project exclusively to the OFF portion of the IPL, where neurons respond to light decrements (Matsuoka et al. 2011b, Sun et al. 2013). In mutant mice lacking ligand or receptor, PlexinA2$^+$ or PlexinA4$^+$ amacrine cell dendrites project to abnormal locations in ON IPL. For example, PlexinA4$^+$ dopaminergic amacrines, normally confined to a single OFF sublamina, project diffusely through much of the ON IPL in these mutants (Matsuoka et al. 2011b). Meanwhile, PlexinA2$^+$ OFF starburst amacrines make a different kind of error, projecting instead to the sublayer normally reserved for ON starbursts (Sun et al. 2013). In neither of these cases is the normal OFF sublaminar projection absent or severely perturbed; rather, neurons send dendrites to two target zones instead of one (**Figure 7**). These results suggest that Sema6A, and possibly other repulsive cues yet to be described, ensure precise dendrite targeting by preventing neurons from encroaching on neighboring territories.

Attractive and repellent cues likely work together. For example, in flies engineered to express a single isoform of Dscam1 in projection neurons, which introduces inappropriate dendro-dendritic repulsion, glomerular targeting is perturbed (Hattori et al. 2007, Zhu et al. 2006). This inappropriate repulsion presumably disrupts the selective adhesion of dendrites sharing common targets,

thereby preventing the sorting mechanisms that establish the rough glomerular map. By contrast, loss of Dscam1 function does not perturb dendrite target selection, although self-avoidance defects do prevent dendrites from completely filling glomeruli. These findings suggest that Dscam1 itself is not critical for targeting but interfering with attraction can change a dendrite's glomerular choice.

Signals from presynaptic partners. As the ultimate purpose of dendrite targeting is to match specific pre- and postsynaptic partners, one might expect afferents to express cues that control dendrite-targeting specificity. In the fly olfactory system, Caps mediates selective dendrite adhesion but is too broadly expressed to explain synaptic partner matching. Instead, two homophilic adhesion molecules known as Teneurins act as attractive cues. They are supplied by presynaptic neurons to recruit postsynaptic partners (and vice versa). The two Teneurins, Ten-a and Ten-m, have complementary expression patterns in the antennal lobe. Projection neurons that express high levels of each Teneurin selectively synapse with olfactory receptor neuron afferents that have high levels of the same Teneurin. Upon loss of *ten-a*, projection neurons that would normally express it reroute their dendrites to glomeruli where presynaptic elements express low Ten-a levels. Similarly, misexpression of either Teneurin causes dendrite targeting to glomeruli where afferents express high levels of the relevant teneurin (Hong et al. 2012). These results suggest that Teneurins act as presynaptic partner-derived cues that refine the rough glomerular map produced by Semaphorin/Wnt guidance cues and by dendro-dendritic selective adhesion. Teneurins also have critical roles in axon targeting and synapse formation, suggesting that they link the interrelated processes of neurite guidance and synapse specificity (Mosca & Luo 2014).

Additional matching cues clearly exist. In the fly, wiring the 50 olfactory receptor neuron–projection neuron classes into discrete glomeruli requires multiple synaptic partnering mechanisms. To date, the only recognition molecules shown to mediate pre- and postsynaptic partner matching other than the Teneurins are Toll-family receptors (Ward et al. 2015). In hippocampal neurons, contact with a glutamatergic axon (the correct presynaptic partner) but not a GABAergic axon (the incorrect partner) causes selective stabilization of transient dendritic filopodia (Lohmann & Bonhoeffer 2008). Likewise, in retina, when dopaminergic amacrine cell processes are directed to inappropriate sublaminae (by plexin/semaphorin manipulation), they recruit the dendrites of postsynaptic partners known as M1-type RGCs to follow them there, presumably by an adhesive transsynaptic mechanism (**Figure 7**) (Matsuoka et al. 2011b). At this point, the molecular basis for such signals is unknown.

DENDRITES WANT TO INTEGRATE SYNAPTIC SIGNALS

Why Does Compartmentalization Matter?

So far, we have focused on developmental mechanisms that specify how dendrites innervate their territories. But dendrites are not simply tubes; they actively transform and integrate synaptic signals from diverse inputs into meaningful outputs. To perform these computations, many neurons develop compartmentalized dendritic arbors, with branches that have distinct electrical properties and synaptic inputs. Segregating inputs to different parts of the arbor helps with the task of integrating those inputs. And domain-specific expression of ion channels allows a neuron to differentially filter its disparate inputs, adjusting the likelihood that each will make it fire. In this way, dendritic domain-specific differences in connectivity and membrane excitability greatly expand a neuron's computational power (London & Häusser 2005, Spruston 2008).

An excellent example of how compartmental dendrite organization influences neuronal function comes from the CA1 pyramidal neuron in the hippocampus (**Figure 8*a***). Like most pyramidal

cells, these neurons have apical and basal dendritic domains. Apical dendrites are further divided into distal and proximal domains that receive two streams of excitatory inputs (Spruston 2008). These domains correspond to the layered anatomy of the hippocampus: The apical tufts at the distal end receive excitatory inputs from the entorhinal cortex (EC) within the region called the stratum lacunosum moleculare (SLM), whereas the proximal regions receive excitatory inputs from hippocampal CA3 axons through the Schaffer collaterals in the stratum radiatum (**Figure 8*a*,*b***). These distinct inputs are accompanied by differences in the number and type of excitatory and inhibitory synapses typical of each dendritic domain (Megías et al. 2001, Nicholson et al. 2006). The proximal and distal dendrite domains express distinct levels of certain neurotransmitter receptors and ion channels, each of which can modulate EC or CA3 inputs in a compartment-specific manner (Hasselmo & Schnell 1994, Nicholson et al. 2006). For example, the cation channel HCN1 is highly concentrated at distal dendritic tufts (**Figure 8*e***), where it contributes to the resting membrane potential and limits synaptic responses from EC but not CA3 inputs. Loss of HCN1 inappropriately strengthens EC inputs and impacts memory formation (Lörincz et al. 2002, Nolan et al. 2004).

Another prominent subcellular compartment is the dendritic spine. These specialized postsynaptic structures are the major sites of excitatory glutamatergic synapses in CA1 neurons and many other cell types. Compared with the dendritic shafts from which they sprout, spines and their synapses possess distinct morphological, biochemical, and electrical properties (Yuste 2013, Yuste & Bonhoeffer 2004). Inhibitory synapses only rarely form on spines, in part as a result of differences in the localization and cell-biological functions of transsynaptic organizing molecules responsible for inhibitory versus excitatory synapse formation (Takahashi & Craig 2013). Spine shape facilitates the compartmentalization of calcium and other biochemical signals, so that signaling events at individual spines will not unduly influence neighboring synapses. Thus, proper function of CA1 pyramidal cells depends on the molecular specialization of dendritic compartments, both on the scale of spines and on the larger scale of the entire apical arbor. The same is likely true for many other neurons throughout the nervous system.

How are dendritic compartments established during development? Because hippocampal layers correspond to pyramidal cell dendritic domains, they represent a useful model to study this question. Here we describe mechanisms that compartmentalize the apical dendrites of hippocampal pyramidal cells.

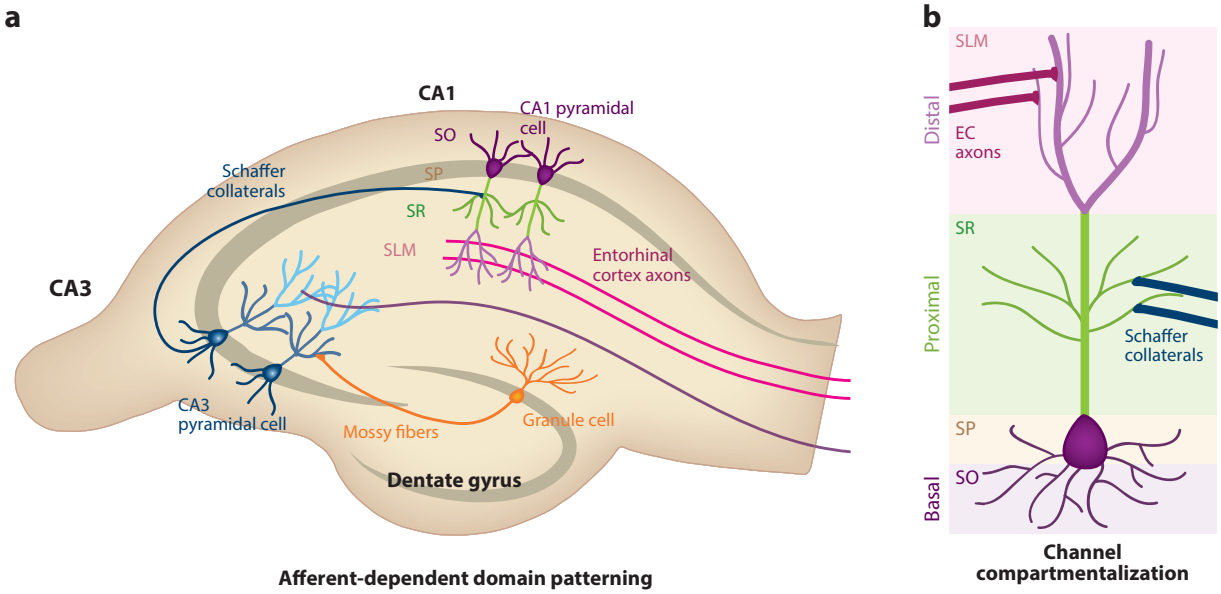
Synapse Recruitment to Specific Dendritic Domains

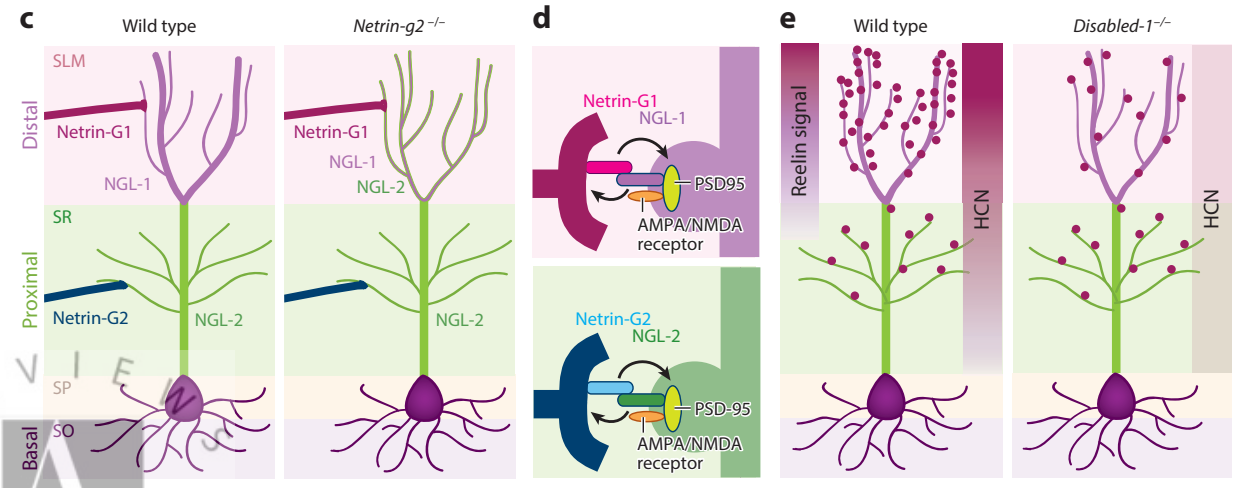
Many neurons receive synaptic input from multiple afferent cell types at different locations in their dendritic arbor. A key mechanism mediating this type of dendritic compartmentalization is signaling from the afferent axons themselves.

Afferents pattern dendritic domains. In CA1 and CA3 pyramidal cells, as well as dentate gyrus (DG) granule cells, distal and proximal domains of apical dendrites receive synapses from distinct afferents. Such organization requires cell recognition and adhesion complexes to establish target domains and to coordinate laminar targeting of afferents with synapse formation. In DG granule cells and CA1 neurons, recognition molecules of the NGL/Netrin-G family regulate the innervation of nonoverlapping dendritic domains. Netrin-G1 and -G2 are glycophosphatidylinositol (GPI)-linked cell surface molecules that act as ligands for the LRR transmembrane proteins NGL-1 and NGL-2, respectively (Kim et al. 2006). These ligands and receptors are distributed in complementary patterns: In CA1, Netrin-G1 is expressed by EC axons, whereas its receptor, NGL-1, is located in corresponding distal dendrites. Likewise, Netrin-G2 proteins are present

in the Schaffer collaterals (CA3 axons), whereas NGL-2 receptors localize in proximal dendritic compartments (**Figure 8*c***). Although this expression pattern might suggest a role for these ligand-receptor pairs in target recognition, analysis of mouse mutants has revealed that they are not required for targeting axonal terminals. Rather, axonal afferents bearing Netrin-G1 or Netrin-G2 transneuronally mobilize their respective receptors to form nonoverlapping NGL-1 and NGL-2 compartments in distal and proximal dendrites, respectively (**Figure 8*c***). In the absence of Netrin-G1 or -G2, afferents target the proper compartment, but the cognate NGL protein diffuses broadly across the dendritic arbor (Nishimura-Akiyoshi et al. 2007). These results suggest that afferents arrange dendritic NGLs into distinct domains.

What is the purpose of domain-specific localization of NGL proteins? NGL-2 is a synaptic cell adhesion molecule that, upon transsynaptic binding, recruits postsynaptic proteins such as





PSD-95 through its C-terminal PDZ domain (Kim et al. 2006). Therefore, NGLs could regulate compartment-specific formation or function of synapses in CA1 dendrites (**Figure 8*d***). Indeed, *NGL-2* mouse mutants show impaired excitatory synaptic transmission and plasticity in the proximal, but not distal, dendrite domain (DeNardo et al. 2012; Matsukawa et al. 2014). The extracellular LRR and cytosolic PDZ domains are both essential for this synaptogenic function, reflecting the transsynaptic organizing role of NGL-2 (DeNardo et al. 2012). Thus, Schaffer collaterals use Netrin-G2 to position NGL-2 within the proximal dendritic compartment, which then nucleates formation of excitatory synapses. Whether distal dendrites use Netrin-G1 and NGL-1 in a similar strategy for forming excitatory synapses in the distal compartment remains to be determined.

In a study comparing synaptic plasticity in the four mutants, mice lacking *netrin-g1* or *NGL-1* showed similar attenuation of plasticity at EC-CA1 connections, whereas SC-CA1 plasticity was selectively enhanced in mice lacking *netrin-g2* or *NGL-2* (Matsukawa et al. 2014). These opposing phenotypes suggest that Netrin-Gs/NGLs function nonredundantly to not only segregate but also differentially control the synaptic information arising from two inputs. In both compartments, Netrin-G/NGL influenced plasticity by presynaptic mechanisms, suggesting a bidirectional role in modulating pre- and postsynaptic properties. Together, these studies demonstrate that input-derived cues are at least one part of the mechanism by which dendritic compartments become specialized to support certain synapses. Netrin-Gs and related cues could also play broader roles in organizing dendritic subdomains. If they can compartmentalize NGLs, they may well target other proteins, such as ion channels, to the correct compartment.

Molecular Cues That Control Synapse Distribution Along Dendrites

The targeting of afferents to particular dendritic regions can be accomplished by selective adhesion at correct sites or by exclusion of axon terminals from incorrect sites. In the hippocampus, the repulsive cues provided by the Semaphorin family, together with their receptors (Plexins and

Figure 8

Laminar organization of dendritic domains of hippocampal principal neurons. (*a*) The layered anatomy of hippocampus subregions, including CA1, CA3, and the dentate gyrus, is defined by lamina-specific arrangement of principal neurons and their inputs. Distal apical dendrites of CA1 and CA3 pyramidal neurons receive long-range excitatory inputs from the entorhinal cortex. Proximal apical dendrites receive short-range hippocampal inputs. For example, mossy fibers from dentate granule cells terminate proximally onto CA3 pyramidal cells and Schaffer collaterals from CA3 terminate proximally onto CA1. These connectivity patterns, and others not shown here, form the anatomical basis of the sublaminae: the stratum oriens (SO), stratum pyramidale (SP), stratum radiatum (SR), and stratum lacunosum moleculare (SLM). (*b*) Dendritic domains of a CA1 pyramidal cell include basal dendrites and proximal and distal subdomains of apical dendrites. In the SLM, distal dendrites receive excitatory inputs from the enthorhinal cortex (EC) axons. In the SR, Schaffer collaterals from CA3 pyramidal cells terminate onto proximal dendrites. (*c*) Excitatory subdomains of CA1 neurons are defined by distinct Netrin-G–NGL adhesion pairs. Afferent-specific Netrin-G expression organizes nonoverlapping Netrin-G1–NGL-1 and Netrin-G2–NGL-2 domains in distal and proximal compartments, respectively. EC axon terminals bearing Netrin-G1 anchor NGL-1 at distal dendrites. Netrin-G2 expressed on Schaffer collaterals mobilizes NGL-2 on proximal dendrites. In the absence of Netrin-G2 (*right*), afferents properly terminate onto their dendritic targets, but NGL-2 is diffusely distributed in apical dendrites. Similarly, NGL-1 is broadly distributed in the absence of Netrin-G1 (not shown). (*d*) Model for input-specific synapse development mediated by Netrin-G–NGL pairs. In proximal dendrites (*bottom*), Netrin-G2–NGL-2 complexes induce development of excitatory synapses through interactions with PSD-95, a postsynaptic scaffold molecule that localizes α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and *N*-methyl-D-aspartate (NMDA) neurotransmitter receptors. Netrin-G–NGL-2 also influences presynaptic differentiation and plasticity. Netrin-G1–NGL-1 could play a similar transsynaptic organizing role in distal compartments (*top*). (*e*) Reelin signaling regulates ion channel compartmentalization in CA1 distal dendrites, including the 60-fold enrichment of HCN ion channels along distal segments. Reduction of Reelin signaling in CA1 cells, through downregulation of the downstream signaling molecule Disabled-1, disrupts the distal-specific enrichment of HCN: HCN becomes uniformly localized along apical dendrites.

Neuropilins), mediate subcellular synapse specificity by restricting afferent inputs to dendritic laminae. Mossy fiber axons from the DG, expressing PlexinA4, project to the proximal domain of CA3 apical dendrites (**Figure 8*a***). CA3 cells express transmembrane Sema6A throughout their dendritic arbors, which repels mossy fibers through PlexinA4 signaling. This repulsion prevents innervation of the incorrect dendritic region, as mutant mice lacking PlexinA4 have diffuse mossy fiber projections across CA3 apical and basal arbors. If Sema6A is also localized to the proximal domain, why can mossy fibers innervate this region? CA3 neurons express the Sema6A receptor PlexinA2, which traffics selectively to the proximal dendrite domain. There, it attenuates the repulsive activity of Sema6A through *cis* interactions, allowing entry of PlexinA4$^+$ mossy fibers. In the absence of PlexinA2, mossy fibers misproject to the CA3 cell-body layer because of widespread Sema6A inhibition in flanking apical and basal dendritic compartments (Suto et al. 2007). Selective adhesion between mossy fibers and CA3 dendrites, mediated by Cadherin-9, may also help overcome Sema-mediated repulsion to promote synapse formation (Williams et al. 2011), although interactions between these two signaling pathways have yet to be explored.

Semaphorin repellents also regulate the compartment-specific density of excitatory synapses in DG granule cell dendrites. Normally in these cells, the density of dendritic spines increases dramatically with distance from the soma. Secreted Sema3F and its receptors Neuropilin-2 and PlexinA3 regulate synapse distribution by restricting formation of excitatory synapses in proximal dendritic segments. The reason for the specific effect of this signaling pathway on the formation of proximal (but not distal) synapses is unclear, but it may result from localization of Neuropilin-2 at the DG inner molecular layer, the dendritic zone closest to DG cell bodies (Tran et al. 2009).

In both of these instances of repulsive patterning, the key step for subcellular synapse formation is trafficking of a repulsive receptor—PlexinA2 or Neuropilin-2—to a specific dendritic compartment. Uncovering trafficking mechanisms will clearly be critical for understanding the development of subcellular synapse specificity.

Establishing the Membrane Excitability of Dendritic Compartments

Pyramidal cell dendrites support signal processing through electrical properties set by ion channels. How are ion channels selectively distributed to their appropriate dendritic domains? Trafficking of HCN1 to the distal domain of CA1 apical dendrites (**Figure 8*e***) is a useful model for tackling this question. HCN1 has an auxiliary subunit, TRIP8b, that exists in approximately a dozen different isoforms as a result of alternative splicing. These isoforms control distinct aspects of HCN1 trafficking, such as promoting cell-surface expression or suppressing inappropriate trafficking to axons. Disruption of TRIP8b and HCN1 interactions leads to uniform distribution of HCN1 throughout the somatodendritic compartment (Piskorowski et al. 2011). Thus, TRIP8b targets HCN1 to the appropriate dendrite location, although the details of how it accomplishes this remain to be worked out.

Interestingly, the distal enrichment of HCN1 channels is lost in dissociated hippocampal neurons, suggesting that a cell-nonautonomous mechanism contributes to HCN1 targeting. Afferent-mediated NetrinG1–NGL-1 signaling, which organizes excitatory synapses in distal dendrites, was a good candidate. However, HCN1 channels traffic normally to distal dendrites in *NGL-1* mutants, suggesting that Netrin-G signaling cannot explain HCN1 targeting (Kupferman et al. 2014).

Instead, Reelin, a large secreted glycoprotein, provides proximodistal patterning information that defines the HCN1 compartment. Reelin and its obligate downstream cytosolic signal Dab1 are highly expressed in the SLM region, in both the developing and mature hippocampus. Constitutive loss of Reelin or Dab1 function causes severe hippocampal patterning defects, but when Dab1 is conditionally deleted from individual CA1 neurons in postnatal mice, neuronal morphology is

normal. Nevertheless, a dramatic loss of HCN1 occurs in distal dendrites following Dab1 ablation. Other distally targeted ion channel proteins, such as GIRK1, are also affected. However, loss of Reelin signals does not generally impair trafficking of proteins to dendrites (Kupferman et al. 2014). These data suggest a model in which Reelin signals, located near the distal tuft of the apical dendrite, induce molecular changes that define the distal dendrite as a distinct compartment. Once the dendrite is patterned by Reelin signals, compartment-specific protein trafficking mediated by TRIP8b and similar molecules could provide each dendritic region with its characteristic complement of ion channels. HCN1 is the first ion channel for which trafficking to a dendritic subdomain is understood at the molecular level. It will be important to identify additional examples to learn whether HCN1 can provide general lessons for understanding how dendritic compartments form.

CONCLUSION AND FUTURE DIRECTIONS

In this review, we discussed how the features that pattern a neuron's dendritic arbor—its shape, size, targeting, and compartmentalization—also contribute to the neuron's function. Proper development of cell type–specific dendritic forms is essential for building a nervous system, and we are beginning to identify some of the factors responsible for this patterning. Type-specific dendrite patterning has been studied in a relatively small number of cell types, however. With continuing efforts to genetically access neuronal subtypes, we can build on what we have learned to understand how other types of neurons achieve their dendrite patterns and how those forms regulate function. Such investigations are important because one hopes that with additional examples, general principles will emerge; at this point they remain difficult to discern.

Another area of importance is to understand how dendritic morphogenesis goes awry in brain disorders. Structural abnormalities in dendritic branching and spines have been observed in human postmortem studies of neurodevelopmental and neurodegenerative disorders such as Down syndrome, autism spectrum disorders, and Alzheimer's disease (Dierssen & Ramakers 2006, Kulkarni & Firestein 2012). Although in some cases these abnormalities may be consequences of the disorder, they could also be important contributors: As we have seen, malformed dendrites degrade neuronal and circuit-level functions and could give rise to cognitive dysfunction. Indeed, human genetic studies of disorders such as autism and schizophrenia have implicated genes involved in neuronal process development and synapse formation (reviewed in Kulkarni & Firestein 2012, Zoghbi & Bear 2012). Studies of Alzheimer's disease and Rett, Fragile X, and Timothy's syndromes are now linking genes to dendritic anatomy and ultimately may provide a link between dendrite phenotypes and neuronal function (Krey et al. 2013, Šišková et al. 2014, Zoghbi & Bear 2012). Investigations relating cellular abnormalities to circuit alterations could be a key strategy in linking connectivity defects with cognitive dysfunction.

DISCLOSURE STATEMENT

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