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Wiring dendrites in layers and columns

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Abstract

The most striking structure in the nervous system is the complex yet stereotyped morphology of the neuronal dendritic tree. Dendritic morphologies and the connections they make govern information flow and integration in the brain. The fundamental mechanisms that regulate dendritic outgrowth and branching are subjects of extensive study. In this review, we summarize recent advances in the molecular and cellular mechanisms for routing dendrites in layers and columns, prevalent organizational structures in the brain. We highlight how dendritic patterning influences the formation of synaptic circuits.

Keywords

Circuit assembly; dendrite development; layer and column; synaptic circuits

Introduction

Neurons form complex and branched dendritic arbors for receiving synaptic inputs. The diverse dendritic morphologies have been used for classifying neuronal types since Cajal. Type-specific dendritic morphology is directly linked to neuronal function. The location and density of dendritic arbors determine the type and the number of inputs a neuron can sample. The size and shape of dendritic trees govern their passive electrotonic properties while the dendritic distribution of ion channels endows active membrane conductance (London & Hausser, 2005; Li, Gervasi, & Girault, 2015). Together, they dictate the computation a type of neuron performs (Reviewed in Magee, 2000). Dendritic morphological defects have been observed in many neurodevelopmental disorders, such as autism spectrum disorders (ASDs), Fragile X syndrome (FXS) and Down syndrome (DS) (Kulkarni & Firestein, 2012; Penzes,

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Cahill, Jones, VanLeeuwen, & Woolfrey, 2013). The degradation of neural connectivity and computation caused by dendritic developmental defects are thought to underlie the cognitive dysfunction associated with these diseases.

In many brain regions, such as retina and cortex, synaptic circuits are organized in layers and columns to facilitate information processing (Figure 1(A-D)) (Mountcastle, 1997; Sanes & Zipursky, 2010). In such a structure, presynaptic terminals carrying distinct types of information form a two-dimensional array within one layer (topographic map) while postsynaptic neurons elaborate dendrites in specific layers and extend dendritic fields of appropriate sizes to receive correct types and number of synaptic inputs. Besides the advantage of packing synaptic circuits densely, the layer and column organization allows efficient connections between appropriate sets of neurons and is thought to be critical for neuronal computation, especially for sensory processing (Haeusler & Maass, 2007; Kaas, 1997). However, the repetitive structure of synaptic circuits in layers and columns poses interesting challenges for circuit assembly. Previous studies have revealed mechanisms by which axons are guided to specific layers and restricted to their cognate columns (Melnattur & Lee, 2011; Sanes & Zipursky, 2010). Recent studies have begun to reveal how dendrites are routed to specific layers and expand appropriate sizes of fields to form synaptic connections with afferents.

In this review, we discuss recent findings on dendritic wiring in the context of columns and layers in the central nervous system (CNS). First, we summarize current understandings of the cellular processes that drive dendritic morphogenesis, drawing examples from studies using cultured mammalian neurons and the *Drosophila* peripheral dendritic arborization neurons (da neurons). We summarize the cellular and molecular mechanisms that route dendrites and specify synaptic connections in layers and columns. We focus on the *Drosophila* and vertebrate visual systems where great advances have been made in recent years.

Cellular machinery driving dendritic morphogenesis

Newly born neurons extend neurites, which further differentiate into axons and dendrites often in response to environmental polarization factors, such as Insulin-like growth factor-1 (Sosa *et al.*, 2006; reviewed in Cheng & Poo, 2012). Dendrites tend to be predominantly postsynaptic and axonal terminals presynaptic, but the input and output regions are often mixed, as seen in the fly optic lobes (Meinertzhagen & O'Neill, 1991; Takemura *et al.*, 2013). A key feature that distinguishes dendrites from axons is the presence of mixed plus- and minus-ended microtubules (MT), which facilitate dendritic branching and transport of organelles, such as the Golgi apparatus. The dendritic Golgi apparatus, or Golgi outposts, in turn shapes dendritic morphology by facilitating MT nucleation at branch points (Ye *et al.*, 2007). The interplay among cytoskeleton, motor-driven transport and organelles allows the formation of complex dendritic trees. Dendritic morphogenesis is a highly dynamic process, with rapid segment extension/retraction and branching. Transient branches become stabilized by external cues or activity to form synapses (Figure 2).

In vitro studies using neuron cultures or explants demonstrated that neurite outgrowth is mediated by actin-based lamellipodia and filopodia which is stabilized by the invasion of MTs, highlighting the importance of cytoskeletal regulators and the interaction between actin- and MT-cytoskeleton components (Dent & Gertler, 2003; Sainath & Gallo, 2015). A recent study using cultured *Drosophila* neurons suggests that initial neurite extension may be driven by MT sliding by the MT motor kinesin-1 (Lu, Fox, Lakonishok, Davidson, & Gelfand, 2013), largely independent of the actin-cytoskeleton. Whether kinesin-mediated MT–MT sliding provides force for initial dendritic extension in vertebrate neurons remains to be determined. Cdc42 and Rac1, two Rho-family small GTPases, play a critical role in driving dendritic elaboration, presumably via PAK1 or the actin-related protein 2/3 (Arp2/3) complex. Live imaging studies using *Xenopus* tectum and chicken retina further suggest that Rac is especially important for branch stability (Li, Van Aelst, & Cline, 2000; Wong, Faulkner-Jones, Sanes, & Wong, 2000). RhoA, however, appears to limit dendritic length at least in part via ROCK (Rho-associated kinase) which phosphorylates myosin light chain and controls actomyosin contractility (Nakayama, Harms, & Luo, 2000; Winter *et al.*, 2001).

After extension, dendritic branches must be stabilized by MTs, a process requiring MT-associated proteins (MAPs) and motor proteins. MAP1A and MAP2 promote MT polymerization and protect them from the MT-severing protein Katanin (De Camilli *et al.*, 1984; Lee, Jan, & Jan, 2009; Sudo & Baas, 2010). Bidirectional motor protein KIF23 (aka. CHO1 or MKLP1) is thought to establish minus-end MT in dendrites and is essential for the formation and maintenance of dendrites (Yu *et al.*, 2000). The minus-end directed motor protein dynein is required for transporting organelles to dendrites. Loss of function of the dynein motor protein Dhc64 and its associated protein Lissencephaly1 (LIS1) inhibited dendritic extension and branching in the fly mushroom body neuron (Liu, Steward, & Luo, 2000). In *LIS1* mutant mice, neural progenitor cells exhibited neurite extension defects while mature pyramidal neurons showed reductions in elimination and turnover rates of dendritic protrusions, suggesting that LIS1 might involve in dendritic extension in mammals (Sudarov, Gooden, Tseng, Gan, & Ross, 2013; Youn, Pramparo, Hirotsune, & Wynshaw-Boris, 2009).

The dendritic localization of organelles, such as Golgi complexes, secretory ER (endoplasmic reticulum) and ribosome, is critical for membrane construction as well as local production and membrane insertion of receptor proteins, and is especially important for dendritic extension and branching. Dendritic Golgi outposts (GOP) are enriched at dendritic branching points; in addition to regulating cargo trafficking, they serve as sites for acentrosomal MT nucleation at nascent branching points (Ori-McKenney, Jan, & Jan, 2012; Zhou *et al.*, 2014). The reduction of dendritic GOPs caused by disruption of the dynein/dynactin adaptor protein Lava-lamp or dynein mutations led to reduced branch number and dendritic complexity (Ye *et al.*, 2007; Zheng, *et al.*, 2008). Moreover, local translation of mRNA by ribosomes provides an instant and specific mechanism for providing precise subcellular localization of proteins, which allows dendrites to sense spatial and temporal environmental cues to mediate dendrite development, synaptic plasticity and memory formation. In *Drosophila* dorsal dendritic arborizing neuron E (ddaE), the ribosomal protein L10 is localized to the branching points of developing dendrites (Hill *et al.*, 2012), suggesting a role of local translation in dendrite development.

The development of terminal dendrites appears to utilize mechanisms distinct from the major dendrites. Depletion of the exocytosis regulator Rop resulted in reduced terminal dendrite outgrowth followed by primary dendrite degeneration, suggesting differential requirements for exocytosis in the growth and maintenance of dendritic compartments. Rop promotes dendrite growth via exocyst, an octameric protein complex involved in tethering vesicles to the plasma membrane (Peng *et al.*, 2015). Furthermore, the membrane protein Raw regulates the extension and stabilization of terminal dendrites via coupling to multiple signaling pathways. Raw is localized to dendritic branching points and promotes dendritic stabilization and adhesion via Tricornered (Trc) kinase. Raw also independently regulates terminal dendritic elongation by modulating the cytoskeleton, a process that involves the RNA binding protein Argonaute 1 (Lee, Peng, Lin, & Parrish, 2015).

Linking cell identity to type-specific dendritic morphologies

How do neurons adapt type-specific dendritic morphologies? Transcription regulation, which specifies neuronal cell fates, befittingly plays a key role in shaping dendritic morphologies. In the fly visual system, diverse types of medulla neurons are specified via a complex temporal network of transcription factors (TFs) and the combinatorial expression of these TF codes, correlates well with their dendritic morphologies (Li *et al.*, 2013). TFs could potentially affect dendritic morphologies by regulating the expression of the cellular machineries that drive dendritic morphogenesis or the receptors that mediate cellular responses to environmental factors. A direct causal link between the combinatorial TF code and dendritic morphology has been demonstrated for fly leg motor neurons (Enriquez *et al.*, 2015) and most prominently, for the peripheral da neurons (reviewed in Jan & Jan, 2010). Four classes (I–IV) of da neurons, which differ in their sensory modality, extend dendrites of very different morphologies to innervate the epidermis (Jan & Jan, 2010). The TFs Abrupt (Ab) and Knot (Kn) act as selectors of distinct dendritic morphologies in classes I and IV da neurons. Furthermore, a single TF is able to control dendrite morphology of neurons through different expression levels. For instance, Cut is expressed at increasing levels in classes II, IV and III da neurons and overexpression of Cut transforms classes II–IV. Cut levels specify distinct morphologies by providing an increasing abundance of proteins that direct branch morphogenesis and stabilization (Sulkowski, Iyer, Kurosawa, Iyer, & Cox, 2011; Iyer *et al.*, 2013). The vertebrate homolog of Cut, Cux1 and Cux2, selectively promote basal and apical dendritic branching in pyramidal neurons, suggesting a functional conservation of TF in regulating dendritic morphologies (Cubelos, Briz, Esteban-Ortega, & Nieto, 2015). Class I da neurons express higher levels of the cell adhesion molecule (CAM) Ten-m than class IV da neurons do, and the differential expression level appears to be critical for the class-selective directional control of dendritic branch sprouting or extension (Hattori *et al.*, 2013).

Initiating dendritic branches at appropriate locations and in correct orientations

Morphological analyses of fly medulla neurons have revealed that the majority of dendritic branches originate from one or two primary branching nodes in specific layers (Fischbach & Dittrich, 1989; Ting *et al.*, unpublished). For example, Tm2, Tm9 and Tm20 have their

primary branching nodes located in the M3 layer while Tm5a and Tm5b neurons extend most dendrites from the primary branching nodes in the M7 layer. Furthermore, medulla neurons project dendrites in specific planar directions: Tm1, Tm2 and Tm9 neurons extend dendrites anteriorly while Tm20 neurons project dendrites posteriorly (Ting *et al.*, 2014; Ting *et al.*, unpublished). These observations suggest that different types of medulla neurons, likely in response to environmental cues, initiate the extension of primary dendrites in type-specific layers and planar directions. Initiating dendritic extension in specific locations and directions could optimize dendritic routing and/or ensure one-to-one correspondence between Tm neurons and the columns their dendrites innervate. The molecular mechanisms for dendritic extension in type-specific layers and planar directions and the instructive environmental cues are not known at this time. In the *Drosophila* ventral cord, motor neurons and interneurons are represented in repetitive patterns through segments and elaborate type-specific dendritic patterns. Kamiyama and colleagues demonstrated that aCC motor neurons establish stereotypical dendrite growth sites via a Dscam1–Dock–Pak1 interaction and Cdc42-mediated cytoskeletal regulation. The pioneer neuron MP1 provides the external spatial cue for Dscam1 localization in aCC, and subsequently the localization of the Cdc42 effector Pak1 to the dendritic initiation sites (Kamiyama *et al.*, 2015).

Establishing a dendritic field of an appropriate size

The size of the dendritic tree determines the number of presynaptic inputs it may potentially receive and therefore significantly affects the computations a neuron can perform. In the layer and column organization, seen in many sensory systems, presynaptic terminals carrying distinct types of information are often arranged in a two-dimensional array, or map, within one layer. Dendritic size thus dictates the size of the functional receptive field and the fraction of the physical world the neuron samples. Several mechanisms have been demonstrated to establish a dendritic tree of an appropriate size. In the *Drosophila* medulla neuropil, afferent-derived morphogen negatively regulates the dendritic sizes of their target neurons, thus matching the presynaptic and postsynaptic partners. The medulla Tm20 neurons elaborate dendrites in single medulla columns and receive inputs from single R8 photoreceptors, conferring one-to-one correspondence, while the amacrine Dm8 neurons have large dendritic fields, which receive ~16 R7 photoreceptor inputs (Ting *et al.*, 2014). Activin signaling proteins derived from R7 and R8 specifically act on their synaptic targets, Dm8 and Tm20 neurons, respectively, suggesting that Activin functions in short range or in a layer-specific fashion. Removing Activin derived from R7 or R8 or disrupting the canonical Activin signaling pathway in Dm8 or Tm20 caused abnormally large dendritic fields and aberrant synapse formation with R7s or R8s, respectively (Figure 3(A,B)). Statistical analyses of Tm20 dendritic patterning suggest that Activin signaling, via transcription regulation, increases the propensity of dendritic termination. Afferent-derived factors, such as neurotrophins, have been shown to positively regulate dendritic elaboration. In mouse cerebellum, parallel fiber afferents, which are presynaptic to Purkinje cells, secrete Neurotrophin-3, signaling via TrkC receptors, to promote the expansion of Purkinje cells' dendrites (Joo, Hippenmeyer, & Luo, 2014). These findings suggest anterograde signaling as an effective mechanism for coordinating afferent-target development.

The mammalian retina is stratified but lacks a clear columnar structure and the assembly of retinal circuits begins with the formation of orderly arrays (or mosaics) of same neuronal types stacked in layers (Novelli, Resta, & Galli-Resta, 2005). Interactions among neurons of the same types, or homotypic interactions, may provide an effective way to control dendritic coverage and size by self-organization. Indeed, live imaging and cell ablation experiments demonstrated that homotypic repulsion among dendrites of the same types of neurons determines the size and coverage of dendrite fields (Eysel, Peichl, & Wässle, 1985; Lohmann & Wong, 2001). Strong homotypic interactions would prevent dendrites of different neurons of the same type (isotypical) from overlapping but allow their dendrites to cover the entire field, a phenomenon called dendritic tiling. In mouse retina, two surface receptors, MEGF10 and MEGF11, are required for the formation of starburst amacrine and horizontal cell mosaics but their function in mediating dendritic homotypic repulsion has yet to be demonstrated (Kay, Chu, & Sanes, 2012). Mammalian Dscam (Down syndrome CAM), which is required for the formation of a mosaic of dopaminergic amacrine cells in the mouse retina, mediates homotypic repulsion (among different neurons of the same type) as well as isoneuronal self-avoidance (see below) (Fuerst, Koizumi, Masland, & Burgess, 2008).

Confining dendrites to a two-dimensional space facilitates dendritic tiling. The dendrites of *Drosophila* da neurons tile the larval body wall to ensure appropriate coverage of sensory terminals (Han *et al.*, 2012). The dendrites of da neurons are attached to the extracellular matrix (ECM) via the interaction between epidermal laminin and dendritic integrin. Defects in dendrite-ECM adhesion in *laminin* and *integrin* mutants lead to non-contacting dendrite crossing and disruption of dendritic tiling. Forward genetic screens further identified a number of signaling molecules that are involved in dendritic tiling. These include a NDR family kinase Trc, its activator Furry (Fry), TOR (target of rapamycin) and SAPK-interacting protein 1 (Sin1) (Figure 4(C); Emoto *et al.*, 2004; Han *et al.*, 2012; Koike-Kumagai, Yasunaga, Morikawa, Kanamori, & Emoto, 2009). Overexpression of integrin in da neurons corrects tiling defects in *sin1* and *fry* mutants, presumably by enhancing dendrite-ECM interactions. Recent studies further suggest that epidermis-derived Semaphorin, Sema-2b, binds to its receptor Plexin-B on da dendrites to regulate dendrite-ECM adhesion (Meltzer *et al.*, 2016). In this context, Sema-2b/Plex-B signaling appears to act through the Trc/Fry signaling pathway and the TORC2 complex to modulate integrin activity.

Dendritic self-avoidance

The multiplicity of dendrites increases the propensity for self-fasciculation and entanglement of dendritic branches, leading to a reduction of coverage and an increased frequency of autapses. Many neurons employ a process called self-avoidance (or isoneuronal repulsion), in which dendritic branches arising from a single neuron repel each other. The daunting task of recognizing and avoiding self-derived dendrites conceivably demands enormous molecular specificity. Two sets of genes, *Dscam1* and *Pcdhs* (clustered protocadherins), have been implicated in mediating self-avoidance in *Drosophila* and mice, respectively. The *Dscam1* locus contains four sets of alternatively spliced exons and is capable of encoding over 38,000 isoforms of immunoglobulin superfamily adhesion

molecules (Schmucker *et al.*, 2000) and the clustered protocadherins (Pcdhs) include three subclusters and encode 58 isoforms of protocadherins via alternative promoters (Wu & Maniatis, 1999). The expression of different isoforms appears to be stochastic with moderate cell-specific bias (Miura, Martins, Zhang, Graveley, & Zipursky, 2013). The Dscam and Pcdhs isoforms are capable of mediating homophilic interactions in an isoform-specific fashion *in vitro* (Thu *et al.*, 2014; Wojtowicz *et al.*, 2007). With stochastic expression patterns and isoform-specific homophilic binding ability, Dscam1 and Pcdhs could encode cell-identity for self-recognition. Many functional studies *in vivo* indeed lend strong support for such a model: in *Pcdhy* mutant starburst and Purkinje cells, dendritic branches fasciculate and overlap, leading to poor dendritic field coverage (Figure 4(A)). In *Drosophila* *Dscam1* mutants, da neurons exhibit dendritic patterning phenotypes similar to those of *Pcdhy* mutants while overexpressing a single Dscam1 isoform leads to strong contact-dependent repulsion (Figure 4(B)). Thus, insects and vertebrates appear to use two very different surface receptors to encode cell identity and to pattern dendrites by self-avoidance.

Routing dendrites to specific layers

The stratification of neuropil, which segregates functional modality in layers (or laminae) to facilitate information processing, is arguably the most common organization feature of the brain (Sanes & Zipursky, 2010). In the insect visual system, the medulla neuropil is stratified into 10 layers, which receive stereotypic innervation by dendrites of medulla neurons and axonal terminals of photoreceptors and lamina neurons (Fischbach & Dittrich, 1989). Based on layer-specific targeting of dendrites and axons, Fischbach and colleagues hypothesized three major visual pathways, which compute ON/OFF motion and color/form (Bausenwein, Dittrich, & Fischbach, 1992), a notion that now receives strong support from functional studies (Behnia, Clark, Carter, Clandinin, & Desplan, 2014; Maisak *et al.*, 2013). In the vertebrate visual system, one target neuropil of the retina, the tectum (or superior colliculus), is composed of stacked layers, with each layer encoding certain visual features, such as light polarity (ON/OFF) and direction-specific motion (Baier 2013; Dhande & Huberman, 2014; Sanes & Zipursky, 2010). In the retina, dendrites of the ON-type (depolarized upon light increment) retinal ganglion cells (RGCs) and amacrine cells populate the inner half of the inner plexiform layer (IPL) to receive inputs from ON-bipolar cell terminals while dendrites of OFF-type RGCs are confined to the outer half of the IPL. The layer-specific routing of dendrites correlates with TF codes (Cherry *et al.*, 2011; Kay, Voinescu, Chu, & Sanes, 2011; Li *et al.*, 2013) and is the most prominent morphological feature for differentiating neuronal types (Fischbach & Dittrich, 1989; Masland, 2012; Ting *et al.*, 2014). During development, axons and dendrites are routed to specific layers and spatial overlapping presumably facilitates the formation of correct synaptic partnership.

How are layers specified and how are dendrites routed to specific layers during development? Developmental analyses in vertebrate retina and fly medulla neuropil have revealed that layers are formed, added and divided through sequential innervation of axons and dendrites, suggesting that selective adhesion might provide the driving force for self-assembly of layers (Baier, 2013; Ting & Lee, 2007). In the vertebrate retina, some RGCs expand their dendritic arbor only in restricted layers, where others initially occupy multiple layers and undergo subsequent remodeling and retractions (Kim, Zhang, Meister, & Sanes,

2010; Mumm *et al.*, 2006; Sanes & Zipursky, 2010). The selective stabilization of dendrites, presumably mediated by the protocadherin FAT3, has been demonstrated for newly born RGCs and amacrine neurons to bias dendritic extension toward IPL (Deans *et al.*, 2011).

Immunohistochemistry of chick retina has revealed that adhesion receptors, including the Ig-superfamily CAMs (Sidekick, Dscam, and Contactin) and cadherins, are enriched in specific IPL layers (Honjo *et al.*, 2000; Yamagata & Sanes, 2008, 2012) which are populated by the dendrites of distinct RGCs and amacrine neurons. Each of these molecules is capable of mediating homophilic interactions *in vitro*, but does not bind to others. *In vivo* ectopic expression of Sidekick-1, Sidekick-2, Dscam, DscamL, or Contactin-2 is sufficient to drive dendrites to a specific layer (Figure 5(A)). Furthermore, knockdown of these genes significantly degrades the layer-specific dendritic routing of these neurons (Yamagata, Weiner, & Sanes, 2002; Yamagata & Sanes, 2008; 2012). 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.

The semaphorin family molecules, well known for their roles in axon guidance, have also been shown to guide dendrites to or away from specific layers. Cortical pyramidal neurons extend apical dendrites toward the marginal zone in response to the diffusible attractant Sema3A (Polleux, Morrow, & Ghosh, 2000). The transmembrane semaphorin Sema6A, which is expressed in the ON-type RGCs and amacrine neurons, serves as a repellent to prevent the invasion of the dendrites of the OFF-type amacrine neurons which express the Sema6A receptors, PlexinA2 or PlexinA4. In mutants lacking Sema6A or its receptors, PlexinA4-expressing dopaminergic amacrine neurons and PlexinA2-expressing OFF-type starburst amacrine neurons misroute their dendrites to the ON-layer of IPL (Figure 5(B)) (Lefebvre, Sanes, & Kay, 2015; Matsuoka *et al.*, 2011).

How important is the layer-specific dendritic routing for correct synaptic circuit assembly and functions? It has been argued that lamination is essential for rapid assembly of neural circuits and optimal wiring but, at least in some cases, not absolutely required for correct circuit assembly or functions. Human patients of double cortex syndrome have a wide-range of symptoms, from severe intellectual disability and epilepsy to essentially normal brain function (Francis *et al.*, 2006). The disruption of cortical layers in the *reeler* mutant mice has surprisingly little effect on the establishment of the somatosensory map and little functional consequences (Guy, Wagener, Mock, & Staiger, 2015; Wagener *et al.*, 2016). In the aforementioned Sema6A mutants, PlexinA4-expressing dopaminergic amacrine neurons misroute their dendrites to the ON layer but their target M1-type RGC, which normally route dendrites only to the OFF layer, directed their dendrites to meet the misrouted amacrine dendrites in the ON-layer. In the astray mutant zebrafish, in which the lamination of RGC axons in the tectum is lost, tectal direction selectivity is severely perturbed at early developmental stages but later compensated by the structural plasticity of tectal dendrites (Nikolaou & Meyer, 2015). While it is difficult to assess the extent of circuit assembling errors without extensive connectome studies, one must concede that even without lamination, many neurons still can find their partners, presumably utilizing matching molecules to specify synaptic connections.

Specifying synaptic connections

Many CAMs, especially the Ig-superfamily proteins, are capable of mediating homo- or heterophilic interactions and have been suspected to specify synaptic connections. These adhesion receptors could conceivably match pre- and post-synaptic partners, thus fulfilling the role proposed originally in Roger Sperry's chemoaffinity hypothesis (Sperry, 1943). Alternatively, they might prevent the formation of an undesired synaptic pair via homophilic repulsion. In the *Drosophila* lamina, each R1–R6 photoreceptor forms a single presynaptic site for four post-synaptic elements that comprises two invariant pairs of cells, L1 and L2, and two other cells. The Dscam1 and Dscam2, via their homophilic repulsion, play redundant roles to exclude the undesirable pair L1/L1 or L2/L2 (Millard, Lu, Zipursky, & Meinertzhagen, 2010). Interestingly, L1 and L2 each express only one of the two alternatively spliced Dscam2 isoforms; cell-specific expression of alternative isoforms thus resulted in only homotypic (L1–L1 and L2–L2) but not heterotypic (L1–L2) repulsion (Lah, Li, & Millard, 2014). Besides functioning in homophilic repulsion, Dscam2 appears to be capable of mediating homophilic interactions. In the lamina neuropil, L4 neurons extend dendrites to receive three L2 inputs in the cognate and two posterior cartridges (Takemura *et al.*, 2011). In *Dscam2* mutants L4s failed to anchor their dendrites to the correct cartridge and instead mistargeted to the incorrect target cartridge (Tadros *et al.*, 2016). How Dscam2 switches between homophilic repulsion and adhesion remains unknown.

While *Drosophila*'s *Dscam1* locus is capable of encoding over 38,000 isoforms, which mediate isoform-specific homophilic interactions, these isoforms are expressed in a stochastic rather than cell-specific fashion, rendering them unsuitable for matching specific synaptic partners. Systematic analyses of the interactions among *Drosophila* IgSF and LRR (leucine-rich repeat) family members have identified a complex interaction network of 21 Dpr (defective proboscis extension response proteins) and 9 Dips (Dpr-interacting protein). Each Dpr binds to 1–4 Dips while each Dip binds to 1–7 Dprs (Özkan *et al.*, 2013). RNA-sequencing analysis revealed that Dpr members are differentially expressed in the R7 and R8 photoreceptors and the lamina neurons, L1–L5, which innervate distinct medulla neurons in specific layers. Protein expression analyses showed that the Dip counterparts are expressed in a complementary layer-specific fashion (Tan *et al.*, 2015). These findings raise the intriguing possibility that Dpr–Dip interactions might specify layer-specific connections. Carrillo and colleagues demonstrated that the Dpr11–Dip- γ pair contributes to the establishment of the connections between R7 photoreceptors and their synaptic target Dm8 neurons. Dpr11 is expressed in the yellow-type R7 photoreceptors (yR7) while Dip- γ is expressed in a subset of Dm8 neurons. In *dpr11* mutants, yR7 axons overshoot the M6 layers where Dm8 dendrites reside. In *dip- γ* mutants, some Dm8 are lost and yR7 axons overshoot the M6 layer, suggesting that Dip- γ is required for Dm8's survival or differentiation (Carrillo *et al.*, 2015). Whether other Dpr/Dip pairs play similar roles in specifying synaptic connections remains to be determined.

Concluding remarks

In the past two decades, remarkable advances have been made in uncovering the complex mechanisms that control dendrite growth and patterning. The cellular machinery, ranging

from signaling components and cytoskeletal regulators, to organelles and secretory pathways, orchestrates different processes of dendritic morphogenesis. Dendritic self-patterning, via self-avoidance and tiling, promotes efficient coverage of dendritic fields. TF codes further link the expression and regulation of intrinsic factors to type-specific dendritic morphologies in the peripheral nervous systems. Some of these findings are now being translated to dendritic morphogenesis in the CNS. The repetitive structure of layers and columns in the CNS poses additional challenges for dendritic routing. Layer-specific dendritic routing is mediated by homophilic adhesion receptors and repulsive receptors, which guide dendrites to or away from specific layers. Presynaptic growth factors regulate the size of the dendritic field, thus providing direct communication between pre- and post-synaptic partners. There is little doubt that additional molecules will be identified for these aspects of dendritic morphogenesis in the future. The organization of the *Drosophila* medulla neuropil hints at the importance of initiating dendritic extension at appropriate locations and orientations. The identification of the receptors and cues responsible for these processes might provide new perspectives for dendritic routing in layers and columns. An important direction of investigation is to examine the dynamic processes of dendritic morphogenesis in developing animals. To date, live imaging has been applied to very few cases in the CNS. Capturing morphological changes and dendritic contacts in real-time will be important to identify critical processes and to resolve different types of developmental defects.

A key goal of studying dendritic morphogenesis in the CNS is to understand how dendritic patterning defects lead to connectivity and functional deficits. With rapid advances in connectome technology, it might be possible in the near future to fully analyze synaptic circuits at the ultrastructural level. For the time being, an array of light microscopic techniques, including GRASP (GFP reconstitution across synaptic partners) and functional imaging methods, allow the characterization of connectivity and functional defects in selected neurons. Characterizing dendritic morphogenesis in the CNS is likely to have profound consequences for our understanding of neurodevelopmental and neurodegenerative disorders. Dendritic morphological defects are associated with numerous neurological disorders, such as DS, ASDs, Alzheimer's disease and schizophrenia. The study of dendritic routing in layers and columns could ultimately provide the missing link from genes to connectivity and to cognition.

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Figure 1.

Layer and column organization in the central nervous system. (A) A schematic illustration of the *Drosophila* visual system. The system comprises the eye, and four optic neuropils: lamina, medulla, lobula and lobula plate. The eye and the lamina are organized in columns while the medulla and the lobula complex form layer and column structures. Visual information received by the photoreceptors in the eye is segregated in medulla layers and columns depending on their spectrum and position in the visual field, respectively. In such a way, each medulla column processes a single visual pixel and each layer is responsible for a visual feature. Representative neurons in each neuropil are shown in different colors. (B) The connection patterns of medulla neurons in columns and layers. Each medulla column is divided into 10 layers (M1–M10), which are innervated by the axons of the photoreceptors and lamina neurons and the dendrites of about 38 types of medulla neurons. The R7 and R8 photoreceptors extend axons to the M6 and M3 layers, respectively, while the lamina neurons innervate the M1–M5 layers. Each medulla neuron elaborates a type-specific

dendritic tree, from certain medulla layer, in a distinct planar direction, to innervate specific medulla layers. For example, the transmedulla neuron Tm20 projects dendrites from M3 layer in the posterior direction to innervate M1–M3 layers while Tm2 dendrites project anteriorly to innervate M2 and M4 layers. Dendrites of both Tm2 and Tm20 neurons are largely confined to a single medulla column, consistent with their role in processing retinotopic information. In contrast, the amacrine neuron Dm8 elaborates a large dendritic field across multiple columns in the M6 layers to receive ~16 R7 inputs. (C) A schematic diagram of the vertebrate retina illustrating the major cell components and their connection patterns. The vertebrate retina is organized in layers but lacks apparent columnar structures. Cone and rod photoreceptors innervate the outer plexiform layer (OPL) where they synapse with horizontal cells (H) and ON and OFF bipolar cells (CB and RB). The ON and OFF bipolar cells innervate the ON and OFF layers of the inner plexiform layer (IPL), respectively. The ON and OFF types of amacrine cells (A) and ganglion cells (G) elaborate dendrites in the corresponding ON and OFF IPL to receive inputs from bipolar cells. (D) A schematic of neocortex layers and columns. The rat neocortex is organized in columns and stratified in four layers (L1, L2/3, L4 and L5). The L1 single bouquet cells (SBC) provide inputs for the bipolar cells (BPC) in the L2/L3 layer, which in turn provide inputs for the pyramidal neurons (PN) in the L5 layers within the same column. The elongated neurogliaform cells (ENGCS) elaborate neurites across multiple columns and provide inhibitory inputs for the pyramidal cells (redrawn from Jiang, Wang, Lee, Stornetta, & Zhu, 2013).

Figure 2.

Dendritic morphogenesis in steps. Dendritic morphogenesis proceeds in several stages. After the initiation of dendritic outgrowth (1) from cell bodies or axon shafts, dendrites undergo dynamic extension and retraction (2). The dendrites form new branches (3), either by splitting the growth cones (dash arrows) or by emerging new branches from the side of the established branches (interstitial branching, arrow). Finally, the terminal branches are stabilized by interacting with other neurites or pruned away (4) before synapse formation (5). A wide range of molecules, including cytoskeletal regulators, signaling molecules, organelles and surface receptors, have been identified for their roles in specific stages of dendritic morphogenesis (see Puram & Bonini, 2013; Shen & Cowan, 2010; Valnegri, Puram, & Bonni, 2015).

Figure 3.

Presynaptic factors control dendritic field size. In the *Drosophila* visual system, the axonal terminals of R7 and R8 photoreceptors form regular two-dimensional arrays in two separate layers, M6 and M3, respectively. The Dm8 amacrine neurons expand their dendrites across multiple columns to receive ~16 R7 inputs in the M6 layer while each Tm20 neuron routes its dendrites between M1 and M3 layers within a single column to receive inputs from a single R8. The TGF β superfamily morphogen Activin derived from R7s and R8s, acts in short-range, to regulate the dendritic field sizes of their respective target neurons. (A) Knocking down Activin in R7s or removing the Activin receptor Baboon in Dm8 results in the expansion of Dm8's dendritic field. (B) Conversely, disrupting R8 Activin or knocking out Baboon in Tm20 caused the expansion of Tm20's dendritic tree and the formation of aberrant synapses between Tm20 neurons and neighboring R8s.

Figure 4.

Dendritic self-avoidance and tiling promote efficient field coverage. (A) Vertebrate clustered protocadherins (*Pcdhs*) regulate dendritic self-avoidance in mouse retina. Retinal starburst amacrine cells (SACs) have radially symmetrical dendritic trees that evenly cover the receptive field. Deleting the entire *Pcdh- γ* gene cluster (*Pcdh γ ⁰*) results in SACs' dendrites crossing and self-fasciculation (center panel). Replacing a single *Pcdh- γ* isoform in *Pcdh- γ* knockout is sufficient to rescue self-avoidance in SACs (right panel). *Pcdh γ ²²*: wild-type, expressing 22 isoforms; *Pcdh γ ⁰*: null mutant; *Pcdh γ ¹*: mutant expressing a single isoform. (B) The *Drosophila Dscam1* gene locus, which is capable of encoding 38,016 isoforms, is required for dendritic self-avoidance of the Class I da neurons. Similar to *Pcdh- γ* 's functions in mouse SAC neurons, expressing a single isoform is sufficient to rescue the dendritic crossing-over phenotype. *Dscam1⁰*: null mutant. *Dscam1¹*: mutant expressing single isoform. (C) Tricornered kinase and Furry regulate dendritic tiling in the class IV da neurons in *Drosophila*. The type IV da neurons tile the body wall with their dendrites: each neuron maintains its own dendritic territory and avoids neighboring dendrites of the same type via homotypic repulsion. Dendrites of *tricornered* and *furry* mutants fail to avoid neighboring dendrites, resulting in overlap of the dendritic fields of type IV neurons.

Figure 5.

Routing dendrites to specific layers. (A) Sidekick 1 (*Sdk1*) mediates layer-specific dendritic targeting and synapse formation. In chick retina, the immunoglobulin superfamily protein *Sdk1* is concentrated in the S4 sub-layer of the inner plexiform layer (IPL). Depletion of *Sdk1* disrupts layer-specific arborization of cadherin-7-positive dendrites (2nd column). Ectopically expressing *Sdk1* in *Sdk1*-negative cells (3rd column) redirects the neurites to the *Sdk1* concentrated layer (4th column), suggesting *Sdk1* is necessary and sufficient for layer-specific synaptic interactions. (B) *Sema6A*-mediated repulsion prevents dendrites from entering incorrect layers. The inner plexiform layer (IPL) is divided into ON and OFF layers. *Sema6A* protein is expressed in the ON starburst amacrine cells (SAC) that innervate the ON IPL while the *Sema6A* receptors *PlexinA2* and *PlexinA4* are expressed in the OFF SAC and dopaminergic amacrine cells (TH⁺). In *Sema6A* mutants, the dendrites of OFF SAC and TH⁺ amacrine cells mistarget to the ON layer. Interestingly, some dendrites of the M1-type retinal ganglion cells follow the TH⁺ dendrites to the ON layer, hinting the presence of a yet-identified cue for these synaptic partners. INL, inner nuclear layer; IPL, inner plexiform layer; TH⁺, dopaminergic amacrine cells; SAC, starburst amacrine cells.