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Molecules and mechanisms of dendrite development in *Drosophila*

Megan M. Corty[1,*], Benjamin J. Matthews[1,*] and Wesley B. Grueber[2,3,†]

Neurons are one of the most morphologically diverse cell types, in large part owing to their intricate dendrite branching patterns. Dendrites are structures that are specialized to receive and process inputs in neurons, thus their specific morphologies reflect neural connectivity and influence information flow through circuits. Recent studies in *Drosophila* on the molecular basis of dendrite diversity, dendritic guidance, the cell biology of dendritic branch patterning and territory formation have identified numerous intrinsic and extrinsic cues that shape diverse features of dendrites. As we discuss in this review, many of the mechanisms that are being elucidated show conservation in diverse systems.

Introduction

Dendrites – processes of neurons that are primarily specialized for information input – are one of nature's remarkable architectural feats, and the diverse growth patterns shown by dendritic arbors raise important developmental questions. The particular shapes of dendrites are important in neuronal function and circuit assembly. Their targets and complexity influence the range of inputs that a neuron receives. In addition, the morphology of a dendritic arbor can impact the processing and integration of electrical signals (London and Häusser, 2005). Studies of dendrite morphogenesis therefore seek to understand the developmental origin of arbor shape and to shed light on the significance of particular morphologies for nervous system connectivity and function.

Dendrite morphogenesis consists of a series of interrelated steps, which include outgrowth and branching, guidance and targeting, cessation of growth and, in some cases, arbor remodeling (see Box 1). Each process is under extensive genetic regulation and has been the subject of intensive study in recent years. In this review, we highlight recent advances in understanding the molecules and mechanisms that function during these key stages of dendrite morphogenesis. We focus primarily on studies carried out in *Drosophila* (Fig. 1) and refer to known or emerging areas of conservation in vertebrate systems where appropriate. We focus on several key questions, including: what are the cell biological mechanisms that specify the distribution of dendritic branches along an arbor? How do dendrites achieve type-specific branching patterns? How is specific dendritic targeting controlled in different neurons? How are dendrites instructed when to stop branching and growing? How does activity impact dendrite development in *Drosophila*? We refer readers to other reviews that cover topics that have thus far been studied primarily in vertebrate systems, including dendritic spine morphogenesis and activity-dependent dendrite growth (Alvarez and Sabatini, 2007; Chen and Ghosh, 2005; Flavell and Greenberg, 2008; Lippman and Dunaevsky, 2005; Redmond, 2008).

Genetic insights into the cell biology of dendrite growth and branching

The growth and specialized functions of dendritic arbors can require large investments of dendritic plasma membrane and proteins during development, and, indeed, the polarized trafficking of cargoes to dendritic branches and the incorporation of new membrane are fundamental processes for proper arbor branching and expansion. Isolated Golgi compartments, termed Golgi outposts, are a component of the secretory pathway found in dendrites of some vertebrate and invertebrate neurons, indicating that local secretory trafficking occurs in dendrites and is a conserved process (Fig. 2) (Horton and Ehlers, 2003; Horton et al., 2005; Ye et al., 2007). In cultured rat hippocampal neurons, Golgi outposts are found in longer and more highly branched dendrites, and manipulations that disrupt Golgi trafficking [including Golgi disassembly, blocking endoplasmic reticulum (ER)-to-Golgi trafficking, or blocking cargo budding from the trans-Golgi network] lead to defects in dendritic growth and maintenance (Horton et al., 2005). The dependence of dendrite growth on Golgi outposts is also conserved in *Drosophila*. A forward genetic screen for mutations that affect dendrite and axon

Box 1. Hotspots of dendrite death

The dendrites and axons of insect neurons can undergo dramatic remodeling during the metamorphic transition from larva to adult to match the stark behavioral differences between these stages. Some dendritic trees and axons are pruned under the control of the steroid hormone ecdysone, acting through the B1 isoform of the Ecdysone receptor (EcR), as well as by matrix metalloproteases and the ubiquitin-proteasome system (Kuo et al., 2005; Kuo et al., 2006; Lee et al., 2000; Marin et al., 2005; Watts et al., 2003; Williams and Truman, 2005; Zheng et al., 2003). Remarkably, in many cells that prune their dendrites, the axon remains fully intact. What accounts for this localized action in the dendrites? Dendritic pruning shares morphological features with apoptosis – in particular, the fragmentation of arbors and their clearing by phagocytes (Williams and Truman, 2005), prompting the examination of apoptotic machinery during remodeling (Kuo et al., 2006; Williams et al., 2006). Caspases are a crucial component of the apoptotic machinery, and in *Drosophila* the initiator caspase Dronc (Nedd2-like caspase – FlyBase) is required for the pruning of da neuron dendrites during metamorphosis (Kuo et al., 2006; Williams et al., 2006). It remains unclear whether Dronc is required for initial dendrite cleavage or only once the severing event has occurred. Importantly, however, caspase activity is very likely to be local, as activated caspases and cleaved caspase substrates are detected selectively in pruning dendritic arbors (Kuo et al., 2006; Williams et al., 2006). How this dendritic specificity is achieved is an important question that could have implications for understanding the mechanisms of dendritic pathology, regeneration and plasticity.

[1]Center for Neurobiology and Behavior, [2]Department of Neuroscience, [3]Department of Physiology and Cellular Biophysics, Columbia University Medical Center, 630 W. 168th St., P&S 12-403, New York, NY 10032, USA.

*These authors contributed equally to this work
†Author for correspondence (e-mail: wg2135@columbia.edu)

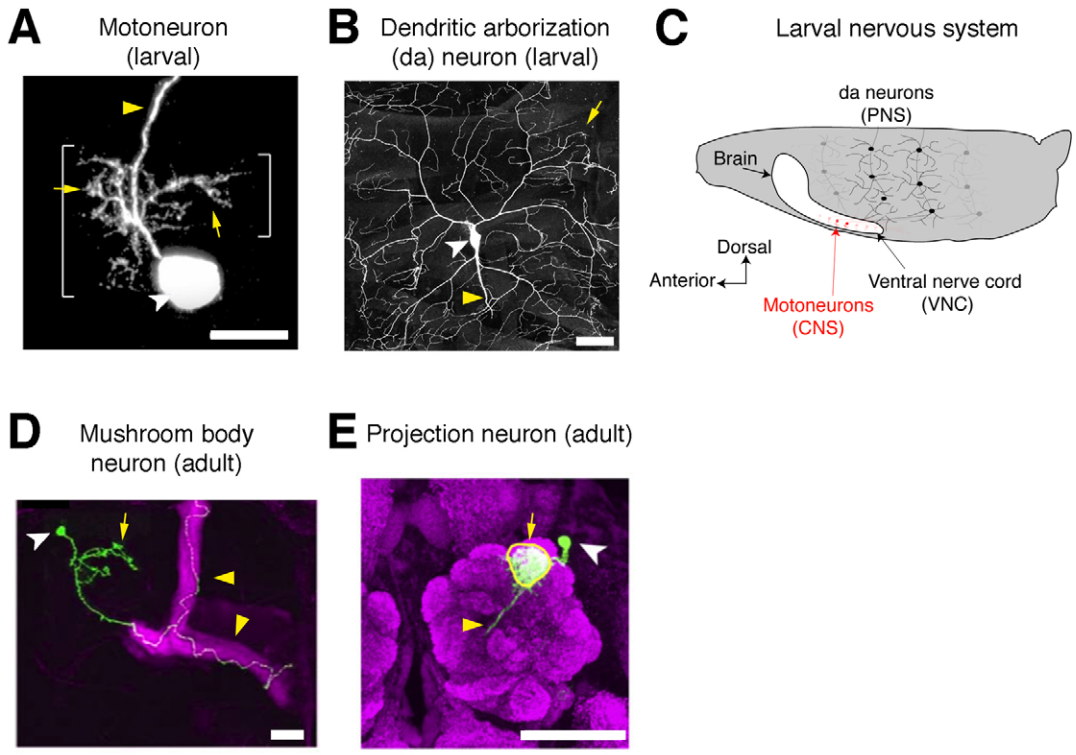

Fig. 1. Diverse morphologies of *Drosophila* dendrites. (**A**) A *Drosophila* RP2 motoneuron projects its dendritic arbor within the ventral nerve cord of the embryonic CNS. Adapted with permission from Ou et al. (Ou et al., 2008). Yellow arrows indicate dendrites, yellow arrowheads indicate axons, and cell bodies are indicated by white arrowheads in this and subsequent panels. (**B**) The dendrites of a highly branched class IV dendritic arborization (da) neuron of a third-instar *Drosophila* larva. Image reproduced with permission from Matthews et al. (Matthews et al., 2007). (**C**) Schematic of a *Drosophila* larva showing the location of da neurons in the peripheral nervous system (PNS) and motoneuron cell bodies (red) within the central nervous system (CNS) (not all segments or cells are shown). Anterior is to the left and dorsal is up. (**D**) A mushroom body neuron (green) elaborates dendrites near the cell body. Image reproduced with permission from Zhu et al. (Zhu, S. et al., 2006). (**E**) A single projection neuron projects its dendrites to a single glomerulus (outlined in yellow) within the antennal lobe (magenta). Image reproduced with permission from Komiyama and Luo (Komiyama and Luo, 2007). Scale bars: 10 μm in A; 50 μm in B,E; 20 μm in D.

morphology using *Drosophila* class IV dendritic arborization (da) neurons (see Glossary, Box 2), recovered mutations in several genes that encode proteins involved in ER-to-Golgi transport, including *sar1*, *sec23* and *Rab1* (Ye et al., 2007). Sar1 is required to initiate vesicle formation for trafficking from the ER to Golgi, and clones mutant for *sar1* show reduced dendrite growth and diffuse Golgi outposts (Fig. 2C) (Ye et al., 2007). Axons are not as strongly affected in these mutants and show only a reduction in small terminal fibers (Ye et al., 2007). Likewise, rat hippocampal neurons transfected with Sar1 siRNA show strongly reduced dendritic length but normal axon growth (Ye et al., 2007), indicating that these distinct cell types utilize evolutionarily conserved mechanisms of dendritic secretory trafficking.

One of the important findings of these studies is that Golgi outposts are selectively enriched in dendrites and are primarily involved in dendrite, but not axon, growth. This result provided insight into the important problem of how polarized dendritic and axonal growth is maintained, but raised the question of how Golgi and other specific cargoes are trafficked to the dendritic compartment. Expression of a dominant-negative version of Lava lamp, a protein that mediates interactions between the Golgi and the dynein complex, caused a redistribution of Golgi outposts and a correlated shift in branches toward the proximal part of the dendritic arbor (Ye et al., 2007). Subsequently, two independent genetic screens for genes that regulate class IV da neuron morphology each found that mutations in the *dynein light intermediate chain* (*Dlic2*) also cause a proximal shift in the distribution of branch points (Satoh et al., 2008; Zheng et al., 2008) (Fig. 2D), as well as of Golgi outposts (Zheng et al., 2008). The multi-subunit dynein complex, of which Dlic2 is a member, is a minus end-directed microtubule motor, and previous studies of *Drosophila* mushroom body neurons have indicated roles for Lis-1 (a protein that interacts with the dynein complex) and the dynein complex components Dynein heavy chain and Dynein light chain in dendritic elaboration (Liu et al., 2000; Reuter et al., 2003). The majority of dendritic microtubules in several major classes of *Drosophila* neurons, including da sensory neurons, appear to be oriented in a minus end-distal arrangement with axonal microtubules oriented oppositely (Rolls et al., 2007; Stone et al., 2008; Zheng et al., 2008), suggesting a model in which dynein functions during dendrite morphogenesis to traffic branching machinery to growing dendritic arbors.

One significant question relates to the identity of the branching machinery that is trafficked by dynein in addition to the dendritic Golgi. The small GTPase Rab5, which is involved in the early endocytic pathway, has been found in association with cytoplasmic dynein (Satoh et al., 2008). In *Dlic2* mutant neurons, endosomes are lost from dendrites and are enriched in cell bodies; the expression of a dominant-negative Rab5 protein prevents the profusion of proximal dendritic branches (Fig. 2E) (Satoh et al., 2008). The basis for the pro-branching effects of Rab5 endosomes is not known, but

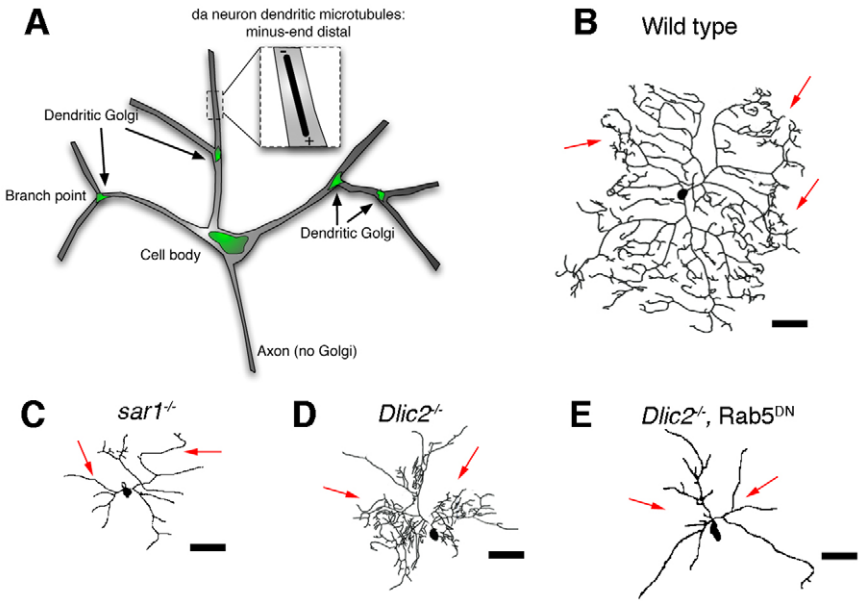

Fig. 2. Organelle trafficking and dendrite morphogenesis. (**A**) Schematic of Golgi distribution in *Drosophila* da neurons. Golgi outposts are localized to dendritic branch points and excluded from the axon. The predominant minus-end distal arrangement of microtubules in these dendrites is also shown. (**B-E**) Dendritic morphologies of wild-type and mutant class IV *Drosophila* da neurons. Arrows indicate dendrites. (B) Tracing of a wild-type class IV da neuron. (C) Tracing of a *sar1* mutant class IV da neuron that shows reduced branch complexity. Sar1 is involved in the formation of COPII vesicles during trafficking from ER to the Golgi. (D) Tracing of a class IV da neuron with a mutation in *dynein light intermediate chain* (*Dlic2*) showing reduced dendrite length and redistribution of branches to areas nearer to the cell body (shown in black). Dlic2 is a component of the dynein complex, a minus-end-directed microtubule motor. (E) Tracing of a class IV da neuron expressing a dominant-negative Rab5 [Rab5(S43N)]. Dominant-negative Rab5 abrogates the proximal hyperbranching phenotype of *Dlic2* mutations. Rab5 is a GTPase that functions in early endocytosis. Tracings in B,C adapted with permission from Ye et al. (Ye et al., 2007). Tracings in D,E adapted with permission from Satoh et al. (Satoh et al., 2008). Scale bars: 75 μm.

it is possible that this activity depends on signaling through endocytosed receptors (Satoh et al., 2008). Mutations in *shrub*, which encodes a homolog of yeast Snf7 involved in trafficking from endosomes to lysosomes, also lead to hyperbranching, potentially owing to the defective modulation of receptor pathways that are important for dendrite branching (Sweeney et al., 2006). Other possible branching machinery trafficked by dynein could include *nanos* (*nos*) mRNA, which localizes to dendrites of da neurons and which might be involved in local translational control to regulate dendrite branching (Brechbiel and Gavis, 2008; Ye et al., 2004). Comparisons of Golgi and endosome dynamics, modes of transport and delivery and molecular cargoes in different cell types should help to unravel the cell biological basis of diverse dendritic arbor branching patterns.

Transcriptional control of dendritic diversity

Dendritic arbors show tremendous morphological diversity, with specific shapes influencing the inputs that a neuron receives and impacting the processing of signals within the arbor. The identification of the developmental programs that endow different neurons with distinct shapes is therefore an important goal. Much work has been focused on how intrinsic transcriptional programs of dendritic growth and branching control characteristic cell-type-specific morphogenesis, much of it carried out in the *Drosophila* peripheral nervous system (PNS).

The embryonic and larval PNS consists of a well-defined array of sensory neurons in each hemisegment. Some PNS neurons have a single dendrite (external sensory neurons and chordotonal neurons), and some have more extensively branched arbors (the multidendritic neurons). The da neurons are one subset of multidendritic neurons that show diverse dendritic morphologies (Grueber et al., 2002; Sweeney et al., 2002), and they are categorized into four classes (I-IV) based on increasing arbor complexity (Grueber et al., 2002) (Fig. 3). Thus, variations in PNS dendrite morphology range from the general (single dendrite versus multiple dendrite) to the specific (different subtypes of multidendritic morphologies). The distinction between a single dendrite morphology of external sensory neurons and a multiple dendrite morphology is specified by the zinc-finger transcription factor Hamlet. The *hamlet* gene is expressed in the immediate precursors of external sensory neurons (and briefly in postmitotic external sensory neurons), where it acts to repress dendritic branching. Lack of *hamlet* expression in the immediate precursors of multidendritic neurons permits these neurons to form highly branched arborizations (Moore et al., 2002).

Genetic screens, as well as studies of genes expressed in all, or specific subsets of, da neurons have identified transcription factors that function to further diversify dendritic branching morphology. The Broad/Tramtrack/Bric a brac (BTB) zinc-finger transcription factor Abrupt is expressed in the simple class I neurons (Fig. 3A) and is required to limit dendritic branching (Li et al., 2004; Sugimura et al., 2004). The expression of Abrupt in the other, more complex classes strongly suppresses dendritic complexity (Li et al., 2004; Sugimura et al., 2004). The transcriptional mechanisms that underlie dendrite simplification by Abrupt remain unknown. Abrupt and the homeodomain protein Cut are expressed in complementary cell classes (Grueber et al., 2003a; Li et al., 2004; Sugimura et al., 2004), and although ectopic expression of Cut can reduce Abrupt levels in

Box 2. Glossary of terms

Amacrine cells
A morphologically diverse class of interneurons in the vertebrate retina that synapse with RGC dendrites. Self-avoidance and tiling of amacrine cell neurites ensure even and complete coverage of the retina.

Antennal lobe
The first relay of the insect olfactory system in the brain consisting of axons of olfactory receptor neurons, dendrites of projection neurons, processes of local interneurons, and glia. Analogous to the mammalian olfactory bulb.

Antennal lobe glomeruli
Discrete regions of the antennal lobe where axons of olfactory receptor neurons synapse with the dendrites of projection neurons and local interneurons. There are ~50 glomeruli in the adult *Drosophila* antennal lobe.

Cortical pyramidal neurons
The main type of excitatory neuron in the vertebrate cerebral cortex. Basic pyramidal neuron dendritic morphology is polarized with a single apical dendrite, which branches into an apical tuft, and numerous basal dendrites.

Dendritic arborization (da) neurons
Insect sensory neurons in the peripheral nervous system that spread multiple branched dendrites across the body wall. Also called md-da neurons, *Drosophila* da neurons are subdivided into classes I-IV in order of increasing branching complexity.

Inner plexiform layer (IPL)
A layer within the vertebrate retina containing axons and dendrites of several retinal neuron subtypes. Many of these cells, such as RGCs and amacrine cells, demonstrate a tiled arrangement across the retina.

Olfactory projection neuron (PN)
Second-order neuron of the insect olfactory system that sends dendrites to discrete glomeruli where they receive inputs from olfactory receptor neurons. Axons project to higher brain centers.

Retinal ganglion cells (RGCs)
A morphologically diverse class of vertebrate retinal neurons that elaborate dendrites in the IPL and project axons through the optic nerve to carry visual information to the brain. Many types of RGCs have a tiled arrangement to ensure even coverage of the retina.

Self-avoidance
The process by which branches from the same neuron recognize and repel each other, leading to branch separation and/or even spreading across a territory.

Tiling
Complete but non-overlapping coverage of a receptive area by arbors of a functionally related group of neurons.

class I neurons, there is no strong evidence that cross-regulation is responsible for their exclusive expression patterns (Sugimura et al., 2004). Whereas Cut is undetectable in class I neurons, it shows progressively increasing levels in class II, IV and III neurons (Blochlinger et al., 1990; Grueber et al., 2003a) (Fig. 3B-D). Loss of Cut from cells that express it leads to a simplification of dendrites, whereas its misexpression leads to morphological switches towards the dendritic pattern of the higher-level neurons (Grueber et al., 2003a). Although Cut acts to increase branching in most classes of da neurons when overexpressed, the highest levels of Cut do not correlate with the greatest number of branches, but rather with the presence of numerous actin-based filopodia-like extensions. One possibility is that Cut levels are more closely associated with branch dynamics (Grueber et al., 2003a; Sugimura et al., 2003) and in this way influence the ability of neurons to build more complex scaffolds. The factors that specify or maintain Abrupt and Cut levels in different classes, the transcriptional targets of these transcription factors, and whether the level of Cut affects targets qualitatively or quantitatively, are among the key questions that remain to be addressed.

Recent studies of the Collier/Olfactory-1/Early B-cell factor (COE) transcription factor Knot (Collier) suggest that dendritic arbor patterns are specified in individual cells by combinatorial use of transcription factors. Knot is expressed, together with Cut, in class IV neurons (Fig. 3D) and is required for the development of their highly branched class-specific arborization. Postmitotic misexpression of Knot in other da neuron classes is likewise sufficient to transform them towards a class IV-like branching pattern (Crozatier and Vincent, 2008; Hattori, Y. et al., 2007; Jinushi-Nakao et al., 2007). Although Cut can exert a moderate positive effect on the amplitude of Knot expression (Jinushi-Nakao et al., 2007), the consequences of such regulation for arbor morphology are not clear. Conversely, Knot activity counteracts the formation of the class III-like actin-based dendritic extensions that are induced by Cut (Jinushi-Nakao et al., 2007). These results suggest that a code for the two most complex morphologies – $Cut^{hi}/Knot^{-}$ (class III) and $Cut^{intermediate}/Knot^{+}$ (class IV) – promotes several of the differences in their class-specific dendritic branching patterns. One possibility supported by overexpression experiments is that Cut promotes F-actin-based dendrite extensions, whereas Knot promotes the growth of a microtubule-based arbor (Jinushi-Nakao et al., 2007). Knot might also regulate physiological features of class IV neurons given that it also regulates the expression of an ion channel subunit encoded by *pickpocket* (and transgenic reporters of *pickpocket* expression) in these cells (Ainsley et al., 2003; Crozatier and Vincent, 2008; Hattori, Y. et al., 2007; Jinushi-Nakao et al., 2007).

Knot regulates branching, at least in part, by positively regulating the expression of Spastin (Jinushi-Nakao et al., 2007), an ATPase that has microtubule-severing activity (Roll-Mecak and Vale, 2005). At appropriate levels, Spastin severing activity might promote complex dendritic branching by creating opportunities for new microtubule polymerization (Jinushi-Nakao et al., 2007). The overexpression of mammalian homologs of either Cut or Knot can at least partially mimic the effect of its *Drosophila* counterpart (Grueber et al., 2003a; Jinushi-Nakao et al., 2007). The rodent homologs of Cut and Knot (the Cux and Ebf transcription factors, respectively) are expressed in the developing brain (Cobos et al., 2006; Garel et al., 1997; Nieto et al., 2004; Wang et al., 1997), but whether they have conserved roles in dendrite morphogenesis is not yet known.

Spineless, a conserved basic helix-loop-helix Period/Ahr/Single-minded (bHLH-PAS) transcription factor, has a unique influence on dendrite diversification. When da neurons are mutant for *spineless*, all four da neuron classes exhibit similar morphologies that are of intermediate branching complexity (Kim et al., 2006). However, most da neurons (with the exception of class IV neurons) do not show an overexpression phenotype (Kim et al., 2006). Thus, in different cells, Spineless acts to either limit or promote branching, perhaps permitting the diversification of a common (maybe a ground or default state) dendritic morphology of intermediate complexity (Kim et al., 2006). How Spineless might accomplish this is not clear. Given that Spineless does not seem to control the expression of Cut or Abrupt in da neurons (Kim et al., 2006), and that both Cut and Abrupt are sufficient to drive class-specific branching when overexpressed in Spineless-expressing neurons, it is conceivable that

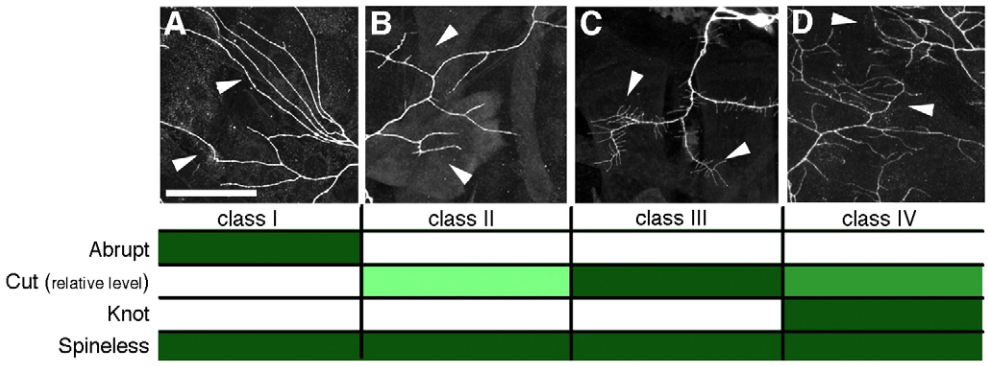

Fig. 3. Diversity of da neuron morphology and transcription factor expression. (**A-D**) Dendritic arbors of class I, II, III and IV da neurons (left to right). Arrowheads indicate regions of arbors that exemplify class-specific branching complexity. Cells are classified according to increasing arbor complexity. The expression status of transcription factors Cut, Knot, Abrupt and Spineless is listed below each morphological class. Filled boxes indicate expression, white boxes indicate no detectable expression. Progressively higher levels of Cut expression are indicated by progressively darker shadings (the degree of shading is not intended to indicate relative levels among the different transcription factors). Images in A-C reproduced with permission from Matthews et al. (Matthews et al., 2007). Scale bar: 50 μm.

Spineless might normally regulate factors that counteract the execution of class-specific programs. Additionally, the molecular mechanism by which Spineless acts is not known, given that its typical heterodimeric partner, Tango (Emmons et al., 1999), is not required cell-autonomously during dendrite morphogenesis (Kim et al., 2006).

The transcriptional codes that mediate dendritic morphogenesis are likely to be complex, and the genes studied so far, along with the few known downstream targets, represent a preliminary stage in our understanding of dendritic diversification. A genome-wide RNAi screen of 730 predicted and known transcriptional regulators identified over 70 candidate genes involved in dendrite growth, branching and routing in a single class of sensory neuron (Parrish et al., 2006). Many of the genes identified are expressed in the nervous system (Parrish et al., 2006) and so should provide good candidates for future studies. This screen, together with several other recent studies, also indicate that mechanisms that modify chromatin structure, including histone modification and ATP-dependent chromatin remodeling, add another level of control over dendrite morphogenesis (Nott et al., 2008; Parrish et al., 2007; Parrish et al., 2006; Wu et al., 2007). Such mechanisms have the potential to further diversify the effects of individual transcription factors in different neuronal types.

Control of dendritic guidance and targeting

The development of dendritic branch diversity is aided by cell-type-specific dendritic targeting. Dendritic guidance and targeting programs polarize arbors to innervate particular regions of the nervous system out of many possible targets, and thus have the potential to impact the inputs that a neuron receives and its function in specific circuits. Studies in vertebrate and invertebrate systems indicate that a first level of targeting control arises from intrinsic programs that are linked to cell lineage and identity (Jefferis et al., 2001; Kelsch et al., 2007; Komiyama et al., 2003; Komiyama and Luo, 2007). These programs, in turn, are likely to dictate how dendrites respond to attractive or repulsive cues in their environment. In addition, local interactions between dendrites (see below) help to define and refine dendritic target boundaries. Thus, a focus of current research is to identify and characterize the transcription factors and guidance signals that control precise dendritic targeting.

Transcriptional regulation of dendritic targeting in the antennal lobe

An extensive analysis of the intrinsic factors that control dendritic targeting has been undertaken in the *Drosophila* antennal lobe (AL) (see Glossary, Box 2), where olfactory information from olfactory receptor neurons (ORNs) is transmitted to second-order olfactory neurons termed projection neurons (PNs) (see Glossary, Box 2) (Fig. 4A). About 150-200 PNs are produced from three major lineages: the anterodorsal (adPN), lateral (lPN) and ventral (vPN) lineages. PN dendrites target one, or a few, out of ~50 AL glomeruli (see Glossary, Box 2) in a lineage and, at least in the case of the adPNs, in a birth order-dependent manner (Fig. 4A) (Jefferis et al., 2001). Within the adPN lineage, PN temporal identity is partly controlled by the action of the BTB zinc-finger protein Chronologically inappropriate morphogenesis (Chinmo), which is required in early-born adPNs for correct axon and dendrite targeting and acts to prevent the adoption of cell fates typical of later-born neurons (Zhu, S. et al., 2006). Although intrinsic programs (as discussed below) are important for PN targeting, and although the early glomerular map forms before the AL is innervated by ORN axons (Jefferis et al., 2004), dendrites also engage in complex interactions with axons and other dendrites as they become restricted to specific glomeruli (Zhu, H. et al., 2006; Zhu and Luo, 2004). For example, disrupting PN dendrite targeting (through manipulation of *Dscam* expression) can cause shifts in ORN axon innervation patterns (Zhu, H. et al., 2006), and, conversely, shifting ORN axon terminals at later developmental stages (through manipulation of Sema-1a signaling) results in altered PN dendritic projections (Lattemann et al., 2007). Thus, although dendritic targeting is prespecified, the final arrangements of dendrites is likely also to arise from an interplay between pre- and postsynaptic partners (Jefferis, 2006; Luo and Flanagan, 2007), which provide an additional, localized level of control over targeting specificity.

Intrinsic transcriptional programs control lineage-specific targeting of PN dendrites by directing their global and local positioning in the AL. Based on the analysis of several families of transcription factors (including POU-domain, homeodomain, BTB zinc-finger and LIM-homeodomain families), it has been shown that some transcription factors, such as Cut, are likely to specify the general AL domain that is targeted by PN dendrites

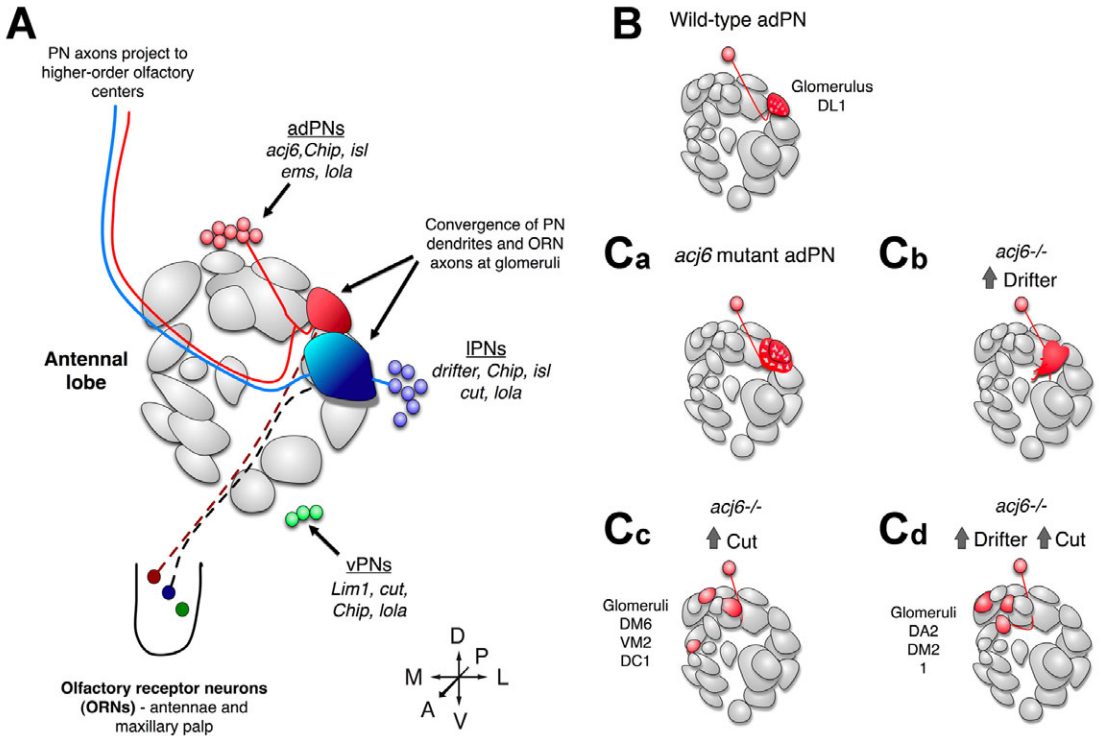

Fig. 4. Transcriptional control of dendritic targeting in the *Drosophila* antennal lobe. (**A**) Schematic organization of the *Drosophila* antennal lobe (AL). For simplicity, only a subset of glomeruli are shown. Projection neurons (PNs) from anterodorsal (adPNs, red), lateral (lPNs, blue) and ventral (vPNs, green) lineages project dendrites to glomeruli where they connect with olfactory receptor neuron (ORN) axons (a vPN projection is not shown here). PN axons extend to higher-order olfactory centers in the brain. Transcription factors discussed in this review are shown. The schematic of glomerular organization is based on data from Couto et al. and is adapted with permission (Couto et al., 2005). (*isl* is also known as *tup* – Flybase.) (**B-Cd**) Cell-autonomous alterations in transcription factor expression redirect dendrite targeting. (B) Wild-type DL1 adPN (red) dendrites normally target to the DL1 glomerulus (shaded in red in the AL). adPNs express *acj6* but not *drifter* or *cut*. (Ca-Cd) Dendrite targeting of genetically manipulated DL1 adPNs. (Ca) *acj6* mutants extend dendrites outside their normal glomerulus. (Cb) *acj6* mutant DL1 adPNs forced to express Drifter partially mistarget to more anterior glomeruli. (Cc) *acj6* mutant DL1 adPNs forced to express Cut target medial adPN glomeruli. (Cd) Expression of both Drifter and Cut in *acj6* mutant DL1 adPNs results in mistargeting of dendrites to medial lPN glomeruli. Schematic based on published data (Komiyama et al., 2003; Komiyama and Luo, 2007).

(Komiyama and Luo, 2007). Other transcription factors, including the POU-domain proteins Acj6 and Drifter (Ventral veins lacking – FlyBase), are expressed in a lineage-specific manner (Acj6 in adPNs and Drifter in lPNs) and specify which local AL glomeruli (see Glossary, Box 2) are targeted by dendrites (Komiyama et al., 2003; Komiyama and Luo, 2007). An example of how global and local transcriptional programs act together to mediate lineage-specific dendrite targeting is provided by studies of the innervation of the DL1 glomerulus by DL1 adPNs (Komiyama and Luo, 2007). DL1 dendritic targeting by adPNs depends on Acj6, and in *acj6* mutant clones dendrites are no longer restricted to glomerular boundaries (Komiyama et al., 2003; Komiyama and Luo, 2007) (Fig. 4B,C). The misexpression of Cut in *acj6* mutant clones shifts dendrites to distant glomeruli in the medial portion of the AL, but these glomeruli are ones that are normally targeted by adPNs, indicating that some lineage information is preserved (Komiyama and Luo, 2007) (Fig. 4C). By contrast, if Cut is misexpressed in *acj6* clones together with the lPN-specific transcription factor Drifter, the medial glomeruli that are targeted are mostly lPN targets (Komiyama and Luo, 2007) (Fig. 4C). Thus, lineage-specific PN targeting can arise from coarse and local instructions provided by combinations of transcription factors.

Additional transcription factors that control PN targeting include the LIM-HD factors Islet and Lim1 and the LIM-binding co-factor Chip (Komiyama and Luo, 2007), as well as the homeodomain transcription factor Empty spiracles (Ems), which is a fly homolog of mouse Emx1/2 that affects the targeting of adPNs at least partly by regulating *acj6* (Lichtneckert et al., 2008). Glomerular targeting in the AL also relies on the *longitudinals lacking* (*lola*) gene. The *lola* locus encodes at least 20 alternative isoforms, most of which are transcription factors of the BTB zinc-finger family (Goeke et al., 2003; Spletter et al., 2007). PNs that lack all *lola* isoforms show disrupted glomerular targeting, ectopic targeting phenotypes, and misregulation of at least some genes important for PN targeting, such as Lim1 (Spletter et al., 2007). The expression of single Lola isoforms does not rescue the loss-of-function phenotypes and produces additional dendrite defects, including disrupted process extension and elaboration outside of normal glomerular boundaries (Spletter et al., 2007). Thus, Lola isoforms are not simply interchangeable and *lola* molecular diversity is important for proper dendritic targeting. Together, the transcription factors identified thus far probably represent a subset of those required for complex glomerular map formation in the AL, and perhaps a full instructive code for glomerular targeting could be reconstructed with the identification of additional factors.

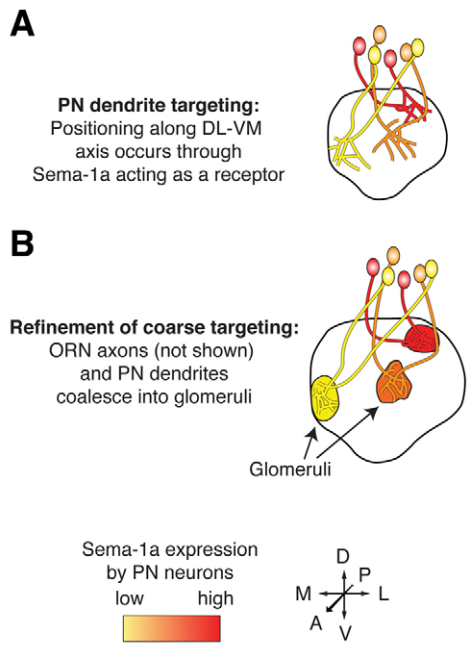

Fig. 5. Graded expression of Sema-1a directs projection neuron dendrite targeting. (**A**) Projection neurons (PNs) that express the highest levels of Sema-1a (red) form protoglomeruli at the most dorsolateral (DL) regions of the *Drosophila* antennal lobe (AL), whereas those that express lower levels target to more ventromedial (VM) regions (orange and yellow). (**B**) Olfactory receptor neuron (ORN) axons (not shown) and PN dendrites coalesce into mature glomeruli through axon-dendrite and dendrite-dendrite interactions (see text). Manipulation of Sema-1a levels in PNs causes autonomous switches in dendrite targeting [see text and Komiyama et al. (Komiyama et al., 2007)]. Adapted with permission from Komiyama et al. (Komiyama et al., 2007).

With the identification of transcription factors that control dendritic targeting, an important question that arises is how these factors are linked to the expression of specific guidance receptors, cell adhesion molecules or components of receptor signaling pathways that affect targeting choices (some of these signals are reviewed below). Links between transcription factor activity and the expression of specific axon guidance factors have been identified in several systems (Kania and Jessell, 2003; Labrador et al., 2005; Lee et al., 2008; Zlatic et al., 2003), but so far such relationships have not been established for dendritic targeting.

Control of dendritic guidance by extrinsic signals and receptors

The targeting of dendrites can occur via several strategies, including exuberant growth followed by selective branch stabilization, spatially restricted outgrowth at targets, and guidance of arbors with respect to major landmarks (Furrer et al., 2003; Morgan et al., 2006; Mumm et al., 2006; Ou et al., 2008; Wong and Ghosh, 2002). Studies of stereotyped axon guidance decisions have identified core cues and receptors (Garbe and Bashaw, 2004; Huber et al., 2003), and data so far indicate that in both vertebrate and invertebrate systems, several of these same families of molecules also function in the guidance and targeting of dendrites, including Semaphorins (Komiyama et al., 2007; Polleux et al., 2000), Robo and Slit (Furrer et al., 2003; Furrer et al., 2007; Godenschwege et al., 2002; Ou et al., 2008; Whitford et al., 2002) and Netrin and DCC/Frazzled/UNC-40 (Furrer et al., 2003; Ou et al., 2008; Suli et al., 2006).

Dendritic targeting by Semaphorins

The Semaphorins are a large family of secreted and membrane-bound proteins that mediate both attractive and repulsive guidance in axons primarily via Neuropilins and the Plexin family of transmembrane receptors (Huber et al., 2003). Roles for Semaphorins in dendritic morphogenesis were initially characterized in vertebrate systems, in which the secreted Semaphorin, Sema3A, acts through neuropilin 1 to orient apical dendrites of cortical pyramidal neurons (see Glossary, Box 2) towards the pial surface of the cortex (Polleux et al., 2000). A recent study that investigated the cues that mediate early dendritic targeting to domains of the *Drosophila* AL identified an important role for the transmembrane Semaphorin, Sema-1a (Komiyama et al., 2007). Sema-1a is present at graded levels across multiple PN dendrites, with the concentration increasing along one specific axis of the AL: the ventromedial-to-dorsolateral axis (Fig. 5). Gain-of-function and loss-of-function manipulations have demonstrated that Sema-1a levels specify initial targeting of PN dendrites, with increasing or decreasing levels of Sema-1a specifying more dorsolateral or ventromedial positions, respectively (Komiyama et al., 2007) (Fig. 5). It is not known how Sema-1a levels are specified in different PNs. Sema-1a function is cell-autonomous, indicating that it does not act as a ligand, but rather acts as a receptor for an as yet unknown ligand in this system (Komiyama et al., 2007). The coarse positional information provided by Sema-1a is presumably refined by subsequent dendrite-dendrite and axon-dendrite interactions (Komiyama et al., 2007; Zhu, H. et al., 2006; Zhu and Luo, 2004). These findings provide an intriguing example of a graded signal (in this case Sema-1a) that contributes to the development of a discrete sensory map (Komiyama et al., 2007; Luo and Flanagan, 2007). Interestingly, Sema-1a is multifunctional during AL development. Unlike in PN dendrites, which use Sema-1a as a cell-autonomous receptor, in ORN axons Sema-1a functions non-autonomously through Plexin A to mediate ORN axon-axon interactions and wiring specificity (Lattemann et al., 2007; Sweeney et al., 2007).

Dendritic guidance by Slit/Robo and Netrin/Frazzled/DCC

The *Drosophila* midline is a model for understanding the molecular cues that control axon navigation in the nervous system (Garbe and Bashaw, 2004). The midline is enriched with guidance cues that can attract or repel axons and functions as an intermediate target for crossing commissural axons. Critically important guidance molecules at the midline are the secreted Netrin proteins, which act through the attractive receptor Frazzled [Deleted in colorectal carcinoma (DCC)] to attract axons, and the secreted Slits, which repel axons through the Roundabout (Robo) receptors (Garbe and Bashaw, 2004).

Similar to axons, *Drosophila* motoneuron dendrites show stereotyped guidance decisions at the CNS midline. Slit and Robo receptors are required for the guidance of *Drosophila* motoneuron dendrites away from the CNS midline (Furrer et al., 2003). Likewise, Netrin, acting through Frazzled (DCC), promotes midline crossing by dendrites (Furrer et al., 2003). A role for Netrin/DCC in midline dendrite guidance has also been described for zebrafish octavolateralis efferent (OLe) neurons in the cranial motor system (Suli et al., 2006). Overexpression of Frazzled and Robo family members in *Drosophila* motoneurons can also impact the placement of their arbors along the medial-lateral axis of the neuropil (Ou et al., 2008). For example, the expression of Frazzled in the RP2 motoneuron results in expansion of medial branches nearer to the midline, whereas Robo or Robo2 (Leak – FlyBase) overexpression

reduces the number of medial branches (Ou et al., 2008). An interesting question is how a common pool of guidance cues can direct dendrites and axons from an individual cell to distinct regions of the neuropil (Furrer et al., 2003). This ability could arise from differential timing of guidance cue expression relative to axon and dendrite growth phases, differential regulation of guidance receptors (Godenschwege et al., 2002), or differential distribution of downstream signaling pathways (Polleux et al., 2000).

In addition to roles for Robo and Slit in regulating midline crossing of dendrites in some motoneurons, a close analysis of the anterior corner cell (aCC) motoneuron in *Drosophila* has revealed a requirement for Slit and Robo in the growth of collateral dendrite branches (Furrer et al., 2007). This role in dendrite outgrowth appears to extend to other systems as well. Notably, Slit and Robo had been previously implicated in apical dendrite growth in cortical pyramidal neurons (Whitford et al., 2002). Furthermore, studies of da neurons have shown that Slit-Robo interactions influence dendrite growth and branching in class IV neurons. In da dendrites, loss of Robo or Slit causes a reduction in the number of higher-order branches and an increase in the average length of the branches that remain, but has no effect on total dendrite branch length (Dimitrova et al., 2008). Interestingly, this study also found similar branching and growth phenotypes in *enabled* (*ena*) mutant da neurons (Dimitrova et al., 2008). *ena* encodes a protein that acts with Robo during repulsive axon guidance (Bashaw et al., 2000), indicating that pathways downstream of guidance receptors might be shared in at least some contexts by axons and dendrites. Together, these studies indicate that Slit and Robo play a conserved role in dendrite branch formation. It remains to be determined how repulsive and branching activities are regulated to give rise to cell-type-specific responses to patterned Slit expression.

Dendritic guidance and targeting mechanisms have to date been studied in only a few neuron types, but these studies have shown that even a limited repertoire of regulators can have diverse effects. For example, axon guidance cues also control dendrite guidance (Netrin, Slit, Semaphorins), and single guidance factors can have diverse activities. Targeting can be diversified through the combinatorial action of a few transcription factors and perhaps also by extensive alternative splicing. We still know little about how guidance cues interact to shape different dendritic arbors, or about how they diversify the targeting of neurons within particular regions of the nervous system. Moreover, the pathways that operate downstream of guidance receptors and transcription factors are almost entirely unknown. Finally, because the cues that mediate dendrite guidance have been identified largely through candidate gene studies of molecules that are known to guide axons, unbiased explorations might reveal unexpected new pathways.

Dendrite-dendrite interactions and dendritic territory formation

The studies reviewed above indicate that the growth and position of dendritic territories are strongly influenced by attractive and repulsive cues derived from their environment. Positive (adhesive) and negative (repulsive) interactions can also act locally between dendritic arbors to delimit the territories that they cover. Interactions between dendrites can function to maintain dendrites within a specific territory, as in fly PNs, which target to glomeruli in the AL (Zhu and Luo, 2004). By contrast, repulsive interactions between branches of the same cell can help to ensure that branches spread out evenly within their territory; if they occur between neighboring cells, these interactions ensure that dendrites stop growing at an appropriate size (Amthor and Oyster, 1995; Grueber et al., 2002; Grueber et al., 2003b; Kramer and Kuwada, 1983; Sagasti et al., 2005; Sugimura et al., 2003). Recent studies have begun to unravel the molecular basis of interactions between dendrites.

Dscam control of dendritic self-avoidance in *Drosophila*

In numerous cell types, dendritic branches that originate from the same neuron (sister branches) will not cross or fasciculate, and this self-avoidance (see Glossary, Box 2) ensures that dendritic arbors spread evenly across their territory (Grueber et al., 2002; Kramer and Kuwada, 1983; Millard and Zipursky, 2008; Sugimura et al., 2003). By contrast, branches from different neurons can co-exist. Selective self-avoidance presents a challenging problem in cell-cell recognition: how do dendrites recognize and avoid only sister processes from among the many cell surfaces in their immediate environment? Each neuron could, in theory, present a unique surface identity, but because large numbers of neurons occupy a limited space, this would demand a high degree of molecular diversity. Several studies in *Drosophila* indicate that *Down syndrome cell adhesion molecule* (*Dscam*), a locus that can generate 38,016 possible isoforms by alternative splicing, provides this requisite diversity and plays a crucial role in self-avoidance (Fig. 6). Dscams are transmembrane immunoglobulin (Ig) superfamily members that show robust homophilic binding via their ectodomains, with little or no heterophilic binding (Wojtowicz et al., 2004; Wojtowicz et al., 2007). Different neurons appear to express distinct combinations of Dscam isoforms, which could allow for discrimination of cell surfaces among neighboring processes (Neves et al., 2004; Zhan et al., 2004). Phenotypic analyses of mushroom body neurons indicate that sister axon branches that lack Dscam fail to segregate during development, consistent with a defect in self-recognition and repulsion (Wang et al., 2004; Wang et al., 2002; Zhan et al., 2004). Furthermore, animals in which Dscam ectodomain diversity has been reduced to a single isoform exhibit severe defects in neural circuit formation, indicating that isoform diversity is crucial for proper development (Hattori, D. et al., 2007).

Several recent investigations of Dscam function during dendrite morphogenesis in *Drosophila* indicate a key role in dendrite self-avoidance. Dendrites of olfactory PNs collapse into compact bundles in the absence of Dscam function, consistent with a role for Dscam in dendrite-dendrite repulsion and in the spreading of arbors (Fig. 6A) (Zhu, H. et al., 2006). Sister dendrites of da sensory neurons normally do not overlap with each other as they spread along the epidermis, and thus self-avoid (Fig. 3, Fig. 6B) (Grueber et al., 2002; Sweeney et al., 2002). However, da neuron dendrites that lack Dscam show extensive self-crossing (Fig. 6Bb) (Hughes et al., 2007; Matthews et al., 2007; Soba et al., 2007). Single Dscam isoforms rescue da neuron dendritic self-avoidance phenotypes (Fig. 6Bc). However, when two different da neurons (the dendrites of which normally overlap) are forced to express the same Dscam isoform at high levels, their dendrites show ectopic avoidance and dendritic field segregation (Fig. 6Bd) (Hughes et al., 2007; Matthews et al., 2007; Soba et al., 2007). Similarly, adjacent PN dendritic arbors forced to express the same Dscam isoform show dendrite separation and spreading across larger areas of the AL (Zhu, H. et al., 2006). Altogether, these data suggest that although single Dscam isoforms are sufficient for self-avoidance, Dscam molecular diversity allows sister branches to selectively recognize and repel each other, while permitting dendritic branches from different neurons to co-exist (Hattori, D. et al., 2007; Hughes et al., 2007; Matthews et al., 2007; Soba et al., 2007).

Several questions remain about how self-avoidance is carried out by Dscam. For example, how is adhesion between Dscam molecules converted to repulsive responses between dendrites? The

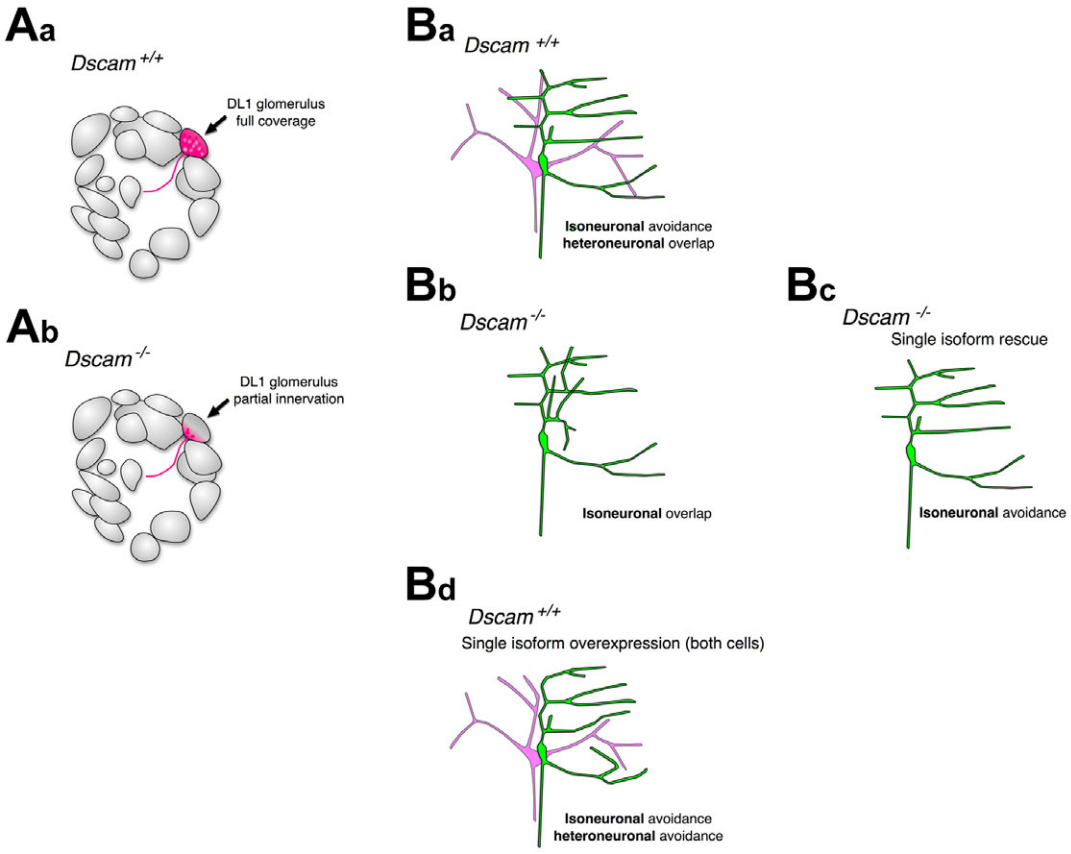

Fig. 6. Role of *Dscam* in dendrite self-avoidance. (**Aa**) Schematic of a wild-type projection neuron (PN) targeting the DL1 glomerulus in the *Drosophila* antennal lobe. Dendrites project throughout the entire glomerulus (red). (**Ab**) In a *Dscam* mutant DL1 clone, dendrites fail to completely innervate their target glomerulus (coverage area in red). Schematic based on published data (Zhu, H. et al., 2006). (**Ba-Bd**) Dscam control of self-avoidance in *Drosophila* da neurons. Schematic of two da neurons and their dendritic arbors (green and pink). (Ba) In a wild-type da neuron, dendrites of each cell self-avoid, but overlap with non-sister dendrites. Isoneuronal refers to the behavior of dendrites from the same cell (sister dendrites) and heteroneuronal refers to the behavior of dendrites from different cells. (Bb-Bd) Schematics of dendritic phenotypes observed in *Dscam* mutant animals. (Bb) In a *Dscam* mutant, the dendrites of each cell fail to self-avoid and overlap extensively throughout their arbors. (Bc) Single isoforms expressed in one *Dscam* mutant cell (green) rescue self-avoidance. (Bd) Overexpression of a single isoform in two cells with dendrites that normally overlap leads to repulsion between branches (heteroneuronal avoidance). Schematics based on published data (Hughes et al., 2007; Matthews et al., 2007; Soba et al., 2007).

cytoplasmic tail of Dscam is required for dendrite repulsion (Matthews et al., 2007), but the signaling events downstream of Dscam in dendrites remain to be elucidated. Questions also remain about how much Dscam diversity exists among different cell types, how stable or dynamic the Dscam isoform composition is in individual cells during development, and how repulsive self-avoidance cues interact with other extrinsic cues during dendrite patterning. Finally, the relationship between self-avoidance mediated by Dscam and self-avoidance control by Tricornered/Furry signaling (see below) is not yet understood.

Dendritic tiling

Tiling (see Glossary, Box 2) is an efficient way of covering an area completely but non-redundantly with neural processes, and is observed in diverse neuron types (Amthor and Oyster, 1995; Grueber et al., 2002; Huckfeldt et al., 2008; Lin et al., 2004; Millard and Zipursky, 2008; Perry and Linden, 1982; Wässle and Boycott, 1991; Wässle et al., 1981). Tiling of dendrites from neighboring, and functionally related, neurons presents an interesting cell recognition problem in development that remains poorly understood. Among da neurons, tiling is influenced by repulsive interactions between the dendrites of neurons in the same morphological class (Gao et al., 2000; Grueber et al., 2003b; Sugimura et al., 2003). The territories of some populations of tiling mammalian retinal ganglion cells (see Glossary, Box 2) are set up by intrinsic mechanisms with dendrite-dendrite interactions then fine-tuning these territories (Lin et al., 2004). The spatial distribution and territories of vertebrate retinal horizontal cells are established by transient homotypic interactions between neurites (Huckfeldt et al., 2008). Finally, *Drosophila* motoneuron dendrites in the CNS show a domain organization similar to tiling that does not appear to rely on dendrite-dendrite repulsion mechanisms (Landgraf et al., 2003). Instead, the dendritic domains of these neurons might be defined by as yet unidentified molecular boundaries set up early in development as the embryo is partitioned into parasegments (Landgraf et al., 2003). Thus, there are multiple possible strategies for defining dendritic field boundaries and tiled arrangements.

Molecular control of tiling in *Drosophila* da neurons

Among *Drosophila* da neurons there are two classes that tile the body wall independently (class III and class IV neurons), and thus tiling in each class is likely to require distinct recognition signals

(Grueber et al., 2002). Neither of these putative recognition signals is known, and Dscam appears to be dispensable for tiling in both classes (Hughes et al., 2007; Matthews et al., 2007; Soba et al., 2007). Several studies indicate that the seven-pass transmembrane cadherin Flamingo (Fmi; Starry night – FlyBase) acts cell-autonomously in dendrites to restrict their growth (Gao et al., 1999; Gao et al., 2000; Grueber et al., 2002; Kimura et al., 2006; Reuter et al., 2003; Sweeney et al., 2002). Fmi appears to be expressed in all da neuron classes and acts during early stages of arbor development to prevent premature dendritic elaboration and at later stages to prevent heteroneuronal branch overlap at a dorsal midline boundary between opposing class IV neurons (Gao et al., 2000; Kimura et al., 2006; Sweeney et al., 2002). The cadherin domains of Fmi appear to be dispensable for its early roles, but are required during its later functions in preventing the overlapping of dendritic fields (Kimura et al., 2006). Mutations in *Tropomyosin 2* cause similar overextension phenotypes as *fmi* mutants and the two genes show a genetic interaction (Li and Gao, 2003). The mammalian seven-pass transmembrane cadherins Celsr2 and Celsr3 have roles in promoting and restricting dendritic growth, respectively, in cultured rat hippocampal and cortical neurons (Shima et al., 2007). Experiments with chimeric and mutated proteins suggest that the different roles can be traced to an amino acid difference in their transmembrane domains (Shima et al., 2007). Homophilic binding between Celsr proteins causes increases in intracellular Ca^{2+}, with Celsr2 stimulating more Ca^{2+} release than Celsr3 (Shima et al., 2007). It is hypothesized that these different Ca^{2+}-release properties might activate distinct intracellular cascades to mediate opposing roles in neurite outgrowth (Shima et al., 2007).

A signaling pathway that involves Furry (Fry) and the nuclear Dbf2-related (NDR) kinase Tricornered (Trc) controls da neuron branching, self-avoidance and tiling (Emoto et al., 2004; Emoto et al., 2006). Trc restricts dendrite branching in all da neurons via negative regulation of the small GTPase Rac1, and promotes self-avoidance and tiling in class IV neurons in a Rac1-independent manner (Emoto et al., 2004). Neurons mutant for *hippo* (*hpo*), which encodes a Ste20 family kinase with important roles in tissue growth control (Harvey et al., 2003), show tiling phenotypes similar to *trc* mutants (Emoto et al., 2006). Trc and Hpo interact genetically, and an association between Trc and Hpo leads to the phosphorylation of Trc at a threonine residue shown to be important for normal dendritic tiling (Emoto et al., 2004; Emoto et al., 2006). Hpo signaling also has a role in maintaining a fully tiled arrangement of neurons through a second *Drosophila* NDR kinase, Warts (Wts), and Salvador, a WW-domain protein that interacts with Wts (Emoto et al., 2006). Studies of Hippo and Trc/Fry provide an anchor for future studies of tiling mechanisms, as they probably represent components of a signaling pathway that is important for dendrite turning in response to like-type dendrites (Emoto et al., 2004), with both upstream and downstream players yet to be identified. Candidate gene studies of receptors or adhesion molecules that might mediate tiling, perhaps by utilizing genome-wide RNAi libraries (Dietzl et al., 2007), might also provide insight into these pathways.

Self-avoidance and tiling control in mammals

What molecule or molecules regulate self-avoidance and tiling in vertebrates? No molecules had been identified until recent studies identified a crucial role for Dscam in a subset of amacrine cells (see Glossary, Box 2) (Fuerst et al., 2008). Vertebrate Dscam is expressed in the nervous system and engages in homophilic binding, but is not highly diversified by alternative splicing of the extracellular domain (Agarwala et al., 2001; Agarwala et al., 2000; Yamakawa et al., 1998). Examination of retinas from mice carrying a spontaneous mutation in *Dscam* revealed disrupted cell body spacing and neurite avoidance deficits in two amacrine cell populations that express Dscam: dopaminergic and bNOS-expressing amacrine cells (Fuerst et al., 2008). In the retina, Dscam functions in subsets of neurons, the arbors of which are segregated from one another in the inner plexiform layer (see Glossary, Box 2), implying that distinct cues regulate self-avoidance and tiling in other cell types that do not express Dscam. Dscam is expressed in the mouse brain, including hippocampus, cerebellum and olfactory bulb, and along the spinal cord (Agarwala et al., 2001; Yamakawa et al., 1998), and it will be important to examine whether it affects dendrite morphogenesis more broadly. Recent work suggests that Dscam is remarkably multifunctional, acting as an attractive or adhesive cue for synaptic matching (Yamagata and Sanes, 2008), and as a receptor for Netrin during axon guidance (Andrews et al., 2008; Ly et al., 2008). Likewise, the identification of other receptors or cell adhesion molecules expressed in select retinal cell types should help to identify the additional regulators of self-avoidance and tiling that are implied by the cell-type-specific action of Dscam (Fuerst et al., 2008).

Neuronal activity-dependent development of *Drosophila* dendrites

The control of dendritic development by neuronal activity is central to the formation of functional circuits and developmental plasticity in vertebrate nervous systems. Neuronal activity in vertebrates can influence dendrite growth, branching and stabilization, as well as induce retraction and pruning of dendrites to refine arbor projection patterns (Buttery et al., 2006; Chen and Ghosh, 2005; Ramos et al., 2007). In vertebrates, neural activity increases intracellular Ca^{2+} via voltage-gated calcium channels leading to the regulation of several intracellular signaling cascades, which can ultimately cause changes in transcription that affect dendrite development (Aizawa et al., 2004; Flavell and Greenberg, 2008; Gaudillière et al., 2004; Redmond, 2008; Redmond et al., 2002; Tao et al., 1998; Wayman et al., 2006).

Several recent studies indicate that neural activity can also have diverse effects on dendrite growth and branching of motoneurons in *Drosophila* (Duch et al., 2008; Hartwig et al., 2008; Tripodi et al., 2008). One recent study identified roles for synaptic contacts and presynaptic activity in restricting growth of embryonic aCC motoneuron dendrites (Tripodi et al., 2008). The effects on dendrite growth are spatially restricted and mediated by two separable cues: growth-slowing effects of synaptic contact are restricted to synaptic branches, while the growth of adjacent, but non-synaptic sister neurites is inhibited by transmitter release. The inhibitory effects of presynaptic transmitter release on non-synaptic sister neurite growth involves protein kinase A (PKA)-dependent signaling (Tripodi et al., 2008). These results raise the interesting possibility that a homeostatic response in motoneuron dendrites adjusts arbor size during development to ensure appropriate levels of synaptic input (Tripodi et al., 2008).

Studies of later-stage motoneurons show that genetic manipulations that increase intrinsic motoneuron excitability (by targeted expression of genetically modified potassium channel subunits) lead to increases in total dendritic growth (Duch et al., 2008; Hartwig et al., 2008). Dendritic overgrowth in cultured hyperexcitable larval motoneurons is prevented when voltage-gated calcium channels are inhibited with a toxin, and normal growth and neuronal activity-dependent responses require the immediate-early transcription factor AP-1 [a heterodimer of Fos (Kay) and Jun (Jra)] (Hartwig et al., 2008), defining a transcriptional pathway by which

neuronal activity can modulate dendritic architecture in *Drosophila*. Manipulations that increase or decrease intrinsic excitability of flight motoneurons likewise lead to dendritic overgrowth (increases in total dendrite length) and thus increase the amount of dendritic surface available for synaptic contacts (Duch et al., 2008). In these cells, increased excitability causes increases in the number of dendritic branches, whereas decreased excitability primarily affects dendrite elongation, indicating that changes in intrinsic excitability have diverse effects on dendritic growth (Duch et al., 2008). Overall, these results demonstrate roles for neuronal activity in *Drosophila* dendrite development. Further genetic studies to dissect the molecular mechanisms that underlie these diverse alterations in structure are likely to identify new components of neuronal activity-dependent pathways that shape dendrite morphology.

Conclusion

In recent years, our understanding of the molecular basis of dendritic growth, branching, targeting and field formation has greatly expanded. In addition to the genes and pathways characterized in recent studies and reviewed here, recent screening approaches spanning different *Drosophila* chromosomes have identified more than 70 new candidate genes from an RNAi-based approach (Parrish et al., 2006), a large number of candidate loci affecting axon and/or dendrite development of da neurons from forward genetic screens (Gao et al., 1999; Grueber et al., 2007; Medina et al., 2006; Satoh et al., 2008; Zheng et al., 2008) and, from a gain-of-function approach, 35 and 51 candidate lines affecting da dendrite morphology and central neuron morphology, respectively (Ou et al., 2008). Although these are only numerical results from various screens, they provide evidence that our understanding of the basic mechanisms of dendrite morphogenesis is still far from complete, but predict rapid progress in the years to come. In particular, progress is likely to come with the identification of the cell biological principles of dendrite growth and branching, with an increased understanding of how transcription factors control dendritic diversity and targeting through the identification of target genes, with the deciphering of the signaling pathways that lie downstream of attractive and repulsive dendritic guidance, and from determining the extent and molecular basis of the neuronal activity-dependent control of morphogenesis. An overarching challenge will be to determine how these numerous points of regulation are integrated by the developing dendrite branch to generate the diverse, yet type-specific, arborization patterns that occur throughout the nervous system. The ability to manipulate various features of dendritic arbors might ultimately help to provide insights into the functional relevance of distinct dendritic patterns.

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