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Dendritic development: lessons from *Drosophila* and related branches

Wesley B Grueber and Yuh Nung Jan[1]

Dendrites show remarkable diversity in morphology and function, but the mechanisms that produce the characteristic forms is poorly understood. Insect systems offer a unique opportunity to manipulate and study identified neurons in otherwise undisturbed environments. Recent studies in *Drosophila* show that dendritic targeting, branching patterns, territories, and metamorphic remodeling are controlled in specific ways, by intrinsic genetic programs and extrinsic cues, with important implications for function. Here, we review some recent advances in our understanding of dendritic development in insects, focusing primarily on insights that have been gained from studies of *Drosophila*.

Addresses
Howard Hughes Medical Institute, Departments of Physiology and Biochemistry, University of California, San Francisco, 533 Parnassus Avenue, Box 0725, San Francisco CA 94143, USA
[1]e-mail: ynjan@itsa.ucsf.edu

Current Opinion in Neurobiology 2004, **14**:74–82

This review comes from a themed issue on
Development
Edited by Barry Dickson and Christopher A Walsh

0959-4388/$ – see front matter

DOI 10.1016/j.conb.2004.01.001

Abbreviations

adPN	anterodorsal projection neuron
da	dendritic arborization
EcR	ecdysone receptor
es	external sensor
lPN	lateral projection neuron
MB	mushroom body
md	multi-dendritic
ORN	olfactory receptor neuron
PN	projection neuron
PNS	peripheral nervous system
TGF	transforming growth factor

Introduction

The dendritic arbors of insect neurons, like those of vertebrates, are renowned for their intricate and diverse branching morphologies. As the primary sites for synaptic or sensory input into neurons, cell-type specific dendritic morphology determines the way that information is presented to, and processed within, the nervous system. For example, the remodeling and *de novo* growth of dendrites during insect metamorphosis enables neurons to serve new functions, and facilitates behavioral loss and novel behaviors in pupae and adults [1–3]. Additionally, insect body wall muscles with similar locations and orientations are innervated by motorneurons with clustered dendritic territories in the CNS, perhaps allowing integration of the activity of subsets of the neuromuscular system ([4], see also Update). Elucidating the factors that control the morphogenesis of dendrites is, thus, fundamental to understanding how the nervous system is wired during development to produce coherent behavioral output.

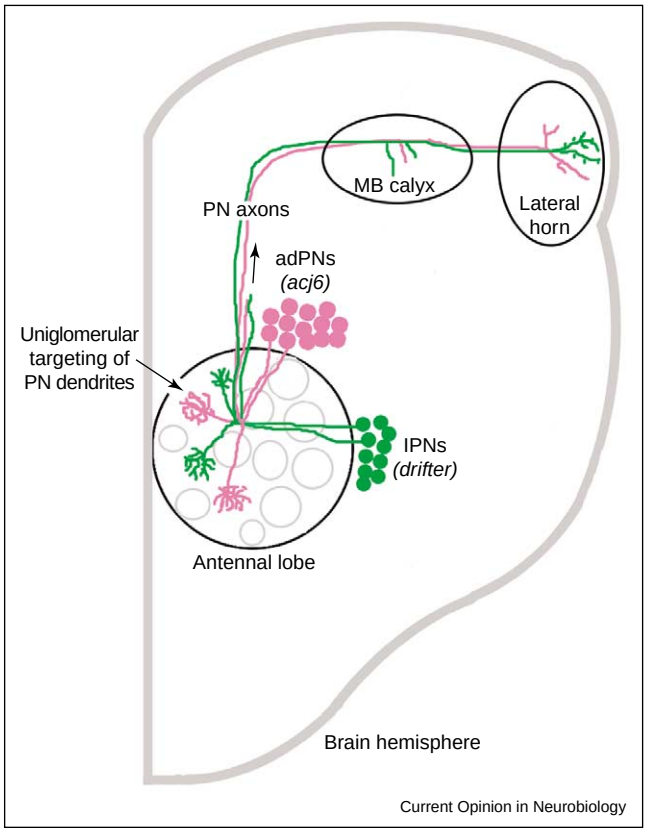
Dendrites progress through several stages of morphogenesis before achieving their mature form. They initiate growth from one or more sites, which, for insect neurons, can be from either the soma or a proximal segment of the axon. Growing dendrites target a particular receptive territory, within which they branch and achieve a type-specific architecture. Eventually, branching dynamics lessen and a mature territory and branching complexity is established. Understanding how dendrites accomplish each step of morphogenesis time after time, animal after animal, presents an enormously complicated problem. Until recently, the small size of *Drosophila* limited its use in this field, because the resolution and stereotypy afforded by studies of individual identified neurons is an absolute necessity. However, methodological advances have overcome some of the challenges that have been imposed by evolution. These advances include the labeling of small neuronal populations using the Gal4/UAS system or selective Green Fluorescent Protein reporter constructs [5,6•,7•,8], the visualization and manipulation of individual neurons using the mosaic analysis with a repressible cell marker (MARCM) strategy [9–13], and skillful application of retrograde and intracellular labeling techniques [4,14,15•]. By enabling analyses of identified neurons in largely undisturbed environments, these advances have opened the complexity of insect dendritic development to combined cellular and genetic analysis.

Here, we focus on the progress that has been made over the past few years in understanding targeting, branching, territory formation and remodeling of insect dendrites. We also refer the reader to other recent reviews that have treated some of the topics covered here, and also some topics that, owing to space limitations, we are unable to treat in detail [16–20].

Dendritic targeting and wiring specificity

An initial step in dendrite morphogenesis is the targeting of growing dendrites to specific territories. Some dendrites arborize more or less uniformly around the cell body, whereas, others grow preferentially in one direction and establish asymmetric or remote territories. Dendrites

Figure 1



The olfactory system of *Drosophila*. PNs (projection neurons) receive input from primary olfactory receptor neurons (not shown) at discrete glomeruli. Dendrites from two distinct PN lineages, the anterodorsal PNs (adPNs) (magenta) and lateral PNs (lPNs) (green), innervate intercalating, but non-overlapping glomeruli (only some dendritic projections are shown, other glomeruli are schematized as grey ovals). AdPNs express *acj6*, whereas lPNs express *drifter*. Axons from adPNs and lPNs project together to the mushroom body calyx, where they sprout collateral branches, and eventually terminate in the lateral horn. Drawing adapted from [10,22•,24].

of second-order projection neurons (PNs) of the olfactory system target glomeruli of the antennal lobe to receive input from primary olfactory receptor neurons (ORNs), while their axons target the mushroom body and the lateral horn of the protocerebrum (Figure 1; [21]). Dendrites appear to play a major role in the achievement of wiring specificity in this system. First, two major PN lineages, giving rise to the anterodorsal PNs (adPNs) and lateral PNs (lPNs) target dendrites to intercalated but non-overlapping glomeruli [10]. Second, before the arrival of ORN axons, PN dendrites create a coarse dendritic map that prefigures later glomerular organization (GSXE Jefferis, L Luo, personal communication; see also Update). Komiyama *et al.* [22•] found that the POU-domain (*Pit-1/Oct-1/2/Unc-86*) transcription factors 'abnormal chemosensory jump 6' (Acj6) and Drifter (Dfr) are expressed post-mitotically in adPNs, and in lPNs and their precursors, respectively [22•]. The uniglomerular targeting of adPN dendrites is disrupted in neurons lacking Acj6, whereas lPN targeting specificity is disrupted in neurons lacking Dfr. Conversely, misexpression of Acj6 in lPNs or Dfr in adPNs causes dendrites to target inappropriate glomeruli, some of which are characteristic of the alternate PN population. The glomerular class of individual PNs can be reliably predicted by their axon projection pattern, suggesting a close relationship between axon and dendrite morphogenesis [23,24]. Komiyama *et al.* [22•], therefore, asked whether axon and dendrite morphogenesis are linked in individual PNs. Indeed, *acj6* and perhaps also *dfr* also control terminal branching of PN axons in the lateral horn. Coordinate control of axon and dendrite morphogenesis in individual neurons would ensure that information is relayed properly through the olfactory system [22•].

Coordinated control of dendrite and axon morphogenesis might be widespread during the development of the *Drosophila* nervous system. For example, efferent motorneurons that innervate neighboring muscles (presumably, having similar functions) have overlapping dendritic arbors in the CNS, although these neurons might not share the same lineage or cell body position [4]. Furthermore, different peripheral muscles are innervated by axons having one of several distinct terminal types. These terminal types were shown to correlate with the complexity of central dendritic arbors [8]. The molecular mechanisms that coordinate central and peripheral morphogenesis of motorneurons are largely unknown. Genes that control selective dendritic clustering in the motor system could be the same ones that govern axon pathfinding and fasciculation in the periphery, such as cell adhesion molecules [4]. Notably, mutations in the plakin 'Kakapo' ('kak'; also known as 'Short stop', 'shot') disrupt terminal axon branching and also cause reduced central dendritic elaboration of RP3 motorneurons, perhaps due to defects in microtubule organization and the localization of axonal proteins [25]. Dendrites of *kak* mutant RP3 neurons form at their correct locations, and only contralateral dendritic processes (which are derived from the axon), not ipsilateral ones (which are derived from the soma), are significantly affected [25]. These observations lend support to the idea that the final form of different axon and dendritic projections involves both shared and distinct molecular machinery.

To find their intended targets, axons and dendrites must sometimes be guided through the same regions of the nervous system. Studies of such systems might provide a basic understanding of how axon and dendrite guidance are mechanistically different or similar. One such region is the CNS midline, a well-established model for studies of axon guidance [26,27]. Like axons, dendrites of efferent motorneurons RP2, RP3, and aCC either remain in ipsilateral neuropil, or project contralaterally across the

midline. Axons and dendrites that belong to the same motorneuron can cross, or not cross, the midline independently, raising the question of whether they use similar guidance cues. Roundabout (Robo) receptor, Commissureless (Comm), Netrin secreted protein and its receptor, Frazzled/DCC, mediate axon guidance at the midline and each has recently been found to fulfill similar roles in dendrites [15•]. Re-supplying wild-type protein to mutant neurons, along with a few neurons nearby, rescues the mutant phenotypes, suggesting that dendritic guidance is mediated cell-autonomously, independent of defects in nearby axons [15•]. How do axons and dendrites from the same neuron make their midline guidance decisions independently? Perhaps, different behaviors of axons and dendrites involve asymmetric trafficking of the same guidance molecules or downstream components of their signaling pathways [15•], or perhaps the differences are due to temporal regulation of guidance molecule expression or abundance, as axons typically grow before dendrites.

Intrinsic control of branch morphology

Just as axon and dendrite morphogenesis are coordinated in single cells to produce precise wiring of the nervous system, the activities of the intrinsic and extrinsic factors that regulate dendrite growth and branching must be properly orchestrated to achieve type-specific morphology. Recent studies of the *Drosophila* peripheral nervous system (PNS) indicate that dendrite identity is specified by transcription factors that are expressed before, and/or after, neuronal birth. The gene *hamlet* (*ham*) encodes a multi-domain zinc-finger protein that controls the feature differences between two lineally related neuron types; one with a single-dendrite morphology (that of the external sensory, or 'es' neuron) and the other with a multiple-dendrite morphology (the 'md' neuron) (Figure 2a; [28•]). In the developing nervous system, *ham* expression is limited to the es precursor and newly born es neuron [28•]. If es neuron precursors are made mutant for *ham*, their progeny acquire an md-like arbor. These transformed md neurons also acquire other characteristics of md fate, including the expression of reporters for an md-specific gene [6•]; however, when *ham* is driven ectopically in post-mitotic md neurons, branching is reduced, with no obvious change in the abundance of an md-specific reporter [28•]. Thus, *ham* plays a key role in the proper acquisition of cell identity in es precursors and, subsequently, influences the progress of dendrite branching in newborn neurons.

The homeoprotein Cut, which is expressed in many different *Drosophila* tissues, is another important regulator of type-specific dendrite morphology in the PNS [29•]. In an analysis of es organ specification by Cut, Blochlinger *et al.* [30] identified variable levels of expression in different md neurons. Cut was subsequently shown to control cell identity within the md group, but not the acquisition of a general md neuron fate [31,32]. The da (dendritic arborization) neurons are the most abundant group of md neurons [33], and have been subdivided into classes I-IV, in order of increasing dendritic branching complexity and territory size [12]. Levels of anti-Cut immunoreactivity correlate with dendrite morphology, with simpler neurons expressing low or no Cut, and highly branched neurons showing higher levels of immunoreactivity [29•]. Over-expression of Cut in low-level neurons causes territories to expand and arbors to acquire branching properties that are characteristic of higher Cut-expression neurons (Figure 2b). Conversely, higher-level neurons that are made mutant for *cut* were shown to acquire simplified dendritic branching morphologies (Figure 2b); furthermore, expression of a human Cut homolog also enhanced the growth and branching of da neurons that normally do not express Cut, raising the possibility of conserved roles for Cut transcription factors in cell morphogenesis [29•]. These data support the notion that proper Cut levels are necessary and sufficient to produce distinct fine dendritic morphologies in the PNS. How *ham* and *cut* regulate morphogenesis (presumably via transcriptional control) remain unanswered, but important, questions.

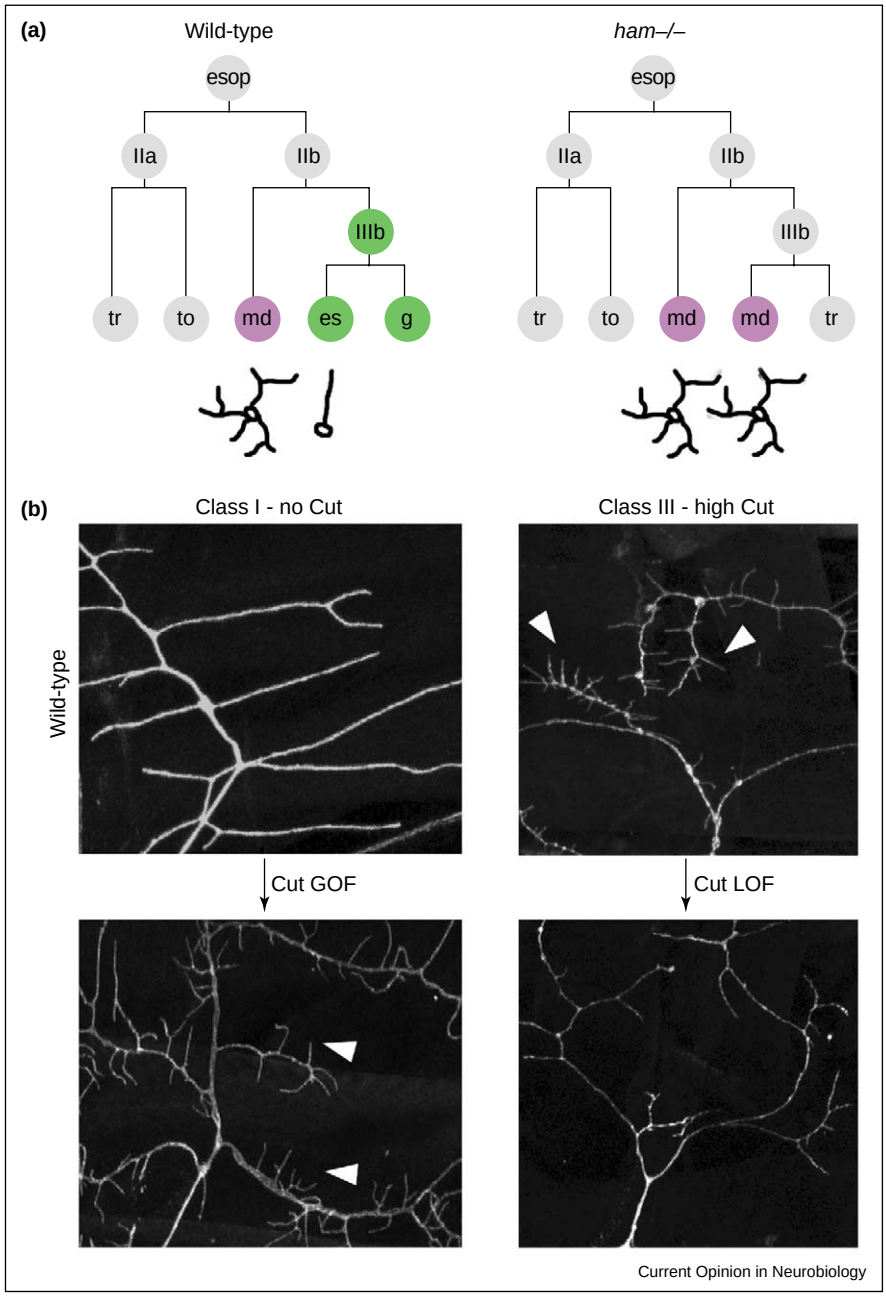
Intrinsic factors that limit dendritic growth

Each neuron has a characteristic dendritic territory that determines the extent and type of sensory or presynaptic input it receives. Unraveling the factors that define territory size is, therefore, an important challenge in studies of dendrite development and nervous system wiring. Several mutations that cause overextension of dendritic arbors were isolated from forward genetic screens [5,34,35]. Included in this group are the protocadherin *flamingo* (*fmi*, also known as 'starry night', 'stan') [5,34,36,37], the 'tramtrack'-like transcription factor *sequoia* (*seq*) [5,38], the actin-binding protein Tropomyosin II [35], and two novel mutations, *heron* and *kali* [34] that have mushroom body (MB) phenotypes that are reminiscent of those caused by *fmi* and *rhoA* mutations, respectively [34,39]. How do these genes normally limit dendritic growth? For *fmi* and *seq* mutants, the overextension of peripheral sensory arbors results, at least partially, from a change in the timing of dendrite outgrowth: in both cases, mutant neurons extend dendrites precociously [13,38,40]. Fmi is also thought to participate in the growth-inhibiting response of dendrites to neighboring fields [40] (discussed later). In *seq* mutants, dendrite overgrowth is correlated with stunted axon growth, suggesting a potential antagonism between these two morphogenetic events [38]. Possibly, axon growth precedes, and cannot overlap with, dendritic growth, as has been shown in retinal ganglion cells [41], and *seq* participates in a switch between these phases of morphogenesis.

Control of territory size by extrinsic factors

Many details of dendrite morphology, such as field sizes and precise branching morphologies, show appreciable

Figure 2



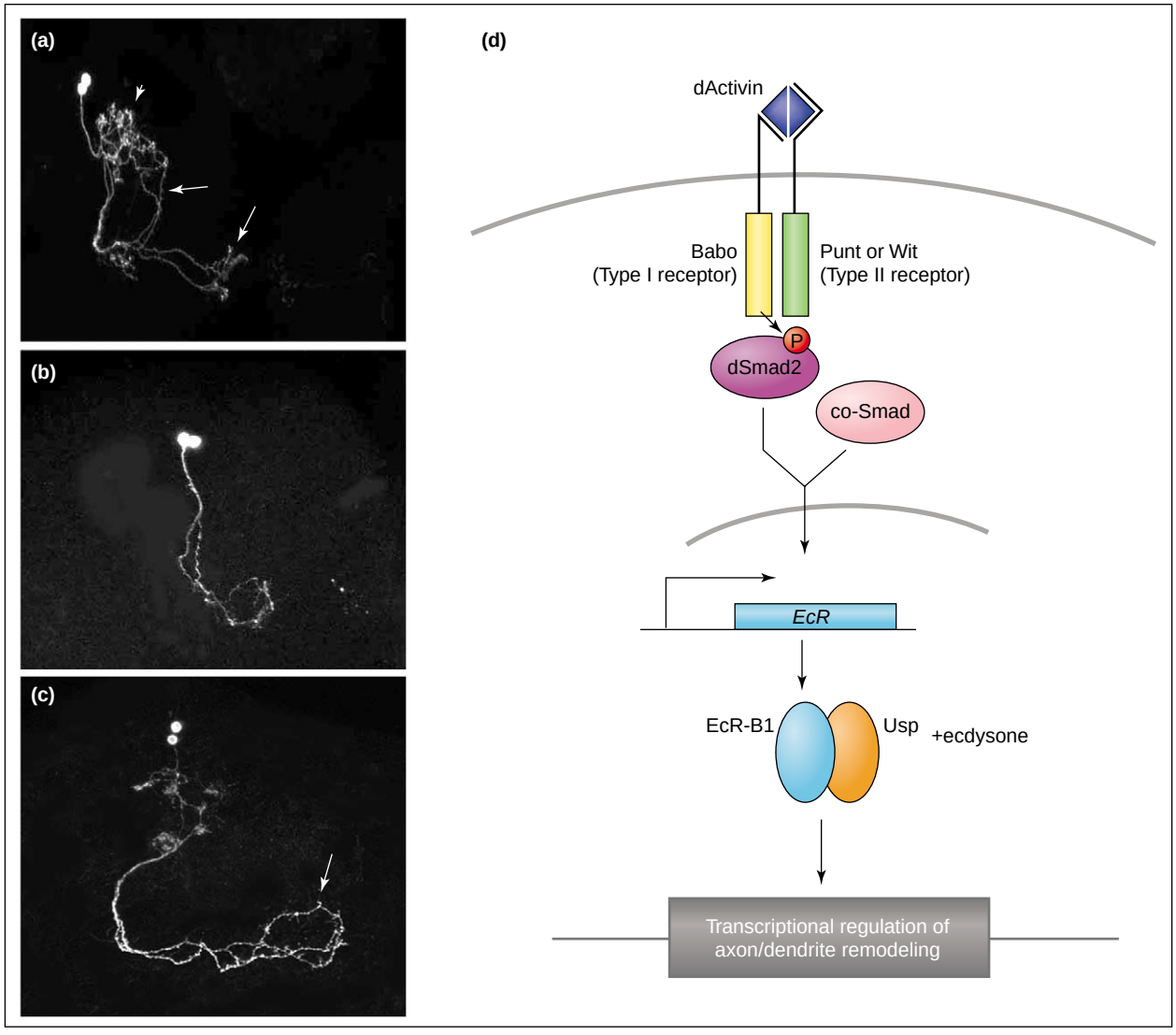
(a) Wild-type and *ham* mutant external sensory organ precursor (ESOP) lineages. Cells that express *ham* are depicted in green. In *ham* mutant lineages, the external sensory organ neuron is transformed to a multidendritic identity. Highly schematized dendrite morphologies are shown below each neuron. es, bristle neuron; g, glia; md, multidendritic neuron; to, tormogen; tr, trichogen. Diagram adapted from [28•]. **(b)** Effect of Cut overexpression and loss of function on dendritic arborization neuron dendrite morphology. Increasing Cut levels (left panels) causes morphological transformations toward the morphology of neurons expressing high Cut, whereas loss of Cut (right panels) from high-level neurons causes simplification of the class-specific fine branching morphology.

variation among cells of the same morphological class, and even among homologous identified neurons [42]. Such variation might be allowed for during evolution, and might even be selected for, because dendrites must integrate into bodies and nervous systems that are, likewise, undergoing dynamic growth. Achieving a functionally appropriate morphology, when faced with extrinsic change, requires that dendrites take developmental cues from their immediate environment. Interactions between dendrites, either belonging to the same cell (isoneuronal

dendrites) or belonging to different cells (heteroneuronal dendrites) operate in such a context, and can make a major contribution to the overall shape and branching morphology of an arbor. Recent studies have focused, primarily, on exclusionary interactions between dendrites, which limit dendrite growth and result in non-overlap between adjacent fields. Heteroneuronal dendrites could also participate in attractive interactions or show selective adhesive preferences, and indeed, recent data suggest that this might be the case in several systems ([4] see also Update). Here, we focus on exclusionary dendritic interactions, and experimental studies that have helped to clarify their role in neuronal morphogenesis.

Isoneuronal branch avoidance occurs broadly in invertebrates, as demonstrated by branch ablation experiments [7•,43–45], live imaging studies [6•,7•] and morphological observations [12,13,46]. Studies of self-avoidance in leech mechanosensory neurons suggest that self-recognition requires physical continuity of branches. The exclusion signal might be activity-based, relying on coincident firing of sibling processes or a synchronous local depletion of a limiting extracellular resource that is required for process extension and/or stabilization [45]. For insect systems, the mechanisms of isoneuronal avoidance remain uncharacterized, but are thought to require repulsive signaling between dendrites [6•,7•].

Figure 3



Two-cell clones of mushroom body γ neurons, **(a)** in larvae, **(b)** 18 hours after puparium formation and **(c)** in an adult fly. Arrows show prominent axon branches that are remodeled, an arrowhead shows dendrites that undergo regression. **(d)** The pathway leading to spatially regulated dendrite regression (adapted from [63•]). Images in (a–c) kindly provided by Tzumin Lee and Xiaoyan Zheng, University of Illinois.

Heteroneuronal branch exclusion can occur at selected territorial boundaries, such as the leech dorsal midline [44,47], and has, so far, been clearly demonstrated only in neurons that also show isoneuronal branch avoidance. When heteroneuronal branch exclusion occurs between all like-type dendrites, a 'tiling' of an entire receptive territory can be produced [6•,12,48,49]. Tiling is probably advantageous when conservation of fine spatial resolution is a necessity, such as when detecting visual stimuli [48], or when discriminating the location of origin of mechanical [49,50•], noxious or potentially damaging stimuli [51•,52•]. Studies of neurons with planar territories suggest that heteroneuronal exclusion and/or tiling involve repulsive interactions between dendrites [6•,7•,40,53,54]. Repulsive dendritic interactions have yet to be identified among groups of neurons with non-planar dendritic territories [55]. In the *Drosophila* da sensory system, laser ablation of tiling class IV neurons, before dendrites of adjacent cells meet, leads to invasion by neighboring dendrites [6•,7•,40]. Conversely, supernumerary class IV neurons (arising as a result of a mutation of the *ham* gene) [28•] can incorporate into the non-redundant tiling, indicating that dendrites, alone, are sufficient to provide reciprocal repulsive signals [6•]. The molecular basis of this signaling between dendrites is, as yet, unknown, but could involve contact-mediated repulsion, or possibly, repulsion following precisely local depletion of a trophic factor. Although these studies indicate that dendritic interactions are required to establish tiling, there is no clear consensus that they are required in the maintenance of non-overlapping dendritic fields. For some class IV pairs, territory boundaries appear to be static without persistent repulsion between abutting arbors [7•]. By contrast, interactions between the dendrites of other pairs appear to persist throughout larval life [6•]. Thus, although compensatory dendrite growth can follow the death or damage of mature neighboring neurons, it is, as yet, unclear which characteristics of particular dendrites encourage this property.

Remodeling dendrites

In holometabolous insects, such as *Manduca* and *Drosophila*, metamorphosis is characterized by the remodeling of dendrites into new pupal and adult forms ([1,2,3,14]; D Williams, JW Truman, unpublished data). During this process, larval-specific dendrites are pruned at the larval–pupal transition, followed by the growth and branching of adult-specific dendrites. Additionally, some neurons remain developmentally arrested in the larva and withhold dendritic development until metamorphosis [14]. Such diverse metamorphic responses are governed by steroid hormones, the ecdysones, acting through nuclear receptor protein heterodimers, consisting of one of three ecdysone receptor (EcR) isoforms (EcR-A, EcR-B1 or EcR-B2) and Ultraspiracle [56,57]. Tissues that show different metamorphic responses to ecdysone express different EcR isoforms [58], with EcR-B1 expressed at high levels in neurons that undergo dendritic pruning [59]. The isolation of isoform-specific EcR mutations [60,61] has allowed several groups to show that EcR-B isoforms, not EcR-A, appear to function generally and cell-autonomously to control dendritic pruning in *Drosophila* [61,62,63•,64]. Zheng *et al.* [63•] performed a genetic mosaic screen to identify additional genes that are required for the remodeling of MB neuron dendrites and axons (Figure 3). Mutations residing in *baboon* (*babo*) a TGF-β (transforming growth factor) type I receptor, and the *babo* transcriptional effector, dSmad2, blocked dendritic and axon remodeling [63•]; *babo* and *dSmad2* mutant neurons also failed to express normal levels of EcR-B1 and; remodeling defects that were observed in $babo^{-/-}$ MB neurons were partially rescued by ectopic expression of EcR-B1, but not EcR-A or EcR-B2 [63•]. These data indicate that Activin/TGF-β signaling is essential for patterned EcR-B1 expression in central neurons, and thus, spatial regulation of ecdysone-induced neuronal pruning and remodeling (Figure 3; [63•]). A major goal that remains is to understand how transcriptional cascades induced by isoform-specific EcR-B activity regulate the complex changes to the neuronal cytoskeleton that underlie dendritic remodeling.

Conclusions and future directions

Several recent studies have shown that the diversity and stereotypy of *Drosophila* dendritic arbors, combined with the many ways that cells can be manipulated in an otherwise undisturbed setting, offer opportunities to address fundamental questions about dendrite morphogenesis. We have discussed only a few of these questions here, but they have provided many directions for future studies. First, links have been uncovered between axon and dendrite morphogenesis, yet axons and dendrites are developmentally, morphologically and functionally different. What are the mechanisms that ensure the specification of dendrites and axons as distinct? And, conversely, how is their development coordinated in single neurons? Second, transcriptional control is emerging as a common means of regulating dendrite morphogenesis. With ever-improving transcriptional profiling technologies, it should be feasible to examine, at single cell resolution, the way in which key transcription factors regulate downstream target genes to control morphogenesis. Finally, only a portion of the *Drosophila* genome has been targeted in forward genetic screens for mutants affecting dendrite morphogenesis. Ethyl methanesulfonate (EMS), P-transposable element and RNAi (RNA interference) approaches, applied to a variety of systems that use different cell-type specific reporters, should help to reveal the spectrum of genes involved in dendrite outgrowth, branching, targeting, tiling and remodeling. With the genetic and transgenic approaches that are available in *Drosophila*, it should, ultimately, be possible to manipulate morphogenesis and further investigate the

in vivo physiological and behavioral importance of these stereotyped features of dendrites.

Update

Jefferis *et al.* [65], studying the origin of wiring specificity in the antennal lobe, found that PN neuron dendritic development occurs independently of presynaptic axons. They propose, instead, that dendritic adhesion between like-type neurons may provide cues that are required for PN dendritic patterning. Landgraf *et al.* [66•], studying the organization of the embryonic motor system, have shown that dendrites of motorneurons form a myotopic map in the CNS that represents the position of body wall muscles in the periphery. It is not yet clear how motorneuron dendrites are partitioned into their domains, although selective dendritic adhesion among functionally related neurons remains an interesting possibility [4].

Acknowledgements

We thank G Jefferis, M Landgraf, M Schubiger, CH Yang and B Ye for discussions and comments, and T Lee and X Zheng for contributing the confocal images used in Figure 3. The work in our laboratory is supported by National Institutes of Health (NIH). WB Grueber is supported by NIH 1 F32 NS43027-01A1. YN Jan is an Investigator of the Howard Hughes Medical Institute.

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• **Embryonic origins of a motor system: Motor dendrites form a myotopic map in *Drosophila***. *PLoS Biol* 2003, **1:**E41. DOI: 10.1371/journal.pbio.0000041.
Here, Landgraf and colleagues identify underlying principles of organization of the *Drosophila* motor system; namely, that dendrites of motorneurons are organized in the CNS in a myotopic map that represents the distribution of the muscles in the periphery. The authors also explore the mechanisms underlying the development of these dendritic domains and find that the cues responsible may be provided when the embryo subdivides into parasegmental units.

Now in press

The work referred to in the text as (D Williams and JW Truman, unpublished data) is now in press:

67. Williams DW, Truman JW: **Mechanisms of dendritic elaboration of sensory neurons in *Drosophila*: Insights from *in vivo* time lapse**. *J Neurosci*, in press.