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Molecular and cellular mechanisms of dendritic morphogenesis

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Summary

Dendrites exhibit unique cell-type specific branching patterns and targeting specificity that are critically important for neuronal function and connectivity. Recent evidence indicates that highly complex transcriptional regulatory networks dictate various aspects of dendritic outgrowth, branching, and routing. In addition to other intrinsic molecular pathways such as membrane protein trafficking, interactions between neighboring dendritic branches also contribute to the final specification of dendritic morphology. Nonredundant coverage by dendrites of same type of neurons, known as tiling, requires the actions of the Tricornered/Furry (Sax-1/Sax-2) signaling pathway. However, the dendrites of a neuron do not cross over each other, a process called self-avoidance that is mediated by Down's syndrome cell adhesion molecule (Dscam). Those exciting findings have enhanced significantly our understanding of dendritic morphogenesis and revealed the magnitude of complexity in the underlying molecular regulatory networks.

Introduction

Neurons distinguish themselves from other cell types partly by their size and shape, especially their unique and often highly branched dendritic trees that remain relatively stable up to decades. As appreciated by Ramón y Cajal a century ago, examining the morphological features of neurons is essential for our understanding of the whole nervous system [1]. Yet, the molecular logics underlying dendritic morphogenesis still remains largely undefined. Cell culture and *in vivo* imaging approaches are instrumental in revealing the roles of a number of extrinsic and intrinsic regulators of this process [2–5]. The application of genetic approaches to identifiable central or peripheral neurons in intact animals, especially *Drosophila*, has provided mechanistic insights into dendritic outgrowth and branching, dendritic targeting, and self-recognition [6–10]. In this review, it is impossible to cover all recent relevant studies, such as dendritic maintenance [10], spine formation [11] or regulation by neuronal activity [12, 13]. Instead, I will focus on transcriptional control, role of membrane protein trafficking, dendritic targeting and self-recognition and highlight some exciting new progresses mostly in *Drosophila* and challenges ahead.

Dendritic Diversity

The size and shape of dendritic arbors are major defining characteristics of neurons [14]. Therefore, the diversity of dendritic morphology closely correlates with the number of neuronal types. Based on some reasonable assumptions, thousands of neuronal types are probably

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present in primate cortex [15]. Comprehensive experimental categorization of all neurons seems to be a task as daunting as the current effort to document all species on the planet. However, studies in the retina offer a glimpse of the enormous diversity of dendritic branching patterns. For instance, the dendritic arbors of retinal ganglion cells (RGCs) are easily distinguishable from those of amacrine cells, and the difference between dendrites of Purkinje cells and granule neurons in the cerebellum is even more dramatic (Figure 1). In most mammalian species, there are about 12 types of RGCs and 30 types of amacrine cells [14]. Each type exhibits a distinctive combination of unique dendritic field size, branching complexity, and dendritic targeting area. Even among the same type of RGCs or amacrine cells, significant variability can be found in their total dendritic length, branch number, and dendritic field size, which are probably influenced by their local microenvironment and neuronal activity.

Dendritic morphology is also highly diverse among various invertebrate neurons (Figure 1). In *Drosophila* and other insects, central neurons are generally unipolar, with one process extending from the cell body and further differentiating into dendritic fine processes and a long-extending axon. For instance, projection neurons (PNs) in the *Drosophila* olfactory system target their dendrites to different glomeruli in the antennal lobe and axons to higher olfactory centers [16]. In the embryonic and larval peripheral nervous system (PNS), each abdominal hemisegment contains 44 sensory neurons scattered in different locations with dendrites ranging from a short single branch to a highly elaborated tree covering almost one-third of the hemisegment under the epidermis [17,18]. In the mammalian brain, neurons with similar dendritic trees are often densely packed together and probably perform redundant roles in a neural circuit. In contrast, each dendritic arborization (DA) neuron in the *Drosophila* PNS occupies a specific field with a stereotyped branching pattern. Therefore, each DA neuron is likely a unique type that receives specific inputs from the body wall and performs nonredundant function.

Transcriptional control of dendritic morphology

As in many other developmental processes, transcriptional factors (TFs) play key roles in dendritic morphogenesis through at least three different mechanisms, depending on the timing and location of their actions. First, some TFs expressed in neuronal precursor cells can influence the size and shape of the postmitotic neurons in the lineage, since they control many aspects of neuronal cell fate, including dendritic morphology. For instance, Sequoia is exclusively expressed in both precursors and postmitotic neurons in *Drosophila* embryos and seems to be a pan-neuronal TF that affects the morphology of all DA neurons with or without external sensory (ES) neuron transformation [19,20]. In contrast, some TFs can do so in a lineage-specific manner. For instance, Hamlet is transiently expressed only in the IIIB precursor preventing its progeny ES neuron from adopting the identities, including the characteristic dendritic branching pattern, of its sibling DA neuron generated from the IIB precursor, which also gives rise to the IIIB precursor [21]. Similarly, Ngn2 in cortical progenitors specifies the dendritic morphology of pyramidal neurons [22]. Identifying other molecules downstream of these TFs in neuronal precursors will shed light on early events of dendritic specification.

Another group of TFs is expressed in different types of postmitotic neurons and may play a general intrinsic role in dendritic morphogenesis. In mammals, reduced activity of NeuroD and CREST, which are widely expressed in the developing nervous system, results in decreased dendritic growth and branching [23,24]. However, the same general TF may have different functions in a cell type-specific manner. An interesting example is provided by a recent study on Spineless (Ss), a bHLH-PAS transcription factor required for the proper dendritic branching of all types of sensory neurons [25]. Loss of Ss function leads to decreased dendritic branching in neurons with more complex morphology but increases branching in neurons with simple

dendrites; however, each mutant neuron maintains its characteristic overall shape and remains easily identifiable [25]. This finding raises the possibility that the same TF may exert opposite effects on dendritic branching, depending on the cellular context.

The third mechanism is through cell-type specific transcriptional regulation. Intriguingly, the expression level of *Cut* in a specific DA neuron correlates, although not strictly, with its dendritic branching complexity. All neurons overexpressing *Cut* maintain their overall characteristic shapes but exhibit distinct phenotypes as in the case of *Ss*: it increases growth and branching dramatically in class I neurons that normally do not express *Cut* and to a lesser extent in class II neurons with low *Cut* expression. In contrast, the length of terminal branches in class IV neurons is reduced by about 40% [26]. Whether these shortened branches are actually transformed into actin-rich protrusions [27,28] characteristic of some class III neurons with the highest *Cut* level (such as *ddaA*) remains to be determined. Conversely, *Cut* mutant DA neurons all show a dramatically reduced dendritic tree: some of them do not resemble any wildtype neurons while others remain easily identifiable [26]. It is needed to determine whether partial loss of *Cut* in high-expressing neurons leads to the appearance of any dendritic features characteristic of neurons expressing *Cut* at lower levels.

TFs can also function in a neuronal type-specific manner to suppress dendritic growth and branching. *Abrupt*, a BTB/POZ-zinc finger protein, is specifically expressed in BD neurons and class I DA neurons and fulfills such a function. *Abrupt* does so in a dose-dependent manner and through a transcriptional program independent of *Cut* [29,30]. The effects of TFs such as *Abrupt* in postmitotic neurons are unlikely through cell fate change, at least judged by the expression of some molecular markers. The opposing effects of *Cut* and *Abrupt* indicate that they control the expression of distinct subsets of target genes, which remain to be identified. Another example of neuronal type-specific regulation was elucidated in a recent study on the Polycomb group (PcG) genes [31], which bind to specific regions of the genome and initiating the posttranslational modification of histones for gene silencing [32]. Interestingly, PcG gene activities seem to be required to maintain dendritic arbors of class IV only but not other DA neurons.

One widely used assay for dendritic morphogenesis is the elegant technique called the mosaic analysis with a repressible cell marker (MARCM) [33]. If the protein of interest and its zygotic mRNA are stable, the absence of visible phenotype in single PNS neuron MARCM clones may not indicate with certainty the lack of gene function, especially when the gene is required for early dendritic outgrowth. Even without these technical hurdles, it seems a major challenge to determine how different TFs interact with each other spatially and temporally to control dendritic morphogenesis: at least 76 TFs contribute to dendritic specification of at least one class of DA neurons in *Drosophila* [34], and more than 300 TFs show region-specific expression patterns in the mouse brain [35]. Identification of unique TFs that are dedicated to specific aspects of dendritic formation and their target genes will be especially informative in the future.

Role of membrane protein trafficking

For many neurons, a highly elaborated dendritic tree requires the need to develop and maintain a surface area thousands times bigger than other cells. In mammalian pyramidal neurons, the somatic Golgi apparatus is polarized toward the apical dendrites, and this polarization precedes the apparent asymmetric growth of apical versus basal dendrites. Moreover, the Golgi apparatus is also present outside of the cell body, in so-called Golgi outposts, which are usually located at branch points along the apical dendrites [36]. These interesting observations suggest that polarized secretory trafficking contributes to the formation of dendritic trees characteristic of pyramidal neurons. Indeed, this notion is supported by pharmacological and gene activity

manipulations in cultured neurons [36]. Golgi outposts and their preferential localization at dendritic branch points are also found in *Drosophila* DA neurons [37]. Mutations in genes encoding essential proteins involved in the secretory pathway lead to reduced dendritic trees but have no effect on axonal growth, further confirming the notion that polarized Golgi and the unique distribution of Golgi outposts are involved in dendritic morphogenesis [37].

Recent studies indicate that normal trafficking of membrane proteins for lysosomal degradation is also important for dendritic morphogenesis. Mutant DA neurons with reduced levels of Shrub, a key component in the endosomal sorting complex required for transport (ESCRT-III) involved in the formation of multivesicular bodies [38], exhibit reduced dendritic field and increased dendritic branching [39]. These changes are likely mediated by dysregulation of many transmembrane receptor molecules, including Notch [39].

Dendritic targeting

Dendrites must grow and branch, but they must also target specific location in neural circuits. For instance, different types of RGCs elaborate dendritic arbors within a specific lamina [14, 40]. In the spinal cord, different pools of motor neurons (MNs) extend their dendrites to different regions in the gray matter [41]. In the *Drosophila* olfactory system, PNs target their dendrites to each one of 50 glomeruli in the antennal lobe [9], which is lineage and birth-order dependent but is independent on presynaptic input [16,42]. Similarly, zebrafish RGCs show active dendritic growth toward their laminar target zones [40]; although, in mammals, dendritic pruning is thought to be the major mechanism of dendritic targeting.

The dendritic targeting of PNs is controlled by both TFs and cell-surface molecules. The POU-domain TFs Acj6 and Drifter are expressed in anterodorsal and lateral PNs, respectively, and are essential and sufficient to specify dendritic targeting of adPNs and IPNs in the antennal lobe [43]. These TFs together with Islet, Lim1, Cut, and Squeeze regulate different steps of dendritic targeting in a combinatorial fashion [44]. Cell type-specific transcriptional control of dendritic targeting is also illustrated in the spinal cord where the ETS-type TF Pea3 is specifically required for two MN pools to project their dendrites away from the central gray matter [41]. Unlike Acj6 and Drifter, the cell adhesion molecule N-cadherin does not play an instructive role to direct PN dendrites to a specific glomeruli. Instead, it is required for dendro-dendritic interactions to ensure the convergence of dendrites of PNs of the same class to a single glomerulus [45]. In contrast, the transmembrane protein Semaphorin-1a (Sema-1a) is expressed at different levels by different classes of PNs. It functions as the graded instructive signal in a cell-autonomous manner to direct PN dendrites to different glomeruli in the antennal lobe, as demonstrated by mistargeting of PN dendrites caused by loss of *sema-1a* or overexpression of Sema-1a at different levels [46]. It remains unknown whether Sema-1a is regulated by any of the TFs mentioned above and what are downstream effector molecules. This interesting finding not only offers novel mechanistic insights into dendritic targeting, but also highlights the importance of molecular gradients in different aspects of neural circuitry formation.

Dendritic tiling

The “stop” signals that limit the size of dendritic fields remain poorly understood. One can consider two different stop mechanisms: one that is dependent on dendritic contact and one that is contact-independent. If tiling is defined broadly as an organizational phenomenon for the same type of neurons to maximally cover a receptive field with minimal redundancy, then their dendritic trees may contact each other during development or have no contacts at all. Genetic mutations that disrupt either the direct dendro-dendritic recognition/repulsion or the intrinsic “ruler” that limits dendritic growth may result in a tiling defect.

One of the best-studied systems is the mammalian retina where the same types of RGCs tile the entire receptive field [47]. Chemical depletion of starburst cells [48] or genetic ablation of most RGCs during development [49] does not result in enlarged dendritic fields of the remaining neurons. These surprising findings indicate that the cell-intrinsic “ruler” plays a predominant role in determining dendritic field size. Similarly, wildtype class IV DA neurons in *Drosophila* exhibit normal dendritic fields when adjacent *PcG* mutant neurons fail to maintain their dendrites at the late larval stage [31], suggesting that dendritic repulsion is not required for maintaining mature dendritic field. However, laser ablation during embryogenesis [31,50–52] or in early larval stages [51,52] does result in the invasion of developing dendrites from adjacent neurons. The latter result was interpreted as the consequence of the lack of direct repulsive dendritic contacts during development. Still, some alternative interpretations such as the lack of competitors for the common target field [53] cannot be completely ruled out.

The same serine/threonine kinase pathway (*Trc/Fry* in *Drosophila* and *Sax-1/Sax-2* in *C. elegans*) may regulate both dendritic contact-dependent and contact-independent tiling. *Trc* or *fry* mutants show increased dendritic branching and significant overlap of dendritic fields between adjacent class IV DA neurons [54]. It seems these two phenotypes can be uncoupled, suggesting that *trc/fry* mutations specifically disrupt a signaling pathway downstream of dendro-dendritic recognition and repulsion, independent of their functions in dendritic branching. In *C. elegans*, ALM and PLM mechanosensory neurons extend unbranched single dendrites to cover the anterior and the posterior half of the animal, respectively. This segregation of dendritic fields requires the cell-autonomous activity of *Sax-1* and *Sax-2*: in mutants, PLM dendrites extend into the anterior half, although without any direct contact with ALM dendrites [55]. This phenotype seems to arise from the failure of PLM to slow its dendritic growth when needed. Considering this finding in *C. elegans*, it will be interesting to quantitatively analyze how *Trc/Fry* also regulate dendritic growth in *Drosophila*.

Dendritic self-avoidance

Unlike dendritic tiling, which refers to the spatial relationship between individual neurons, self-avoidance indicates the interactions between sister branches, first described for leech axons [56]. Dendritic self-avoidance is also found in different neuronal cell types, including RGCs [57] and *Drosophila* DA neurons [17,18]. It was proposed that *Trc/Fry* [54] and the tumor suppressor *Hippo* [58] control dendritic self-avoidance since mutations in their genes result in the apparent self-crossing of terminal dendrites of only some DA neurons but have no effect on dendritic bundling [59].

In contrast, mutations in the gene encoding Down’s syndrome cell adhesion molecule (*Dscam*) cause dendritic crossing as well as bundling of even secondary dendrites in all *Drosophila* DA neurons [59–61] (Figure 2). *Dscam* is a special molecule in the immunoglobulin superfamily, which has tens of thousands of alternatively spliced isoforms [62]. Each isoform shows a higher binding affinity to itself and may have unique functions in neural circuitry assembly, since *Dscam*-null mutations cause defects in axonal growth and branching, which can not be fully rescued by individual isoforms [63–65]. However, a single isoform can restore self-avoidance in *Dscam*-null mutant neurons. Moreover, overexpression of the same isoform in two different DA neurons that normally have overlapping dendritic fields causes dendritic repulsion [59–61]. These exciting findings suggest that the cell-surface recognition molecule *Dscam* mediates dendritic cell-avoidance. This notion has been suggested by earlier reports that *Dscam* is required for sister axon branches to segregate and that loss of *Dscam* in PNs causes clumped dendrites and a dramatic reduction in dendritic field size [63,64,66]. Intriguingly, it seems that *Dscam* is not required for the dendro-dendritic recognition in tiling, suggesting that the two processes may utilize different recognition mechanisms.

A number of questions remain to be addressed. First, the developmental stage at which Dscam exerts its function is unclear. In vivo live imaging indicates that the secondary dendrites of class I DA neurons are already well separated from each other around the end of embryogenesis and afterwards increase in length as the body size increases [19,52]. Therefore, other mechanisms must keep these branches far apart during larval development. To explain part of the observed mutant phenotypes, Dscam has to function during initial outgrowth of secondary branches. Detailed time-lapse analysis will reveal whether they stay apart during early development in a manner similar to axons in the leech embryo [67]. Second, it will be interesting to determine how many Dscam isoforms are expressed in each DA neuron and the extent of overlap between neurons. Third, it will be important to identify the downstream effector molecules and determine how they convert signals from Dscam homophilic binding to cause repulsion. Last but not least, Dscam does not have as many isoforms in mammals [62] and most dendrites in *Dscam* mutant DA neurons remain well separated from each other, indicating the presence of other mechanisms for dendritic self-avoidance.

Conclusions

The rapid progress in our understanding of dendritic morphogenesis is accompanied by an exponential increase in related studies that cannot be comprehensively covered by this review. It seems that total dendritic branch number and length, and likely the size of dendritic field, can be affected by numerous molecules, ranging from a large number of transcriptional regulators, membrane trafficking machineries, cytoskeletal or mRNA associated proteins, to many cell surface and intracellular signaling pathways and some previously unsuspected players. Maybe it is not that surprising at all, since dendrites are such delicate structures and subject to influences of many perturbations in the molecular regulatory network. Many interesting questions concerning more specific aspects of dendritic development remain to be further addressed, such as dendritic targeting and stop mechanisms. However, some of the major challenges now are not only to continue the discovery of individual genes but also to understand at the system level the functional relevance of dendritic morphological changes. Moreover, understanding the relationship between dendritic abnormalities and a number of neurodevelopmental and neurodegenerative disorders will also be of great importance.

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Figure 1. Dendritic diversity in mammals and flies

(a) Side view of a retinal ganglion cell. (b) Side view of an amacrine cell. (c) A cerebellum granule neuron. (d) A Purkinje cell, adapted from [1]. (e) A cortical pyramidal neuron. (f) A bipolar dendritic (BD) neuron. (g) A *Drosophila* projection neuron, adapted from [16]. (h) An external sensory (ES) neuron. (i) A dendritic arborization (DA) neuron adapted from [17] that is grouped as one of the class I DA neurons [18]. (j) A ddaC neuron adapted from [17] that is grouped as one of the class IV DA neurons [18]. Class I–IV DA neurons are grouped based on their increasing dendritic branching complexity [18]. The sizes of different types of neurons are not precisely proportional to each other.

Figure 2. Schematic representation of dendritic self-avoidance in *Drosophila* PNS
(a) A wildtype class I DA neuron showing well-separated secondary and tertiary dendritic branches. (b) A *Dscam* mutant DA neuron with dendritic bundling and crossing as highlighted by shaded dots, indicating a defect in self-avoidance.