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# Dendritic Morphogenesis

*Building an Arbor*

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## Abstract

Neurons are polarized cells with an axon and a dendritic arbor extending from the soma. Although the molecular mechanisms underlying axon guidance are rapidly being elucidated, those that regulate the orientation, morphology, and elaboration of dendritic processes are largely unknown. Several recent papers address these issues, and propose a set of molecular strategies that control dendrite development. This review discusses these papers and what they reveal to us about how cell signaling orchestrates neuronal form and connectivity during development.

**Index Entries:** Dendrite; axon; Trks; cyclic nucleotides; semaphorin; neuronal polarity; Notch.

## Introduction

Pyramidal neurons, the primary excitatory neurons of the cortex, function to convey information to various cortical and subcortical structures. These cells are highly polarized with their major orientation axis perpendicular to the pial surface. Pyramidal neurons have a single axon that grows down towards the white matter, and multiple, short basal dendrites that remain mostly restricted to the same layer as the soma. In addition, they have a single apical dendrite that extends towards the pial surface, crossing several cortical layers en route, and then branches extensively. The resultant arbor integrates information received from superficial cortical layers. Hence, apical dendrites play a critical role in cortical information processing. The molecular mechanisms underlying dendrite formation in the developing cortex are starting to be elucidated. Several recent publications have identified familiar favorites, implicated in cell signaling in other developmental processes, as being important. These include molecules known to play a role in axon guidance, neuronal survival, and neurogenesis. The recent data suggest these cues are also important in dictating the direction, shape, and extent of dendrite branching and will be dealt with sequentially below.

## Orientation Signals for Dendrite Growth

Why does the apical dendrite initiated by the pyramidal cell always extend towards the pial surface? A recent paper addresses this question, and also provides an elegant explanation for why the axons of these cells extend in the opposite direction *(1).* Such directed outgrowth of neuritic processes suggests the involvement of chemotropic mechanisms, known to play critical roles in directing axon trajectories *(2).* Chemotropic cues secreted from distant sources diffuse and form gradients that influence the directions taken by extending axons. These cues are called chemoattractive or chemorepulsive based on their ability to reorient axons towards or away from their source, respectively.

To test the possibility that an extrinsic cue(s) dictates the orientation of apical dendrites, a series of experiments were carried out in vitro using a "slice-overlay assay." This assay was used previously to examine the control of extracellular signals over cortical-axon guidance *(3),* and more recently to assess their influence on dendritic morphogenesis *(1).* Dissociated embryonic day 15 (E15) cortical neurons from GFP-expressing transgenic mice were plated onto wild-type neonatal cortical slices in culture, and the morphology of the GFP-positive cells that differentiated into neurons exhibiting a typical pyramidal cell morphology (one major apical dendrite and several basal dendrites) were examined after 5 d *(1).* The majority of GFP-positive cells extended their readily identifiable apical dendrite towards the marginal zone (MZ) when transplanted onto the cortical plate (CP) (Fig. 1A). In contrast, apical dendrites were randomly oriented when cells were placed on the white matter (WM). Because cells placed in the CP acquired the correct morphology in vitro, the authors proceeded to examine possible tissue and molecular influences on dendrite orientation using a modification of the slice-overlay assay. The authors placed the WM of one cortical slice adjacent to the MZ of a second slice prior to transplanting the GFP-positive neurons onto the WM (Fig. 1B). Using this configuration, it was shown previously that the MZ repulses pyramidal axons *(3).* In contrast, the recent study found apical dendrites were directed towards the MZ of the second slice *(1).* This result was independent of whether the axons were oriented appropriately. These data suggest that a molecule(s) secreted from the MZ is capable of attracting the apical dendrite to the pial surface.

A clue as to the molecular nature of the secreted cue was provided by the analysis of semaphorin 3A (Sema3A) null mice *(3,4).* Sema3A is a member of the semaphorin family that is expressed in the developing CP *(5),* and was previously shown to be chemorepulsive for cortical axons *(3).* In Sema3A null mice, many of the cortical neurons had apical dendrites that were not directed towards the pial surface (Fig. 1C). The disorientation observed was shown qualitatively, but not quantitatively, to be comparable to that encountered when GFP-positive neurons were placed on the WM away from the endogenous source of Sema3A. Furthermore, in the slice-overlay assay, a blanket source of exogenous Sema3A completely disrupted the orientation of apical dendrites of GFP-positive neurons placed in the CP, whereas a localized source of Sema3A attracted the apical dendrites of the GFP-expressing neurons. Taken together, these data suggest that a Sema3A gradient acts to orient and attract apical dendrites towards the pial surface. In the knockout animals, axons appear less disoriented than the apical dendrites *(1,3).* Indeed, in these experiments pyramidal neurons were retrogradely labeled by injecting fluorescent carbocyanine dyes into the WM of cortical slices, indicating that a significant number of cells with axons had projected correctly towards this area. These data suggest the action of redundant cues in the orientation of cortical axons but not apical dendrites. The complete subcellular and cellular selectivity of Sema3A action has yet to be determined; an effect on basilar dendrites was not mentioned, nor was the morphology of other cortical cell

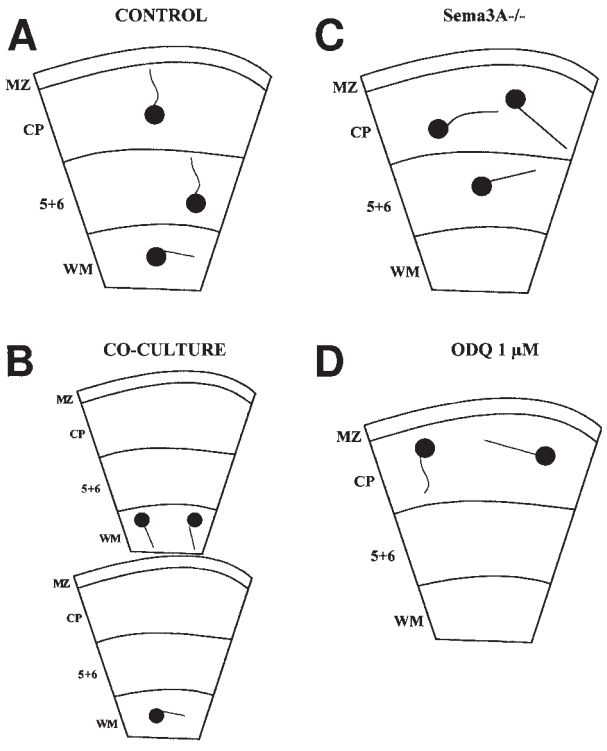


Fig. 1. The marginal zone (MZ) secretes a molecule that is chemoattractive for the apical dendrites of pyramidal neurons: A cortical slice overlay assay was used to investigate the cellular and molecular mechanisms involved in the orientation of apical dendrites of cortical neurons towards the pial surface. Pyramidal neurons from an E15 GFP transgenic mouse were placed on a neonatal cortical slice and cultured for 5 d. **(A)** In control, cells placed in the cortical plate (CP) or layers 5 and 6 projected an apical dendrite towards the MZ. In contrast, dendrite orientation was random when cells were placed in the white matter (WM). **(B)** GFP-positive neurons placed in the WM showed a strong orientation preference towards the MZ of a second cortical slice placed nearby. **(C)** A role for Sema3A was suggested by the observation that dil-labeled dendritic projections were oriented in a random fashion in a transgenic mouse null for Sema3A. **(D)** Slices incubated with an SGC inhibitor revealed the involvement of SGC. SGC inhibition resulted in the dendrites of GFP-positive neurons being oriented randomly.

types analyzed. A caveat for Sema3A's role as a chemotropic regulator of cortical neuron morphology is that Sema3A is expressed throughout the developing CP. The authors postulate, however, that the higher density of neurons in the superficial layers of the CP might allow for a Sema3A gradient to be generated.

Incubating the GFP slice cultures with a function-blocking antibody to Neuropilin–1, a high-affinity semaphorin receptor, partially disoriented the dendritic projections, pointing to the receptor's involvement in mediating Sema3A signaling. Intriguingly, immunohistochemical analysis showed that Neuropilin-1 was present on both axons and dendrites of cortical neurons. So why is the axon not also directed in the apical direction given that it too expresses one of the necessary components of the receptor complex? Recent studies investigating how cyclic nucleotides influence the polarity of the response of axonal growth cones to guidance cues provide a possible explanation *(6).* Experiments with *Xenopus* spinal cord axons show that the chemorepulsive effect of Sema3A can be converted to chemoattraction when intracellular cyclic GMP (cGMP) levels are elevated pharmacologically *(8).* Thus, one possibility is that an asymmetrical distribution of cGMP within the cortical neuron could allow apical dendrites and axons to sense Sema3A as attractive or repulsive, respectively *(1).* Polleux and colleagues *(1)* provide support for this idea by showing immunocytochemically that soluble guanylate cyclase (SGC), the enzyme that synthesizes cGMP, is found at higher levels in the pole of the cell where the apical dendrite is generated, and subsequently in the proximal apical dendrite itself. Such assymetric localization was characteristic of neurons developing in culture and in vivo. Moreover, addition of either 1H-[1,2,4] oxadiazolo [4,3-a] quinoxalin-1-one (ODQ), a specific inhibitor of SGC, or Rp-8-pCPT-cGMPS, a specific inhibitor of all three cGMP-dependent protein kinase isoforms, to the slice-culture assay disrupted oriented dendrite outgrowth but not outgrowth itself (Fig. 1D). Because pyramidal neurons still sprout apical dendrites

it seems most likely that SGC's involvement in dendrite formation is restricted to determining the site of dendrite generation and not dendrite initiation. ODQ also inhibited the chemoattractive influence of a localized source of Sema3A. These data strongly argue that high levels of cGMP are required for Sema3A's chemoattractive effect on apical dendrites. Impairing SGC function, however, did not cause repulsion of dendrites by Sema3A, suggesting that changing cGMP levels does not act as a polarity switch. This is in contrast to a recent study showing that altering cGMP levels in *Xenopus* spinal-cord growth cones switched the polarity but not the magnitude of the axonal response to Sema3A *(8).* Potentially, cyclic nucleotides acting downstream of the same extrinsic cue regulate different signal transduction mechanisms in axons and dendrites. The observation that SGC inhibition had no effect on the directed growth of cortical axons towards the white matter also supports the idea that distinct transduction mechanisms are compartmentalized within the cell *(1).*

In addition to providing convincing evidence for the involvement of a semaphorin in orienting cortical dendrite growth, these experiments are the first to demonstrate that separate compartments of the same neuron can respond differently to a single guidance cue based on the asymmetric localization of cyclic nucleotide-dependent mechanisms. Interestingly, brain-derived neurotrophic factor (BDNF) also has differential effects on a cell's neurites; BDNF promotes axonal and inhibits dendrite arborization of *Xenopus* retinal ganglion cells (RCG) *(9).* The polarity of the chemotropic effect of BDNF on *Xenopus* spinal-cord neurons was shown to be dependent on intracellular cyclic nucleotide levels, but in this case cyclic AMP (cAMP) levels *(10).* Thus, it is possible that adenylate cyclase similarly regulates the differential response of RGC axons and dendrites to BDNF. Alternatively, this phenomenon could be partially explained, as discussed next, by the combinatorial expression of isoforms of the BDNF receptor, tyrosine receptor kinase B (TrkB).

## Signals for Patterning the Dendritic Arbor

Pyramidal neurons in different cortical layers have the same basic morphological organization, but have very different dendritic shapes and sizes. Presumably, the variability reflects differences in function. Studies indicate that the neurotrophins may play a large role in patterning dendritic arbors *(11,13).* Neurotrophins and their receptors, the Trks, are expressed differentially in the various cortical layers. Exogenous application of any one of the four neurotrophins to P14 ferret visual cortical-slice cultures altered specific patterns of dendritic growth in distinct ways *(11).* For example, BDNF stimulated dendrite outgrowth of neurons in layer 4, but inhibited outgrowth from layer 6 neurons. In contrast, neurotrophin-4 (NT-4) enhanced dendrite outgrowth of layer 6 neurons. An endogenous role for neurotrophins in patterning dendritic growth was confirmed subsequently with specific Trk receptor bodies (Trk-IgGs) used to inhibit Trk function *(12).* Interestingly, basal and apical dendrites responded independently of one another to different neurotrophins *(11).* In fact, results from the Trk inhibition experiments indicate that endogenous neurotrophins may function to regulate only basal and not apical dendritic morphogenesis *(12).* Thus, the response of individual neurons to each of the four neurotrophins is highly specialized and complex, with the effects varying depending on the particular neurotrophin, cortical layer, and region of the dendritic arbor concerned.

These data, similar to those discussed earlier with regards to the differential effects of Sema3A on axon and dendrites *(1),* argue for the compartmentalization of neuronal responses to extrinsic cues. In the case of Sema3A, it was asymmetrical localization of SGC within the cell that provided a general mechanism whence cellular responses can be polarized *(1).* Similarly, differences in signal transduction systems and patterns of gene expression might lead to quite different dendritic growth responses to the same neurotrophin signal *(12).* Yacoubian and

Lo *(13),* recently invoke an additional receptor-based mechanism to explain this phenomenon, whereby the effects of a given neurotrophin also depend on the complement of Trk receptor isoforms expressed by the neuron. These authors examined the role of Trk receptors on dendrite branching. Trks include TrkA, TrkB, and TrkC *(14).* TrkB in particular is highly expressed in the cortex. Currently, three mammalian TrkB isoforms have been identified, the full-length isoform and two truncated isoforms, T1 and T2 *(14).* The latter both lack a cytoplasmic tyrosine-kinase domain, and can act as negative regulators of full-length TrkB *(15,16),* or may signal using their own transduction cascade *(17).*

Yacoubian and Lo *(13)* examined a role for the two major TrkB isoforms, full-length Trk B and T1, in regulating the dendrite morphology of pyramidal neurons of layer 6 of the visual cortex. Using particle-mediated gene transfer, organotypic slices prepared from P14 ferret visual cortex were transfected with the TrkB isoforms. At this age, only the full-length TrkB is expressed at appreciable levels. Dendritic morphologies of transfected neurons were visualized independently by co-transfection with blue fluorescent protein. While both transfected proteins were uniformly distributed over the cell, the effects of the two TrkB isoforms were different. Both increased dendritic growth, but in separate regions of the developing arbor and in distinct ways. Misexpression of full-length TrkB increased the number of short branches in dendritic regions proximal to the soma, whereas T1 caused net extension of pre-existing dendrites in regions more distal. Several specific issues need to be resolved before the involvement of Trk receptors in dendrite outgrowth is completely understood. First, we do not know if the net extension observed in the transfection experiments is due to an enhanced rate of dendrite extension or an inhibition of neurite retraction. Second, the outgrowth stimulated by either construct was similar for basal and apical dendrites, whereas previously inhibiting endogenous Trk signaling only affected the growth of basal dendrites *(12).* Finally, it is unclear why these data contradict observations made earlier, using the same experimental model, indicating that BDNF was inhibitory to dendrite outgrowth of layer 6 neurons *(11,12).*

Interestingly, the two isoforms were mutually inhibitory when co-activated with BDNF or neurotrophin-4/5 (NT-4/5; *13).* For instance, providing excess BDNF enhanced the addition of proximal branches in control and full-length TrkB transfected neurons, but surprisingly blocked the distal growth induced by T1 transfection. The latter inhibition presumably involved the activation of endogenous full-length TrkB and indeed was reversed by application of a kinase inhibitor, K252a. In contrast, T1-transfection inhibited the stimulatory effects of BDNF on proximal dendritic growth. It was postulated that proximally T1 acted as a dominant-negative to inhibit the activation of full-length TrkB by BDNF *(15,16),* given that excess ligand was unable to reverse the effects of T1 transfection *(13).* In contrast, in more distal dendrites, excess ligand impaired the T1-dependent induction of outgrowth, denoting a different mechanism of T1 action. Possibly, T1 in distal dendrites acts to sequester a ligand, or activates its own transduction mechanism *(17).*

In summary, these data suggest a receptor-based mechanism by which a single extrinsic cue can differentially regulate branching in separate regions of the dendritic arbor. In this case, the actions of neurotrophins such as BDNF and NT-4/5 depend on the complement of TrkB receptors expressed by the pyramidal neurons. The authors hypothesize that the ratio of T1 to full-length TrkB determines what mode of dendritic growth is produced. Because the corresponding levels of T1 and full-length TrkB change dramatically during development, so might the type of dendritic outgrowth. Early in embryonic development, only full-length TrkB is expressed, with T1 expression increasing postnatally and predominating in the adult *(18,19).* Thus BDNF could promote dendrite formation and branching early in development via the full-length receptor, and enhance the extension of pre-existing branches via T1 later in development *(13).* Pre-

sumably, sufficient activation of T1 overcomes the inhibition of distal-neurite extrusion caused by neurotrophin activation of the full-length TrkB. The possibility of generating many diverse responses to a single ligand by the combinatorial expression patterns of various TrkB isoforms is heightened by the identification of many Trk isoforms with extracellular or cytoplasmic insertions and deletions in the avian visual system *(20,21).* Different receptor combinations, however, are not sufficient to explain the differential responsiveness of different classes of dendrites to Trk ligands. Similar to what was discussed for Sema3A, differential localization of signaling cascades to different regions of the neurons must also be present. How else, for example, would T1 act as a dominant negative for full-length TrkB in proximal dendrites and perhaps activate its own separate signaling mechanism in more distal compartments?

## Stop Signals for Dendritic Growth

As with most growth processes, in addition to having signals that promote growth, it is important to have cues that subsequently regulate and limit that growth. Indeed, the dendritic arbors of cortical neurons stop growing upon reaching a mature size *(22).* Notch1, a cell-surface receptor, appears to be an important mediator of the stop signal. One way to ensure that the dendritic arbors of individual pyramidal cells do not overlap is to have dendrites stop growing when they contact the processes of other neurons. Notch is a perfect player for mediating this important regulatory influence because this receptor mediates interactions between cells *(23–25).* Processing of full-length Notch generates two fragments that associate with each other at the membrane *(26).* The larger fragment (p180) contains most of the extracellular domain, whereas the smaller fragment (p120) contains the transmembrane and cytoplasmic domains. Notch has partners in crime, its ligands Delta, Jagged, and Serrate. Upon ligand binding, the cytoplasmic domain of the receptor (Notch ICD) is cleaved and translocates to the nucleus.

A cluster of recent papers provide strong evidence that Notch inhibits dendritic growth and thus may act as an important regulatory switch for dendritic morphogenesis *(27–30).* To explore the role of Notch in dendritic morphogenesis, it was first important to place the appropriate players within the developing CP *(29,30).* Both Notch1 and Notch2 receptors, and their ligands Delta1 and Jagged 2, are expressed throughout the cerebral cortex *(30).* Given that Notch ICD is thought to be the critical component mediating the downstream effects of Notch-receptor activation *(26,31,32),* various methods were used to investigate the subcellular localization of the intracellular domain in developing cortical neurons in vitro and in vivo *(29,30).* Interestingly, Notch ICD is predominantly restricted to the nuclei of post-mitotic rat and mouse embryonic neurons and to the cytoplasmic and membrane components of dividing ventricular zone cells. In mouse, the more mature neurons were the ones that showed the highest levels of nuclear Notch ICD both in vivo and in vitro *(30).* In contrast, in cultures where the neurites of embryonic cells had not yet contacted each other, no appreciable increase in nuclear Notch ICD levels or Notch activity was observed. These data point to nuclear Notch and Notch activity increasing concomitant with expanding numbers of interneuronal contacts and restricted growth capacity of neurons.

Subsequent experiments tested whether Notch signaling regulates cortical dendritic morphology *(29,30).* These studies involved transfecting mouse or rat embryonic cortical neurons in culture with dominant negative and constitutively activated Notch constructs designed to inhibit or activate Notch signaling, respectively. Misexpression of constitutively active Notch1 and/or Notch-2 halted neurite growth in cultures that would normally exhibit exuberant growth *(29,30),* and caused premature retraction of neurites in cultures that had

ceased growing *(30).* Yet, the complexity of the branching pattern was increased *(29,30).* Importantly, co-culture of cortical neurons with stably transfected cells expressing the Notch ligand Delta1 mimicked the effects of constitutive Notch activation. However, the source of the Delta signal must be considered. Mammalian neuroblastoma cells (N2a cells) showed inhibited neurite extension when exposed to Delta1-expressing quail cells, but N2a cells misexpressing Delta1 actually exhibited enhanced neurite extension *(28).*

To confirm that Notch signaling is required for dendritic morphogenesis, functional inhibition experiments were performed. One group used Notch1 antisense and dominant-negative strategies *(29),* while the other took advantage of intracellular modulators of Notch signaling, Numb-like and Deltex *(30).* In the mouse embryonic cortical cultures, Numb-like and Deltex acted to inhibit Notch activity *(30).* Both approaches resulted in enhanced neurite extension, but inhibited branching *(29,30).* This was true even in high-density cultures that had already stopped growing *(30).*

During development, the brain encounters a packing problem, whereby the greatest number of neurons and their processes must be fit into the available space. Having a system where neuronal growth is tightly controlled to fill only the existing space provides an elegant solution to this problem. These studies argue convincingly that early in development, unimpeded by close neighbors, dendrites extend exuberantly to fill the available space. Subsequently, contacts with the dendritic processes of adjacent neurons activate Notch-ligand signaling, resulting in mutual restriction of dendrite extension and increased branching of existing neurites *(30).* Hence, Notch activation provides not only a stop signal, but a "fill-in" signal as well. That Notch and Delta continue to be expressed in the adult CNS raises the possibility that they may also play a role in regulating the stability of neurites and synaptic connections as the organism ages. Interestingly, a family of proteins implicated in Alzheimer's disease, the presenilins, is required for Notch cleavage and activation *(33,34).* Thus, certain neurological diseases potentially arise from a breakdown of Notch's ability to modulate dendritic morphology *(30).*

## Conclusions

Evidently, dendrite morphogenesis is controlled by molecular strategies that also effectively regulate aspects of earlier embryonic development. The prevailing idea arising from the studies discussed in this review is that neurons actually have a large say in determining their ultimate shape and function. Intracellular transduction mechanisms and/or combinations of receptors will dictate how a neuron responds to a given extrinsic cue. In addition, neuron-neuron interactions regulate the eventual size and shape of the dendritic arbor. Thus, although extrinsic information is important, it is ultimately the neuron that makes the decisions that regulate neuronal form and connectivity.

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