Review

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Regulation of dendrite morphogenesis by extrinsic cues

Pamela Valnegri[1,2*], Sidharth V. Puram[2*,†], and Azad Bonni[1,2]

[1] Department of Anatomy and Neurobiology, Washington University in St Louis School of Medicine, St Louis, MO 63110, USA
[2] Department of Neurobiology, Harvard Medical School, Boston, MA 02115, USA

Dendrites play a central role in the integration and flow of information in the nervous system. The morphogenesis and maturation of dendrites is hence an essential step in the establishment of neuronal connectivity. Recent studies have uncovered crucial functions for extrinsic cues in the development of dendrites. We review the contribution of secreted polypeptide growth factors, contact-mediated proteins, and neuronal activity in distinct phases of dendrite development. We also highlight how extrinsic cues influence local and global intracellular mechanisms of dendrite morphogenesis. Finally, we discuss how these studies have advanced our understanding of neuronal connectivity and have shed light on the pathogenesis of neurodevelopmental disorders.

Extrinsic cues regulate distinct steps in dendrite morphogenesis

To establish proper connectivity, dendrites transition through fundamental developmental stages from growth and guidance, to branching and pruning, to self-avoidance and tiling. The regulation of dendrite patterning can be broadly divided into cell-extrinsic and cell-intrinsic mechanisms. In the nervous system, cell-extrinsic cues consist of secreted or transmembrane signals as well as neuronal activity in response to trans-synaptic transmission. By contrast, cell-intrinsic pathways represent cell-autonomous mechanisms that are influenced by environmental cues but do not strictly depend on extrinsic cues to operate within neurons. These factors characteristically regulate intracellular neuronal responses to extrinsic cues [1,2].

Early studies of dendrite morphology were heavily focused on secreted cues such as neurotrophins and their effectors, the receptor tyrosine kinases (RTKs) [3]. However, additional cell-extrinsic cues and mechanisms of dendrite patterning have been identified (Table 1). For example, contact-mediated signaling through Down syndrome cell adhesion molecule (DSCAM) and similar molecules have provided significant insights into the targeting of dendrites, whereas ligand-gated and voltage-gated calcium channels and their respective downstream effectors have shed light on how neuronal activity regulates dendrite morphogenesis.

The cell-intrinsic pathways driving dendrite patterning have been recently reviewed [2]. We focus on the cell-extrinsic regulators of dendrite morphogenesis. We discuss the role of three major classes of extrinsic regulators: secreted cues, contact-mediated factors, and neuronal activity. The list of specific molecules driving these distinct forms of regulation continues to expand. A general concept emerging from these studies is that, exactly as in the case of cell-intrinsic regulation of dendrite morphogenesis [2], extrinsic cues regulate diverse aspects of dendrite development from their growth and branching to pruning and maturation (Figures 1 and 2).

Secreted cues

Neurotrophins

Neurotrophins represent a family of secreted proteins, consisting of nerve growth factor (NGF), brain-derived growth factor (BDNF), neurotrophin 3 (NT-3), and neurotrophin 4 (NT-4), that act on neurons through members of the tyrosine receptor kinase (Trk) family [4]. In the rodent cerebral cortex, neurotrophins promote dendrite growth and arborization, but this effect varies depending on the specific neurotrophin, cortical layer, and location of the dendrites [5].

Specific deletion of the BDNF receptor TrkB in cortical pyramidal neurons, by crossing mice harboring a floxed allele of *Trkb* with mice expressing Cre downstream of the CaMKII driver, reduces dendrite complexity [6], and disruption of the TrkB dynein-mediated transporter Snapin decreases dendrite growth [7]. Interestingly, Trk receptors are also expressed as different splice variants, and these variants mediate distinct effects on dendrites [8], potentially offering another layer of control beyond the effects of specific cognate neurotrophin/Trk family members. Recent studies reveal that dendrite growth and branching is modulated by relative intracellular differences in NT-3/TrkC signaling. TrkC knockout mouse Purkinje neurons have reduced dendrite complexity, which is rescued by the removal of the TrkC ligand NT-3 from cerebellar granule neurons [9].

Although neurotrophins have essential roles in dendrite patterning, the precise downstream mechanisms remain to be identified. Neurotrophins may stimulate activity-dependent pathways to induce dendrite growth [10]. Recent studies link neurotrophin signaling to the activity-dependent phosphorylation of glycogen synthase kinase-3β

Corresponding author: Bonni, A. (bonni@wustl.edu).
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[*] These authors contributed equally to the manuscript.
[†] *Current address:* Department of Otolaryngology, Massachusetts Eye and Ear Infirmary and Harvard Medical School, Boston, MA 02114, USA.

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Table 1. Summary of cell-extrinsic molecular drivers of dendrite morphogenesis

Secreted cues	Neurotrophins NGF, BDNF, NT-3, NT-4 (targeting tyrosine receptor kinases)
	Semaphorins
	Netrin/Frazzled/DCC and Slit/Robo
	Wnts
	Ephrins
	Reelin
	Bone morphogenetic proteins
Contact-mediated regulators	Cadherins and protocadherins
	Adhesion G-protein-coupled receptors
	DSCAM
	Integrins
	Fusogens and other transmembrane proteins
Neuronal activity and calcium signaling	VGCCs
	NMDARs

(GSK3β) at serine 9 in hippocampal neurons, which inhibits GSK3β activity and promotes dendrite growth [11]. Interestingly, GSK3β activation appears to trigger phosphorylation of the scaffold protein gephyrin, and thereby reduces $GABA_A$ receptor levels – causing hyperexcitability and dendrite retraction [11].

Semaphorins

Several diffusible secreted factors that control axon guidance have also been implicated in dendrite patterning. Semaphorins Sema2A and 2B, and Sema3A (as well as the transmembrane Sema1A) regulate dendrite targeting and branching in mammalian cerebral cortical neurons and fly olfactory neurons [12–14]. Mouse genetic studies reveal a role for Sema3A in regulating apical dendrite formation in hippocampal CA1 pyramidal neurons [15].

Notably, the Sema3A receptor neuropilin1 (NRP1) is uniformly expressed along axons and dendrites, suggesting that NRP1 expression may not explain differential effects of Sema3A on axons and dendrites. Recently, the protein kinase TAO kinase 2 (TAOK2) has been suggested to collaborate with NRP1 in directing Sema3A-induced basal dendrite growth [16]. Expression of TAOK2 stimulates Jun kinase (JNK) activity and thereby restores basal dendrite arborization in NRP1-deficient neurons. Substrates of JNK that mediate Sema3A-induced basal dendrite arborization remain to be identified. Interestingly, TAOK2 is an autism spectrum disorder susceptibility gene, and deficits in basal dendrite development upon TAOK2 downregulation may mimic the underdeveloped neuron morphology associated with autism [16].

In an alternative mechanism specifying the Sema3A response, guanylate cyclase and cGMP have been observed to be localized in apical dendrites but not in basal dendrites or axons [13]. These results have been extended in *Xenopus* spinal commissural interneurons, where Sema3A-induced cGMP stimulates Ca(V)2.3 channels and growth of dendrites [17]. Other studies suggest that Fyn and cyclin-dependent kinase 5 (Cdk5) operate downstream of Sema3A signaling [18], whereas in cultured hippocampal neurons Sema3A inhibits protein kinase A (PKA) signaling leading to reduced phosphorylation of the protein kinases LKB1 (liver kinase B1) and GSK3β, thereby inhibiting axon formation and triggering dendrite growth [19].

Semaphorins and their receptors, the plexins, are also involved in directing lamina-specific neurite arborization in the developing mouse retina [20]. Recent studies suggest that Sema6A and its receptor plexinA2 (PlexaA2) control direction-selective responses to visual stimuli by regulating the dendrite morphology and stratification of the starburst amacrine cell in the mouse retina [21]. Semaphorins may also regulate dendrite development in neurons generated in the adult mouse hippocampus [22].

Netrins and Slits

The *Drosophila* midline is enriched with secreted guidance cues including Netrins and Slits which act through Frazzled and Robo (Roundabout) receptors, respectively. *Drosophila* motoneuron dendrites make stereotyped guidance decisions based on these midline ligand–receptor interactions. Slits appear to drive motoneuron dendrites away from the central nervous system (CNS) midline [23]. By contrast, Netrin promotes midline-crossing of dendrites in flies [24].

In the rodent cerebral cortex, Slit1/Robo interactions regulate the growth of pyramidal neuron apical dendrites [25]. The secreted repulsive guidance cue Slit2 and its cognate Robo receptor have also been implicated in self-avoidance of dendrites in Purkinje neurons in the mouse cerebellar cortex, where aberrant signaling of these pathways alters motor behavior in animal models [26]. In conditional knockout studies, Slit2 and its receptor Robo2 are required for cell-autonomous self-avoidance of Purkinje neuron dendrites [26].

How a common pool of guidance molecules controls the morphogenesis of both axons and dendrites remains an important question in the field. Genetic studies in *C. elegans* provide some insight. The serine/threonine kinase Par4 (LKB1) and UNC-40 (DCC, deleted in colorectal cancer) promote dendrite growth in response to UNC-6 (Netrin), whereas the receptor UNC-5 repels axon growth downstream of UNC-6 [27]. Additional studies have shown that UNC-6 (Netrin) acts non-cell-autonomously on neighboring dendrites via the receptor UNC-40 [28], offering a further layer of regulation. Thus, the effect of UNC-6 and other secreted cues may depend not only on the specific receptors and downstream signaling molecules but also on the surrounding cellular milieu.

Wnts

Wnts (wingless) bind to Frizzled receptors and signal through the scaffold protein Dishevelled (Dvl) [29]. Among the Wnt proteins, Wnt7b, which is expressed in the mouse hippocampus, appears to regulate dendrite growth and arborization [30]. Wnt7 and Dvl stimulate dendritic elaboration through the activation of the Rho family GTPase Rac and the protein kinase JNK (c-Jun N-terminal kinase). Wnt3a and Wnt5a may also regulate dendrite development in olfactory bulb interneurons [31]. These Wnt proteins act through canonical and non-canonical downstream signaling to exert opposing functions on dendrite growth [31]. Wnt5 acts as a repulsive guidance cue for projection neuron (PN) dendrites in *Drosophila*. The spatially