Cell. Mol. Life Sci.
DOI 10.1007/s00018-017-2588-8

Cellular and Molecular Life Sciences

REVIEW

Mechanisms regulating dendritic arbor patterning

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Received: 4 December 2016 / Revised: 14 June 2017 / Accepted: 6 July 2017

Abstract The nervous system is populated by diverse types of neurons, each of which has dendritic trees with strikingly different morphologies. These neuron-specific morphologies determine how dendritic trees integrate thousands of synaptic inputs to generate different firing properties. To ensure proper neuronal function and connectivity, it is necessary that dendrite patterns are precisely controlled and coordinated with synaptic activity. Here, we summarize the molecular and cellular mechanisms that regulate the formation of cell type-specific dendrite patterns during development. We focus on different aspects of vertebrate dendrite patterning that are particularly important in determining the neuronal function; such as the shape, branching, orientation and size of the arbors as well as the development of dendritic spine protrusions that receive excitatory inputs and compartmentalize postsynaptic responses. Additionally, we briefly comment on the implications of aberrant dendritic morphology for nervous system disease.

Keywords Dendrite morphogenesis · Dendritic spines · Pruning · Dendritic self-avoidance · Intrinsic and extrinsic regulators · Neuronal activity

Abbreviations

AD	Alzheimer disease
AMPA	α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor
ASD	Autism spectrum disorder
bHLH	Basic helix-loop-helix
CaM	Calmodulin
CaMK	Ca^{2+}/calmodulin-dependent protein kinase
CaMKK	Ca^{2+}/calmodulin-dependent protein kinase kinase
CBP	CREB-binding protein
Cdc20	Cell division cycle protein 20
Cdc42	Cell division control proteins 42
Cdk5	Cyclin-dependent kinase 5
CREST	Calcium-RESponsive Transactivator
CREB	cAMP-response element binding protein
DSCAM	Down syndrome cell adhesion molecule
ERK	Extracellular signal-regulated kinases
FMRP	Fragile X mental retardation protein
GAP	GTPases activating proteins
GEF	Guanine nucleotide exchange factor
GOPs	Golgi outposts
GSK-3β	Glycogen synthase kinase 3β
HD	Huntington disease
HDAC	Histone deacetylase
JNK	c-Jun N-terminal kinase
L1CAM	L1 cell adhesion molecule
LimK1	LIM domain kinase 1
LTP	Long-term potentiation
MAP	Microtubule-associated protein
MAPK	Mitogen-activated protein kinase
MARCKS	Myristoylated alanine-rich C-kinase substrate
MEF	Myocyte enhancer factor 2A
MEK	MAPK/ERK kinase
mTOR	Mammalian target of rapamycin
NCAM	Neural cell adhesion molecule
NHE6	Na^+/H^+ exchanger 6
NMDAR	*N*-methyl-D-aspartate receptor
PAK	p21-Activated kinase

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Published online: 22 July 2017

PD	Parkinson disease
Pea3	Polyoma enhancer activator 3
PI3 K	Phosphoinositide 3-kinase
PKC	Protein kinase C
Rac1	Ras-related C4 botulinum toxin substrate 1
Ret	Rearrangement in transformation
ROCK	Rho-associated protein kinase
TAOK2	Thousand-and-one-amino acid 2 kinase
TrkB	Tropomyosin receptor kinase B
Tsc1	Tuberous sclerosis complex 1
VSCC	Voltage-sensitive calcium channel

Introduction

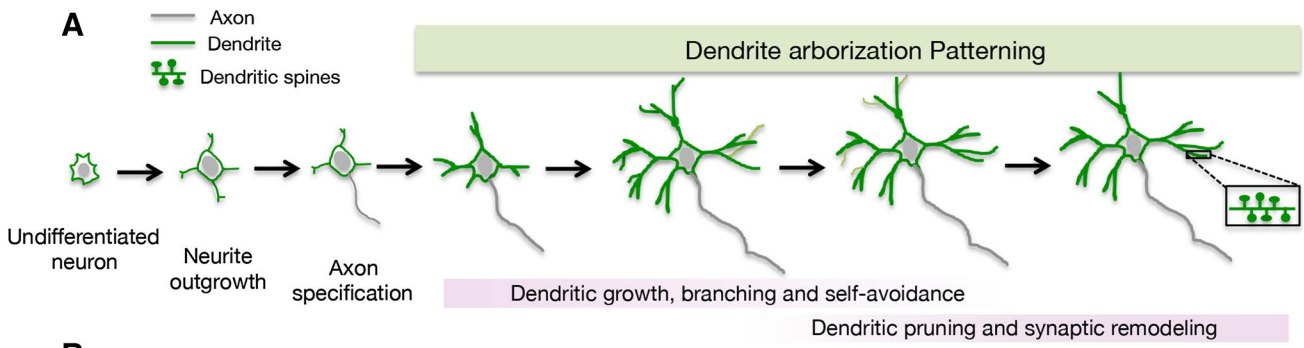
Neurons are highly polarized cells. After leaving the cell cycle, developing post-mitotic neurons elaborate their axons and dendrites in patterns characteristic for each neuronal type. While axons grow to their appropriate targets, dendrites arborize to meet the needs of specific receptive fields and form specific synapses to ensure proper connectivity. Thus, dendrites receive input through synaptic connections and axons transmit integrated signals from one neuron to another. This neuronal assembly during development is a highly controlled process since the establishment of aberrant connections can lead to the development of various diseases of the nervous system such as psychiatric and cognitive disorders.

The dendrites are the main receptor structures of neurons. In many neuronal types, including retinal ganglion neurons, forebrain pyramidal neurons and cerebellar granule neurons, the axon generation and specification precede the development and elaboration of their dendrites [1]. Although different neuronal types have specific programs for dendritic development, we can distinguish some fundamental steps common to all of them (Fig. 1). First, dendrites extend away from the cell body towards their target field using guidance signals. In this stage, dendritic processes grow in length and diameter, acquiring molecular features that distinguish them from the axons [2]. Second, dendrites grow and develop extensive neuron-specific branch patterns to cover the target region. Third, dendrite growth is spatially restricted to a defined area by stop-growing repulsive dendro-dendritic interactions between branches that arise from a single soma, known as dendritic self-avoidance, or between dendrites from different neurons that share the same function, known as dendritic tilling. These two spacing mechanisms ensure that arbors maximize their spread across a territory while minimizing the redundancy of the innervated area [3]. Fourth, dendrites differentiate and develop specialized synaptic structures. In cortical and hippocampal pyramidal neurons,, these structures are named dendritic spines [4]. Finally, dendrite pruning involves the refinement of the dendritic connections and the modification of the dendritic trees through the retraction and elimination of the dendritic branches and synaptic contacts that are non-essential for the formation of the developing circuits. Therefore, dendritic pruning is a mechanism that ensures that only those dendrites that are properly innervated undergo maturation [5]. For example, in the mouse cerebellum, highly elaborated arbors are pruned to eliminate excessive dendrites, thereby yielding dendritic branches that will persist after development. These remaining dendrites then undergo a process of postsynaptic differentiation and maturation, for which they develop specialized structures for synapse formation (Fig. 1) [6, 7].

All of these steps involve dynamic changes in dendritic shape that allow the establishment of proper wiring and synaptic connectivity. Dendrites are plastic structures that display dynamic changes during development and adulthood in response to both experience and damage caused by disease.

These different developmental stages involved in dendrite morphogenesis require coordinated interaction between environmental cues (extrinsic factors) and cell type-specific signaling modulators (intrinsic factors). Extrinsic cues regulating dendrite morphogenesis include cell–cell adhesion molecules, soluble guidance cues and secreted neurotrophic factors, as well as activity-dependent calcium signaling. On the other hand, the term intrinsic factor refers to those molecules which do not strictly depend on external cues for their activity but can be influenced by them. These intrinsic factors include a plethora of molecules that are compartmentalized in neurons, such as transcription factors, cytoskeletal regulators and motor proteins as well as secretory membrane pathways and regulatory RNAs [8, 9].

In this review, we summarize the cellular and molecular mechanisms that contribute to generate diverse dendritic branching patterns in the vertebrate nervous system in the context of general principles that govern its synaptic circuit organization. In addition, we discuss how different aspects of dendrite patterning such as dendritic size and shape, targeting of dendrites to specific layers and dendrite compartmentalization determine the function of vertebrate mature neurons. Elucidating the developmental mechanisms that control the wiring of dendritic structures may provide the basis to understand how dendritic defects cause circuit dysfunctions associated with neurodevelopmental disorders. For a more comprehensive review of the molecular mechanisms controlling dendrite patterning in the invertebrate nervous system, see Dong et al. [10] and Lefebvre et al. [11].



B

		Dendritic growth and Branching	Dendritic self-avoidance and pruning	Postsynaptic differentiation and spine development
Extrinsic Factors	Secreted cues	BDNF, NT3, NT4/ Trks GDNF/GFR α 1/NCAM HGF/Met BMPs NRG1/ErBb2-4 Wnts Sema3A (directional growth) Slit/Robo Reelin	Slit2/Robo2*	BDNF/TrkB GDNF/GFR α 1/NCAM HGF/Met NRG1/ErbB2/4
	Contact-mediated cues	Celsr2/3 Protocadherins Integrin α 3 DSCAM L1CAM	EphrinA5/EphA7 EphB/EphrinB3 Cadherin Fat3 γ Protocacherin* DSCAM* Integrins	Integrin β 1 Integrin α 3/ α 5 DSCAM Sidekick EphB/EphrinB3
	Neuronal activity and calcium signaling	NMDARs VSCC CamKI/CamKII α /CamKIV MAPK	NMDAR2B CamKII β VSCCs	NMDAR VSCC CamKK/CamKI CAMKv

Fig. 1 Cell-extrinsic regulators of dendritic arborization. The figure includes **a** an overview of the critical stages for the establishment of dendritic patterns in vertebrates, and **b** a summary of the main extracellular factors regulating each of these steps of dendrite development. *Asterisk* indicates molecules that mediate dendritic self-avoidance

Dendrite patterning and its relevance for neuronal function

The arrangement of dendrites has critical implications for neuronal information processing. The relationship between dendrite morphology and function indicates that each type of neuron has adapted its dendritic architecture according to its specific role in the neural circuit. To accomplish this, dendrites acquire appropriate size, branching, locations and compartmental organization.

The volume covered by a dendritic arbor has strong influence on neuronal function since it determines the size of the receptive field and the physical signals that the neuron can detect. Thus, the larger the dendritic tree develops, the greater the amount of synapse it can receive and the information it has to process. In this way, it is important that the dendritic size must be matched to the density of presynaptic terminals. This matching assesses and determines the degree of convergence among the elements of each neuronal circuit. Therefore, whether a dendritic tree is large enough to receive many axonal inputs, the information will be pooled and averaged but whether dendritic arbors are small relative to presynaptic terminals, the input from a single neuron will be transmitted to multiple postsynaptic neurons, creating parallel circuits. In vertebrates, several developmental mechanisms have been identified to establish dendritic arbors of appropriate form and size. Afferent-derived factors (such as neurotrophins and neurotransmitters) and dendro-dendritic repulsive interactions such as self-avoidance or repulsion among dendrites of different neurons of the same type represent effective mechanisms for coordinating afferent-target development.

In many brain areas, such as retina, cerebellum, hippocampus and cortex, synaptic circuits are organized in

layers to facilitate information processing [12]. Many types of neurons grow their dendrites in a targeted manner to meet their presynaptic partners in specific layers. For example, in the visual and olfactory systems of vertebrates, neurons send dendrites to stratified neuropil areas in the retina or to single glomerulus in the olfactory bulb [12, 13]. Thus, targeted dendritic growth contributes to ensure synapse specificity by limiting presynaptic partners to those axons that project to the same layer. Lamination is essential for optimal assembly of neuronal circuits. However, at least in some cases, laminar organization is not completely required for correct circuit assembly and function. Surprisingly, in a mouse model of disturbed cortical organization (reeler mouse), which is characterized by a loss of cortical lamination, there are few functional consequences and little incidence on the assembly of the somatosensory maps [14, 15].

Dendrites are dynamic structures that integrate synaptic inputs from multiple signals into useful outputs. To carry out these computations, neurons develop compartmentalized dendritic arbors that have different synaptic inputs and electrical properties. A good example of how compartmental dendritic organization affects neuronal function is represented by hippocampal CA1 pyramidal neurons. These neurons show dendritic domain-specific differences in membrane excitability and connectivity that greatly expand their computational ability. As other pyramidal neurons, these neurons have apical and basal dendritic domains positioned on distinctive layers of the hippocampus. While the basal domain is located in the stratum oriens (SO), the apical tufts at the distal end receive excitatory inputs from the entorhinal cortex (EC) within the stratum lacunosum moleculare layer (SLM). However, the proximal apical domain receives excitatory inputs from hippocampal CA3 axons through the Schaffer collaterals in the stratum radiatum (SR) (Fig. 2) [16]. Each domain presents differences in the density of excitatory and inhibitory synapses that receive and expresses distinct levels of neurotransmitter receptors and ion channels. These differences between distal and proximal apical domains permit the modulation of EC or CA3 excitatory inputs in a compartment-specific manner [17, 18].

Dendritic spines represent postsynaptic subcellular compartments where most excitatory inputs are received. These structures are micron-sized protrusions along the dendritic shaft that have distinctive morphological, biochemical and electrical properties [19]. Spine morphology facilitates the compartmentalization of calcium and other biochemical signals on individual spines, minimizing interspinal crosstalk and supporting spine-specific synaptic plasticity. Additionally, spines can directly regulate the sensitivity of a synapse by compartmentalizing neurotransmitter receptors,

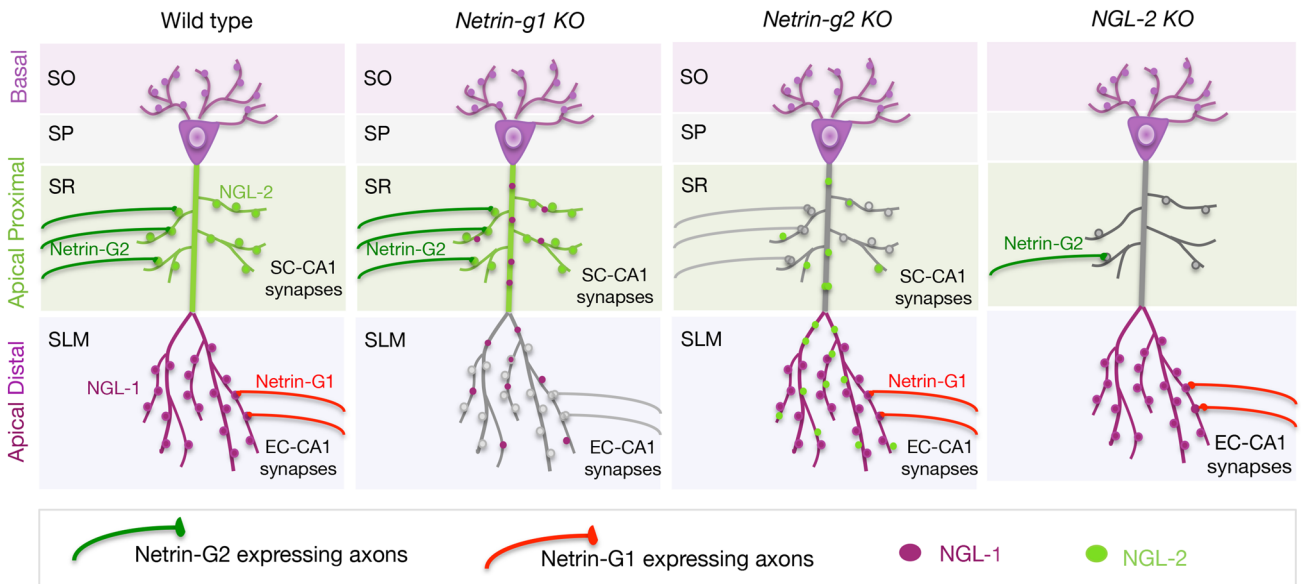


Fig. 2 Laminar organization of the apical dendritic domain of hippocampal pyramidal neurons. Afferent-dependent control of NGL receptor localization by axonal Netrin-G ligands. NGL-1 and NGL-2, which are expressed in CA1 apical dendrites, are anchored by axon-derived Netrin-G1 and Netrin-G2, respectively. Entorhinal cortical (EC) axons bearing Netrin-G1 anchor NGL-1 at distal apical dendrites, whereas Netrin-G2 expressed on Schaffer collateral (SC) terminals organize NGL-2 on proximal apical dendrites. In the absence of Netrin-Gs as extrinsic cues, NGLs are diffusely distributed in apical dendrites. NGL-2 regulates SC-CA1 excitatory synapse development in proximal apical dendrites. Synaptic densities and dendritic spines are disrupted in the SR of *NGL-2* knockout mice (*last column*). Hippocampal layers: stratum oriens (SO), stratum pyramidale (SP), stratum radiatum (SR), stratum lacunosum moleculare (SLM) are indicated

either by restricting receptor diffusion out of spines and/or maintaining spine-selective storage pools [20].

Finally, compartmentalized Golgi, known as Golgi outposts (GOPs) provide another level of dendritic compartmentalization involved in branching of mammalian hippocampal dendrites [20–22]. GOPs, are discussed in more detail below, in the context of secretory pathways and dendrite morphology.

Regulation of dendrite development by extrinsic cues

Secreted and diffusible cues

Neurotrophins

Neurotrophins constitute a family of structurally related proteins, consisting of nerve growth factor (NGF), brain-derived growth factor (BDNF), neurotrophin 3 (NT-3), and neurotrophin 4 (NT-4). Neurotrophin signaling through Trk receptors represents one of the most studied molecular complexes that promote dendrite morphogenesis and spine formation of developing dendrites in different brain regions, including the cerebral cortex, the hippocampus and the striatum [23, 24]. In the neocortex, the dendritic effects promoted by neurotrophins vary depending on the neurotrophin, the cortical layer, and the location of the dendrite in the apical or basal domain of the dendritic arbor [25, 26]. In agreement with a role of BDNF as a dendritogenic factor, conditional deletion of its receptor (TrkB) in cortical pyramidal neurons induces dendritic retraction and neuronal loss. These results indicate that BDNF/TrkB signaling is required for the maintenance of specific neuronal populations in the adult neocortex [27].

In hippocampal pyramidal neurons, BDNF increases the number of primary dendrites and dendrite branches near the cell body [28]. In addition, elevated BDNF levels promote dendrite complexity of hippocampal dentate gyrus granule cells (GCs) in vivo [29]. Recently, it was established that BDNF plays a critical role in dendrite development of adult-born GCs by acting as an autocrine factor [30]. These effects of BDNF on dendrite arborization pattern of GCs are critical for the incorporation of young cells into existing hippocampal circuits.

Dendritic effects promoted by neurotrophin receptors are regulated by downstream signals triggered from different intracellular compartments and locations. Previous reports indicate that the downstream signaling pathways involved in BDNF-induced dendritic branching include the activation of the PI3K/AKT/mTOR (mammalian target of rapamycin) kinase, the MAPK/CREB-dependent induction of different transcriptional factors involved in dendrite development (see below) and the Cdk5-dependent activation of the Rho GTPase Cdc42 to regulate the actin cytoskeleton [28, 31, 32].

Recent studies have begun to reveal how dendrites placed in specific layers expand their sizes to form synaptic connections with afferent axons. Although in many cases neurotrophins may originate from sources other than afferents, the mouse cerebellum provides a clear example of dendrite regulation by presynaptic neurotrophins.

Dendrite morphogenesis of Purkinje neurons in the mouse cerebellum has been shown to depend on relative intracellular differences in NT3/TrkC receptor signaling in vivo [33]. While sparse TrkC knockout mice present reduced dendrite growth and branching of Purkinje cells (PCs), global knockout for this receptor has no effect. Strikingly, removal of NT3 from cerebellar granule cell parallel fiber afferents rescued the dendritic defects caused by sparse TrkC disruption in PCs, revealing that presynaptic NT3 is required for TrkC-dependent competitive dendrite morphogenesis of cerebellar Purkinje neurons [33]. Thus, these findings indicate that anterograde signaling serves to coordinate afferent-target development.

Interestingly, the BDNF and NT3 receptors, TrkB and TrkC, are expressed as different splice variants having short cytoplasmic tails lacking the tyrosine kinase domain [26]. Although the physiological contribution of truncated Trk receptors for dendrite morphology is not completely known, there is evidence that truncated TrkB (TrkB.T1) increases total dendritic growth, while full-length TrkB (TrkB-FL) increases proximal dendritic branching of pyramidal cortical neurons [34]. It was also reported that overexpression TrkB.T1 in hippocampal neurons induces the formation of dendritic filopodia through a mechanism which do not require neurotrophin binding [35].

All this evidence demonstrates that neurotrophins and their receptors have essential roles in dendrite patterning. However, how a limited repertoire of neurotrophins and Trk receptors promotes a diverse array of dendritic arborization patterns is a question that has recently begun to be answered. As such, recent studies have identified key cell-specific regulators of the diverse array of dendrite morphologies promoted by neurotrophins in the central nervous system (CNS). These studies establish that engagement of Trks with specific LRR transmembrane proteins (such as Slitrk5, Lingo1 and Lrig1) represents a general mechanism that explains how neurons within a particular region of the nervous system expand the repertoire of neurotrophin signaling outputs to generate dendritic diversity and complex patterns of neuronal connectivity. In this regard, Slitrk5 and Lrig1 modulate BDNF-promoted dendritogenesis of striatal GABAergic and hippocampal pyramidal neurons, respectively. Interestingly, deletion of Lrig1 preferentially increases the proximal complexity of apical CA1-CA3

pyramidal neurons, revealing a novel mechanism involved in apical/basal dendrite patterning [36, 37]. Thus, LRR proteins offer additional regulatory mechanisms on Trk signaling that expand neurotrophin actions at different neuronal locations and stages of the developing nervous system [38].

Endocytosis and endosomal signaling are crucial cellular mechanisms that link neurotrophin-promoted Trk signaling to dendrite arborization [39]. Several lines of evidence indicate that Trk receptors signal from intracellular organelles and that this process is regulated by Rab GTPases [40]. However, how Trk activation coordinates cell surface and endosomal signaling, membrane trafficking, cytoskeleton dynamics and local protein translation to generate dendrite morphology and spines has only recently begun to be addressed. Two recent studies have identified important endosomal proteins involved in the control of TrkB-mediated dendrite morphology. In one of these studies, the authors demonstrate that BDNF regulates Rab11-mediated recycling endosome dynamics to induce dendritic branching of hippocampal neurons by promoting TrkB localization in dendrites [41]. In the other, loss of endosomal Na^+/H^+ Exchanger 6 (NHE6) produces an overacidification of the endosomal compartment that results in attenuated TrkB signaling and neural circuit defects that are in part due to impoverished neuronal arborization [42]. Consistent with this observation, mutations in NHE6 were associated with Christianson syndrome, a neurogenic disorder characterized by intellectual disability, autistic features and microcephaly [43].

In agreement with the critical roles played by neurotrophins in dendrite development, altered BDNF-TrkB signaling has been implicated in the pathophysiology of neurodegenerative and psychiatric disorders including: AD, PD, HD, autism spectrum disorders (ASD), bipolar disease and epilepsy [44–50].

GDNF ligands

Glial cell line-derived neurotrophic factor (GDNF) is another soluble factor able to promote the survival and morphological differentiation of different neuronal populations in the central and peripheral nervous system [51]. A feature of the GDNF receptor complex is the requirement of two kinds of subunits, one specialized in transmembrane signaling, represented by either the c-Ret tyrosine kinase receptor (Ret), or the neural cell adhesion molecule (NCAM), and the other subunit involved in ligand binding, namely the GDNF family receptor α1 (GFRα1) [52, 53].

Although several studies have provided evidence showing that different neurotrophic factors play important roles in regulating specific patterns of dendritic arbor growth and branching, little is known about the role of GDNF family ligands and their receptors in dendrite development. A very recent study shows that postsynaptic engagement of GDNF and GFRα1 is required for proper development of hippocampal dendritic arbors and spine maturation through NCAM signaling. The specific deletion of GFRα1 in glutamatergic neurons affects the dendritic arborization of CA1 and CA3 pyramidal neurons in vivo. In agreement with this data, a decrease in dendritic spine formation and dendrite complexity was also observed in cultured hippocampal neurons lacking GFRα1 and NCAM expression [54].

Hepatocyte growth factor (HGF)

Hepatocyte growth factor and its receptor tyrosine kinase c-Met induce the development of cortical pyramidal dendrites by stimulating growth and complexity during a critical period of development, when extensive synaptogenesis is taking place [55]. In agreement with this, the transfection of pyramidal cortical neurons with a c-Met dominant-negative mutant receptor results in much smaller and less complex dendritic arbors than control transfected neurons. Later studies established that HGF controls cortical dendrite complexity through the activation of the MAPK/CREB-signaling pathway [56].

In hippocampal neurons, HGF increases the number of dendrites and promotes dendrite elongation through a mechanism that requires activation of the Akt/GSK-3β pathway and decreases phosphorylation of the microtubule-associated protein 2 (MAP2) [57]. Furthermore, genetic deletion of Met disrupts dendrite morphology and leads to altered dendritic spine morphogenesis and glutamatergic function in the intact hippocampus [58]. Decreased levels of MET itself and altered levels of molecules associated with the HGF/MET pathway have been documented in brain tissues from patients with ASDs [59–61].

Bone morphogenetic proteins (BMPs)

Bone morphogenetic proteins are important molecules involved in the control of cytoskeletal remodeling during neuronal morphogenesis. BMP members signal through a heteromeric complex of type I and type II BMP receptors. In embryonic cortical neurons, inhibition of p21-activated kinase blocks BMP7-induced cofilin phosphorylation, prevents remodeling of the actin cytoskeleton and inhibits dendrite formation [62].

Another member of the bone morphogenetic protein subclass, GDF5 (growth differential factor 5) regulates the dendritic growth of pyramidal hippocampal neurons via a high-affinity receptor complex consisting of BMPR1B and BMPR2, which activates intracellular SMADs and upregulates the expression of the basic helix-loop-helix transcription factor HES5. The apical and basal dendritic arbors of the hippocampal pyramidal neurons lacking GDF5 are

markedly stunted compared with those of wild-type mice [63].

Neuregulins (NRGs)

Neuregulins comprise a large family of EGF-like signaling molecules that transmit their signals to target cells by interacting with transmembrane tyrosine kinase receptors of the ErbB family (ErbB2-4). NRG is initially synthesized as a transmembrane protein which then undergoes proteolytic processing, whereby the extracellular EGF-containing fragment is released into the extracellular environment to bind ErbB receptors [64].

NRG1 has been shown to promote dendritic growth from different neuronal types such as retinal ganglionic neurons [65], cerebellar granule cells [66], and hippocampal neurons [67]. Conditional loss of ErbB2/ErbB4 receptors in the CNS impairs dendritic spine maturation and affects excitatory transmission. Conversely, soluble NRG1 increases the number and maturation of dendritic spines in cultured hippocampal neurons [68]. In agreement with accumulating evidence indicating that ErbB4 expression is high in GABAergic interneurons selective ablation of ErbB4 in parvalbumin-positive GABAergic interneurons reduces spine density and excitatory synapse number in the hippocampus and in the layer 3 of the prefrontal cortex (PFC) [69–72]. Interestingly, dendritic spine density is drastically reduced in the PFC and hippocampus of schizophrenia patients [73–75], suggesting that this mouse may represent a useful in vivo model to investigate the pathophysiological mechanisms underlying this disorder.

Wingless (Wnts)

Wnt signaling regulates neuronal connectivity by controlling axonal pathfinding as well as dendrite morphogenesis and synapse formation. Wnts are secreted glycoproteins that bind to Frizzled receptors and signal through the scaffold protein Dishevelled (Dvl). Downstream from Dvl, Wnts can signal through different signaling pathways, the canonical or WNT/β-catenin pathway, the planar cell polarity (PCP) pathway and the Wnt/calcium pathway [76]. During dendritogenesis, Wnt7b increases the complexity of hippocampal neurons via the non-canonical PCP pathway [77]. In particular, Wnt7 and Dvl stimulate dendritic growth and branching through the activation of the GTPase Rac1 and the JNK (c-Jun N-terminal kinase). Furthermore, another member of the family, Wnt-2, also promotes dendritic growth and branching of primary hippocampal neurons [78]. Consistent with these findings, hippocampal neurons from mice lacking Dvl1 show reduced dendritic arborization. Wnt3a and Wnt5a also control dendrite development of olfactory bulb (OB) interneurons [79]. In these neurons, Wnt5a induces dendritic branching, whereas Wnt3a inhibits dendrite complexity, probably acting through the non-canonical and canonical signaling pathways, respectively. Moreover, Wnts have been involved in dendritic spine development and synaptic plasticity. Thus, Wnt7a and Wnt5a signaling promote dendritic spine formation and stimulate excitatory synaptic strength in hippocampal neurons [76, 80].

Growing evidences suggests that deregulation of the Wnt canonical pathway could be involved in the pathogenesis of neurodegenerative diseases such as AD, PD, ALS and HD [81].

Semaphorins

To target an appropriate location, growing dendrites use positional cues for navigation to the right area, and several axon guidance cues have been implicated in the control of dendrite growth orientation and morphology. Semaphorin 3A (Sema3A) has been described as a chemoattractant for cortical pyramidal apical dendrites growing up towards the pial surface [82]. In addition, Sema3A-mutant mice show increased proximal bifurcation of CA1 pyramidal apical dendrites in the hippocampus [83].

Recently, the protein kinase TAOK2, a known autism spectrum disorder (ASD) susceptibility gene, was identified as an important molecular determinant for basal, but not apical, dendrite formation of cortical pyramidal neurons in response to Sema3A. Disruption of the Sema3A receptor, neuropilin 1 (Npn1), either by knockout or knockdown strategies, results in reduced branching and growth of basal dendrites, a phenotype that was partially rescued in vivo by overexpression of TAOK2 [84]. Because TAOK2 is an ASD susceptibility gene, the deficits in basal dendrite arborization observed in TAOK2-mutant mice support the idea that impoverished dendritic morphology contributes to the under-connectivity that may underlie this pathology.

Semaphorins are also involved in the control of spine distribution and morphogenesis in the mouse brain. Normally, the density of dendritic spines increases with the distance from soma in dentate gyrus granule cells (GCs) in vivo. Sema3F and its receptors Neuropilin-2 and Plexin A3 regulate compartment-specific density of excitatory synapses, by restricting formation of excitatory synapses in proximal dendritic segments of GCs [85, 86].

Slits

In addition to acting as a potent repellent for cortical axons, Slit1 also increases dendritic growth and branching of developing cortical neurons. Conversely, inhibition of Slit–Robo interactions by either Robo-Fc fusion proteins or dominant-negative Robo receptor attenuates these

effects. These findings indicate that Slit–Robo interactions may have a significant influence over the specification of cortical neuron morphology by regulating both axon guidance and dendritic patterning [87].

The multiplicity of dendrites increases the propensity for self-fasciculation and entanglement, leading to a reduction of the area covered by the dendritic arbor. To avoid this, dendrites from the same neuron usually develop non-overlapping arborization patterns via self-avoidance, a process requiring isoneural contact-dependent recognition and repulsion. A recent study established that Slit2 and its receptor Robo2 are implicated in dendritic self-avoidance of cerebellar Purkinje cells. Interestingly, deletion of both molecules leads to excessive dendritic self-crossing without affecting arbor size and shape. Specific deletion of Robo2 in PCs is also associated with motor behavioral defects [88].

Reelin

Reelin is a secreted glycoprotein that promotes hippocampal dendrite development through the very low-density lipoprotein receptor (VLDLR) and apolipoprotein E receptor 2 (ApoER2) and the adaptor protein Dab1 [89]. Dendrite complexity of hippocampal neurons is severely reduced in homozygous mice deficient in reelin signaling both in vivo and in vitro. In addition, PCs in reeler mice have reduced dendritic arborization patterns [90]. Interestingly, in mice in which the reelin adaptor proteins Crk and Crk-like (CrkL) are mutated, PCs that failed to migrate had conical dendrites with abnormal arborization and reduced dendritic complexity, whereas dendrites of properly positioned PCs displayed a normal planar dendritic morphology, despite maintaining reduced dendritic complexity [90]. In addition to its role in dendrite morphology, several recent studies have found that reelin is important for hippocampal dendritic spine formation in vitro and in vivo [91, 92].

Contact-mediated signals

Leucine-rich repeat transmembrane proteins

In addition to the previously mentioned role of LRR proteins as modulators of neurotrophin receptor signaling, these proteins are expressed at the synapses where they contribute to target specificity, working as trans-synaptic cell adhesion molecules.

Several closely related LRR protein families play a critical role in the organization and function of neural circuits, coordinating pre- and postsynaptic elements during synapse formation, pathway-specific synapse development and synaptic plasticity [17].

In hippocampal pyramidal neurons, distal and proximal apical dendrites receive synaptic contacts from different afferents. This circuit organization requires cell recognition by trans-synaptic cell adhesion molecules that coordinate targeting of afferents with synapse formation in specific layers. Recognition molecules of the NGL/Netrin-G family represent a clear example of how afferents compartmentalize apical dendrites to arrange synapses into distinct dendritic domains in CA1 hippocampal pyramidal neurons. Netrin-G2 is a GPI-linked cell surface molecule that acts as a ligand for the LRR-containing transmembrane protein NGL-2. In the CA1 hippocampus, this ligand receptor complex is distributed in complementary patterns in the stratum radiatum [93]. Netrin-G2 ligand is present in Schaffer collaterals (CA3 axons), whereas NGL-2 receptor is located in proximal dendritic compartment (Fig. 2). NGL-2 is a cell adhesion molecule that upon trans-synaptic engagement recruits postsynaptic adaptor proteins, such as PSD95. Interestingly, the laminar NGL-2 expression patterns become diffuse in Netrin-G2 knockout mice, suggesting that axonal Netrin-G2 may restrict NGL-2 to specific dendritic compartments [93]. NGL-2 knockout mice show impaired excitatory synaptic transmission and decreased spine density in apical CA1 proximal dendrites [94, 95]. Thus, NGL-2 regulates Schaffer collateral axon-specific excitatory synapse development in proximal apical dendrites of CA1 pyramidal neurons. A similar pathway-specific role for NGL-2 was identified in the horizontal cell axon-rod photoreceptor synaptic connection in the mouse retina [96].

Cadherins and protocadherins

Cadherins and protocadherins are transmembrane proteins that mediate Ca^{2+}-dependent homophilic cell adhesion [97]. Several members of the cadherin/protocadherin superfamily have been implicated in dendrite arborization, in addition to their roles in synapse development. Drosophila Flamingo is a seven-pass transmembrane cadherin that is necessary for dendrite patterning. Downregulation of mammalian Flamingo homologs, Celsr2 and Celsr3, regulate dendrite growth in an opposite manner. In particular, downregulation of Celsr2 results in a substantial simplification of dendritic arbors of cortical pyramidal and Purkinje neurons, probably due to dendritic branch retraction [98], whereas knockdown of Celsr3 in hippocampal slices leads to increased dendrite complexity [99].

Conditional loss of the γ-protocadherin (γ-Pcdh) gene cluster, which is constituted by 22 γ-Pcdh genes, results in severe defects in cortical dendrite arborization. From a mechanistic point of view, γ-Pcdhs appear to promote dendrite arborization by negatively regulating the PKC/MARCKS (myristoylated alanine-rich C-kinase substrate)

signaling pathway [100]. In a more recent study using transgenic and conditional knockout mice to manipulate γ-Pcdh repertoire in the cerebral cortex, Molumby and colleagues demonstrated that the complexity of a neuron dendritic arbor is determined by homophilic interactions between neurons and astrocytes. Thus, cortical pyramidal neurons expressing only one of the 22 γ-Pcdh can present either exuberant or minimal dendrite arborization, depending only on whether surrounding cells express the same isoform [101].

Additionally, genetic ablation of the γ-protocadherin gene cluster also disrupts dendritic self-avoidance in retinal starburst amacrine cells (AC) and Purkinje cerebellar neurons. Surprisingly, the replacement of the 22 γ-protocadherin genes with a single isoform restores dendritic self-avoidance [102].

In the visual system, directional guidance is critical for dendritic arbor placement. Dendrite number and orientation are robustly controlled and coordinated by the laminar organization of the retina. Retinal ACs migrate towards the inner plexiform layer (IPL), and then retract their trailing processes, thereby acquiring an unipolar morphology with a single dendritic arbor projecting to the IPL. Thus, dendrites oriented toward the IPL are preferentially stabilized, whereas others are eliminated by pruning [103]. The atypical cadherin Fat3, which is expressed by ACs, restricts dendrite number to ensure that ACs develop their dendrites toward the IPL [104]. In mice lacking Fat3, pruning is defective and ACs develop an extra dendritic arbor projecting ectopically away from the IPL [104, 105]. These findings highlight the critical role played by the atypical cadherin Fat3 as a key regulator of dendrite morphogenesis and retinal circuit assembly.

Cell adhesion molecules (CAMs)

Significant insights into the mechanisms that contribute to dendrite patterning have come from studies of the members of the Ig-superfamily (IgSF) of cell adhesion molecules, such as Down Syndrome Cell Adhesion Molecule (DSCAM), Sidekick, Contactin and L1CAM.

In the chick retina, adhesion molecules, including Sidekick, DSCAM and Contactin are highly expressed in specific IPL layers, which are populated by the dendrites of different RGCs and amacrine neurons. Each of these molecules functions through homophilic interactions to direct lamina-specific synaptic connections in this structure. Knockdown of these genes significantly affects the layer specific dendritic routing of these neurons (Fig. 3). Together, these studies support the idea that selective adhesion underlies assembly of IPLs and thereby regulates precise dendrite targeting to specific layers. In the chicken retina, DSCAM has also been implicated in the control of synaptogenesis, synaptic plasticity and dendrite complexity [106–108], whereas in the mouse retina, DSCAM regulates neurite arborization, mosaic tiling, and dendritic self-avoidance [109, 110].

DSCAM expression is dynamically regulated in cerebral cortex, where it also contributes to regulate pyramidal dendrite arborization and spine formation during cortical circuit development. Mice bearing the spontaneous mutation DSCAM^{del17} show early impairments in pyramidal neuron dendrite branching that is recovered by adulthood, as well as lasting defects in spine density and morphology [111]. DSCAM is overexpressed in Down syndrome (DS) brains and has been involved in the pathogenesis of retardation [112].

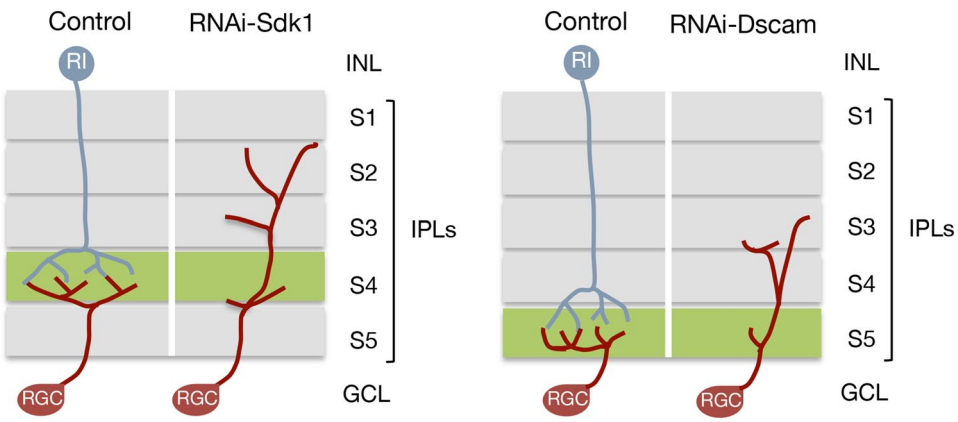


Fig. 3 Targeting dendrites to specific chick retinal layers. Dscam and Sidekick (Sdk1) proteins direct lamina-specific synaptic connections. Processes of retinal interneurons (RI) (such as amacrine and bipolar cells) establish synapses on dendrites of retinal ganglion cells (RGCs) in specific sublaminae (S1-S5) of the inner plexiform layer (IPL). Knockdown of Sdk1 affects laminar patterning of Cadherin-7-positive RGCs in S4 sublayer. Similarly, depletion of Dscam by RNA interference disrupts the laminar pattern of R-Cadherin-positive RGCs in S5 sublayer. Most of the Dscam and Sdk1-positive RGCs express R-Cadherin and Cadherin-7, respectively. *GCL* granular cell layer, *INL* inner nuclear layer

Hundreds of mutations in the L1CAM gene have been reported in patients with neurological defects and severe mental retardation [113–117]. Conditional deletion of L1CAM affects axonal growth and dendritic arborization, and also causes impairments in neuronal excitability and action potential (AP) generation [118]. Thus, these findings suggest that clinical manifestations of L1CAM mutations detected in humans could partially be due to defects in normal axon and dendrite development.

Integrins

Integrins are a class of transmembrane extracellular matrix receptors that function as α/β heterodimers that activate signaling cascades regulating cytoskeletal-signaling pathways. During dendrite development, β1 integrins are particularly associated to hippocampal dendrite stability and spine elongation [119], and α5 integrins are linked to spine formation [120]. In addition, it was demonstrated that in the mouse hippocampus, integrin α3 is critically required for late postnatal stability of dendrite arbors, dendritic spines and synapses [121]. In these neurons, integrin α3 promotes dendrite growth and complexity acting through the Arg non-receptor tyrosine kinase/p190RhoGAP/RhoA GTPase signaling pathway.

Ephrins

Most receptor tyrosine kinases bind soluble ligands, which is likely the reason why these interactions mediate long-range intercellular communication. Eph receptors (Eph) instead, bind membrane-bound ephrin ligands expressed by neighboring cells to mediate short-range signaling events that modulate both neuronal shape and contacts [122].

Although the roles of Eph/ephrin signaling in axon guidance have been studied extensively, much less is known about the contribution of Eph/ephrin signaling in dendrite morphogenesis and spine development. It has been reported that EphB receptors have a redundant role in determining dendrite morphology in hippocampal neurons. Triple knockout mice lacking EphB1, EphB2 and EphB3 receptors exhibit decreased dendrite complexity in the hippocampus [123]. The transmembrane ligand for Eph receptors, EphrinB3, has been implicated at postsynaptic terminals as a receptor that transduces reverse signals into developing dendrites of murine hippocampal neurons. Thus, axonal EphB binds postsynaptic EphrinB3, which interacts with Grb4, Pick1 and syntenin to transduce distinct reverse signals into developing dendrites to control dendritic pruning, spine maturation and synapse formation [124].

More recently, it was demonstrated that EphA7 receptors localized to dendritic shafts and spines of pyramidal cortical neurons mediate the ability of the ligand Ephrin-A5 to reduce dendritic morphology and induce dendritic self-avoidance, via the signaling proteins Src kinase and mTOR (mammalian target of rapamycin) regulator Tsc1 (tuberous sclerosis complex 1) [125].

Collectively, these studies highlight the intricate signaling mechanisms used by ephrins and Eph receptors to control dendrite arborization patterns in the brain.

Neuronal activity

In addition to secreted and contact-mediated cues calcium signaling, induced by neuronal activity, plays a central role in the control of dendritic arborization patterns and connectivity in the developing brain. Calcium influx from voltage-sensitive calcium channels (VSCCs) and NMDA receptors provide a major way for calcium entry to activate downstream signaling pathways that control dendrite morphology [126–128].

The calcium/calmodulin-dependent protein kinases (CaMKs) represent major targets of calcium signaling downstream from VSCCs and NMDA receptors in neurons. Binding of intracellular calcium to calmodulin activates CaMKs, which have divergent functions in dendrite patterning. CaMKIIα phosphorylates the transcription factor NeuroD to stimulate dendrite morphogenesis, while CaMKIIβ induces dendrite retraction and pruning in the rodent cerebellar cortex by a mechanism that requires both phosphorylation of the APC ubiquitin ligase coactivator cell-division cycle protein 20 (Cdc20) and inhibition of the Cdc20-APC ubiquitin ligase activity at the centrosome [129, 130].

In addition to regulating calcium-mediated dendrite patterning, members of the CaMKs are also involved in the control of dendritic spine development. For example, CaMKK/CaMKI promotes formation and stabilization of mushroom-shaped spines in hippocampal neurons [131]. More recently, it was reported that CaMKv, a pseudokinase of the CaMK family, regulates dendritic spine morphogenesis and maintenance in a Ca^{2+}-dependent manner. In addition, knockdown of CaMKv in CA1 hippocampal neurons impairs spatial memory [132].

The mitogen-activated protein kinase (MAPK) is another target protein whose activation is triggered by calcium influx from VSCC and NMDA receptors. Several repeated and spaced stimuli of hippocampal neurons stabilize MAPK activation and promote the formation of new dendritic filopodia [133]. Accordingly, the neuronal activity patterns critically determine the persistence of the MAPK activation and the structural plastic changes in dendritic architecture.

Notably, it has been established that the molecular mechanisms that control activity-dependent dendrite

patterning can be uncoupled from those that regulate dendritic growth. In particular, loss of NMDA receptor 2B (GluN2B) in isolated single dentate gyrus GCs results in normal dendritic growth rates and supernumerary primary dendrites due to pruning defects. Significant dendrite patterning defects without changes in general dendritic growth were also detected in mutant barrel cortex layer 4 spiny stellate cells (bSCs) lacking GLuN2B. Therefore, while control bSCs direct their dendrites towards a single barrel, mutant bSCs maintain dendrites in multiple barrels [134]. Collectively, these studies demonstrate that GLuN2B is required for dendrites to acquire patterns appropriate for their function in vivo.

Regulation of dendrite development by intrinsic molecules

During nervous system development, the different types of neurons find similar environmental factors, but they are able to respond in different ways depending on the intrinsic molecules that they express. Thus, the specific pattern of intrinsic factors expressed by a neuron can determine the cellular interpretation of a similar environmental cue allowing neurons to generate different patterns of dendritic architecture.

Transcription factors

Transcription factors are essential molecules in the establishment of the great diversity of cell types in the nervous system by regulating the expression patterns of genes that determine the morphological features and functional properties of the different types of neurons. Several transcription factors have been implicated in dendrite morphogenesis in mammalian brain [8, 130]. Many of these studies indicate that the different transcription factors regulate diverse steps of dendrite development (see Table 1).

FoxO6, a FoxO family of Forkhead transcription factor member, which is highly expressed in the mammalian CNS, has been involved in the establishment of neuronal polarity [135, 136]. Knockdown of FOXO proteins in primary cerebellar granule and hippocampal neurons as well as in the cerebellar cortex in vivo leads to an unpolarized neural morphology. Foxo6 plays a critical role in axo-dendritic polarization directly stimulating the expression of the protein kinase Pak1, which acts locally in neuronal processes to induce neuronal polarization [137–139]. At later stages of the dendrite development FOXO knockdown in *C. elegans* results in a concomitant reduction of axonal growth and increase in dendrite length, indicating that during neuronal morphogenesis Foxo6 inhibits the initial growth of dendrites favoring axonal development [140]. Mice

Table 1 Transcriptional and translational regulators of dendrite and spine morphogenesis in neurons

Molecule	Function	References
Transcription factors		
Foxo6	Neural polarization and inhibits dendritogenesis	[137, 138]
Ngn2	Neural polarization and dendrite arborization	[142, 143]
NeuroD	Dendrite growth, and spine development	[130, 144]
CREB	Dendrite growth	[78, 147, 148]
CREST	Dendrite growth and dendrite arborization	[153, 155, 156]
MEF2A	Dendrite postsynaptic differentiation	[157]
Cux1/2	Dendrite growth, branching and spine development	[158, 162]
Sp4	Dendrite outgrowth and branching	[164]
	Limits dendrite arborization	[165, 166]
Etv4/Etv5	Dendrite growth and spine development	[178, 179]
Regulatory RNAs		
miRNAs		
miR-9	Dendrite growth and spine transmission by inhibition of REST	[207]
miR-134	Activity-dependent dendrite development by inhibition of Pumilio2	[210]
	Activity-dependent spine retraction by inhibition of LIMK	[206]
miR-132	Dendrite development by inhibition of p250/GAP	[151, 212]
miR-137	Inhibits dendrite morphogenesis and spine development by inhibition of the ubiquitin ligase mind bomb-1	[209]
CircRNAs	Highly enriched in dendrites. Control miRNA function acting as miRNA sponges. They can storage, localize and sorting miRNAs	[209, 219, 220]

The table includes a list of the transcriptional factors and regulatory RNAs (miRNA and circRNAs) involved in different stages of vertebrate dendrite development

deficient in FoxO6 display normal learning but impaired memory consolidation in contextual fear conditioning and novel object recognition. A genome-wide analysis of gene expression in the hippocampus of FoxO6 mutant and wild-type mice both before and after a novel object learning task revealed that FoxO6 regulates a program of genes involved in dendrite morphology and synaptogenesis. Consistent with this, FoxO6-deficient mice show reduced dendritic spine density in hippocampal neurons [141].

Members of the basic helix-loop-helix (bHLH) family of transcription factors have also been shown to control essential aspects of development of the nervous system. Neurogenin 2 (Ngn2) is a member of this family, which has been implicated in the control of apical dendrite morphology in neocortical pyramidal neurons by promoting the outgrowth of polarized leading process during the initiation of radial migration [142]. The ability of Ngn2 to promote a polarized leading process requires the phosphorylation of a single tyrosine residue at position 241 (Y241). Expression of a mutated form of Ngn2, NgnY241F, results in multipolar dendrite morphology with no apical dendrites, indicating that Tyr241 phosphorylation is required for specifying the dendritic morphology of pyramidal neurons [142]. It has also been described that Ngn2 is implicated as a key regulator of Purkinje cell (PC) dendritogenesis. Ngn2-null PCs exhibit hypomorphic poorly branched dendrites that fail to achieve their typical arrangement in vivo [143]. These findings establish that Ngn2 plays important roles both in the control of early dendrite specification as well as in dendrite arbor morphogenesis.

Neurogenic differentiation 1 (NeuroD or BETA2) is another member of the basic helix-loop-helix transcription factor family, essential for the development of the CNS. It was described that genetic knockdown of NeuroD1 by RNA interference in cerebellar granule neurons, both in primary culture and in organotypic slices inhibits dendritogenesis but does not have any effect on axonal growth. As several transcription factors, NeuroD function in dendritic morphogenesis is regulated by external cues such as trophic factors and neural activity. The activity-induced protein kinase CaMKIIα catalyzes NeuroD phosphorylation at Ser336, stimulating primary granule cerebellar dendrite growth [130]. In agreement with this, the attenuation of NeuroD activity by the microRNA-190 (miR-190) as well as the inhibition of CaMKIIα results in decreased spine stability of hippocampal neurons, which can be rescued by NeuroD overexpression [144]. These findings indicate that NeuroD is important for dendrite growth and spine development. In agreement with a crucial role of these molecules in neuronal development, mutations in NeuroD1 locus were associated to a syndromic disorder characterized by diabetes and neurological abnormalities such as learning difficulties, severe cerebellar hypoplasia and visual impairment [145].

The cAMP-response element binding protein (CREB) plays a critical role mediating calcium-induced dendritic growth in cortical neurons via activation of a specific transcriptional program [146]. CREB is constitutively bound to DNA and after phosphorylation by the kinase CaMKIV, in Ser133, binds to the CBP (CREB-binding protein) activating gene transcription and stimulating dendrite development [147]. The expression of a dominant-negative form of CREB blocks calcium and CamKIV induced cortical dendritic growth, indicating that CREB is required for activity-dependent dendrite extension [148]. In addition to the CAMKIV signaling pathway, another study performed in hippocampal neurons indicates that activity-dependent dendritic arborization in response to NMDAR activation requires sequential activation of CAMKK, CAMKI and MEK/ERK to enhance CREB activity [78]. These findings indicate that different signaling pathways can trigger CREB-dependent transcription and dendrite growth depending on the cellular context. Several CREB target genes involved in dendrite development have been identified, including BDNF and Wnt-2. Thus, neuronal activity induces CREB-dependent transcription of BDNF and Wnt-2 molecules, which as previously mentioned, stimulate dendritic growth and maturation [78, 149]. In addition, screening of potential CREB target genes identified the micro RNA, miRNA-132 as a CREB target [150]. It was observed that overexpression of miRNA-132 in cortical neurons increases the number of primary neurites, while blocking miRNA-132 function decreases neurite growth [151]. Sequence variations in CREB1 promoter and introns have been associated with depression, linking the CREB-signaling pathway to the pathophysiology of mood disorders [152].

The Calcium-RESponsive Transactivator (CREST) is a gene that links activity-dependent transcription to dendrite growth. Mutant mice deficient in CREST show defects in cortical and hippocampal dendrite development [153]. Interestingly, CREST-null neurons are not able to elaborate dendrites in response to depolarization, indicating that CREST is required for calcium-dependent dendritic growth and branching. The mechanism of activation in response to neural activity appears to be different than others activity-dependent transcription factors. CREST binds to the CREB-binding protein (CBP) and the chromatin remodeling protein BRG-1 [154] through distinct domains. While the association with CBP facilitates the transcription, the association with BRG1 suppresses CREST-mediated transcription in resting neurons by recruiting histone deacetylase (HDAC) complex to the promoter. Upon calcium influx the HDAC complex is released and CBP is recruited to the promoter by a CREST-dependent mechanism leading to transcriptional activation of genes involved in dendrite development [155]. Interestingly, mutations in CREST

have been associated to amyotrophic lateral sclerosis (ALS). One of the identified CREST mutations in the ALS patients was found to introduce a stop codon removing the nine amino acids involved in the interaction of CREST with CBP. The introduction of this mutant in cortical neurons under depolarizing conditions resulted in the inhibition of dendrite growth and a markedly decreased complexity of the dendritic arbors [156].

Other activity-dependent transcription factor involved in dendrite morphogenesis is the myocyte enhancer factor 2A (MEF2A). Knockdown studies revealed that MEF2A plays a key role in the morphogenesis of dendritic claws, specialized cup-like structures involved in postsynaptic differentiation of cerebellar granule neurons, in vivo. Downregulation of MEF2A results in a reduction of dendritic claws, but not in total dendrite growth, indicating that MEF2A plays a crucial role in dendrite postsynaptic differentiation. It has been described that MEF2A is dephosphorylated at Ser408 by calcineurin in response to neuronal activity, promoting a switch from sumoylation to acetylation at Lys403, which results in the activation of MEF2A and inhibition of dendrite claw differentiation [157].

Over the past years, the homeobox transcription factors Cux1 and Cux2 have emerged as novel regulators of dendritic branching, spine morphology and synapses in certain cortical neurons. Knockout and knockdown analysis reveal that Cux1 and Cux2 are intrinsic and complementary regulators of dendrite branching, spine development and synapse formation of the upper layer neurons of the cortex [158]. These factors control the number and development of dendritic spines partly through direct regulation of the expression of chromatin remodeling genes, Xlr3b and Xlr4b, which are implicated in cognitive defects [159, 160]. In agreement with these observations Cux2-deficient mice showed defects in working memory indicating that Cux2 influences circuits involved in cognition [161]. Interestingly, changes in Cux1 and Cux2 levels have distinct effects in the development of apical and basal cortical dendritic arbors. Cux2-deficient mice shows that the reduction in total length of cortical dendrites is more pronounced in the apical compartment, while the knockdown of Cux1 in cortical neurons shows a stronger effect in dendrite development of basal dendrites [162].

The Zinc finger (ZF) transcription factor Sp4 is highly expressed in the developing hippocampus and cerebellum [163] and it has been involved in dendritic development. Sp4 activity is likely to be highly dependent upon the cellular and developmental contexts of its expression. In dentate granule neurons of the hippocampus, Sp4 promotes dendrite growth and branching [164] but in developing cerebellar granule neurons, Sp4 limits dendrite branching and promotes activity-dependent dendritic pruning [165, 166]. Thus, knockdown of Sp4 results in an increased number of highly branched dendrites during maturation of cerebellar granule neurons in dissociated cultures and in organotypic slices [165], while overexpression of Sp4 promotes dendritic remodeling in depolarizing conditions. Different Sp4 target genes that mediate pruning have been identified. Nwk2 was described as a target of Sp4 that regulates dendrite development and NMDA receptor GluN1 levels in developing c0erebellar granule neurons. Knockdown of Nwk2 in these cells increase primary dendrite number, mimicking Sp4 knockdown phenotype, whereas exogenous expression of Nwk2 in Sp4-deleted neurons rescued dendrite number [167]. Furthermore, it was reported that Sp4 can bind to the NT3 promoter repressing its expression [166]. As NT3 is known to promote dendrite development, this finding indicates that Sp4-dependent repression of NT3 plays an essential role restricting dendrite branching. During the last years, alterations at the Sp4 locus have been associated to psychiatric disorders, such as bipolar disorder and schizophrenia [168, 169]. Reduced levels of the Sp4 protein have been described in the cerebellum and prefrontal cortex (PFC) of subjects with bipolar disorder and associated with severe negative symptoms of schizophrenia [170, 171]. Additionally, mice with reduced Sp4 expression displayed deficits in learning and memory [172] and decreased long-term potentiation in hippocampal slice recordings [173].

Finally, the Pea3 (Polyoma enhancer activator 3) subfamily of ETS (E26 transformation specific) transcription factors, which comprise three members, namely Etv1, Etv4 and Etv5 (also named Er81, Pea3 and Erm) has emerged as a group of relevant mediators of proper dendrite morphogenesis. Interestingly, these factors have been described to be downstream effectors of neurotrophic factors in different neuronal populations [174–177]. Thus, the induction of Etv4 in response to GDNF was shown to be essential to control dendrite patterning in specific spinal motoneuron pools [178]. Recently, Etv4 and Etv5 have been reported to be involved in pyramidal hippocampal dendrite development. Gain and loss of function experiments indicate that these two transcriptional factors are required for proper development of hippocampal dendritic arbors and spines. Genetic ablation of Etv4 and Etv5 in hippocampal neurons causes deficits in dendritic size and complexity of CA1 hippocampal dendritic arbors, which are associated with impaired cognitive functions. It was demonstrated that Etv4 and Etv5 are induced in response to the neurotrophin BDNF, supporting that these two molecules are part of a transcriptional program required for proper hippocampal dendrite connectivity triggered by BDNF [179].

Although the transcriptional control of gene expression represents a major mode of cell-intrinsic regulation for neuronal development, the function of transcription factors has to be considered in the context of other cellular partners.

Certainly, the combination of the transcription factors present in a neuron at defined times and cellular conditions regulate the expression of specific transcriptional programs, resulting in different dendrite morphologies. As we described, several transcription factors have emerged as key regulators of dendrite patterning in vertebrates. However, it remains essential to decipher how these distinct molecules are integrated to elaborate specific dendritic architectures.

Control of dendrite development by RNA molecules

Local protein translation in dendrites

Several studies over the last 20 years have shown the important regulatory functions of different families of RNA in neuronal dendrite development. The localization of mRNAs and translation in specific neuronal compartments allow polarized cells to regulate the expression of a specific repertoire of genes rapidly in response to local external cues. This enables strict and rapid control of local protein concentration in specific compartments. Dendritic shafts and spines contain polyribosomes, translation factors and mRNAs, indicating that the mRNAs can be translated in these locations. Dendritic local translation has been described in response to different external factors, and plays a crucial role in synaptic plasticity [180–182]. Different mRNAs with diverse cellular functions have been localized in dendrites including, mRNAs coding for cytoskeletal molecules (i.e., β-actin, MAP2, LIMK1), signaling factors (i.e., CaMKIIα, PKMζ), neurotrophic factors (i.e., BDNF), as well as different subunits of neurotransmitter receptors of the AMPA (i.e., GLuA1 and GLuA2) and NMDA (i.e., GluN1) families [183–186].

It is well established that mRNAs can be located into axons and dendrites, but the precise mechanism by which specific sets of mRNAs are transported, targeted and distally translated are under active investigation. Dendrites contain mRNAs that are transported to specific subcellular compartments based on the presence of specific sequences or structural motifs usually located in the 3′ untranslated region [182]. The importance of the correct location of these coding mRNAs was demonstrated in a mouse model lacking the CamKIIα 3′ UTR, which showed a significant reduction of CamKIIα in post synaptic densities (PSDs) and a reduction in the late phase of long-term potentiation (LTP) as well as memory impairments [187]. Another example of the importance of mRNA location involves the local translation of the neurotrophin BDNF. It has been previously established that short 3′ UTR BDNF-mRNA is restricted to cell bodies whereas long 3′ UTR BDNF-mRNA is transported to dendrites for local translation [188]. It was reported that dendritic translation of BDNF from long 3′ UTR BDNF-mRNA is required for spine maturation and pruning in rat hippocampal neurons, indicating that dendritically synthesized BDNF is a key regulator of structural plasticity [189].

For local translation, the transcripts are packaged with ribonucleoproteins (RBPs) into RNA granules or ribonucleoproteins particles (RNPs) and transported along the cytoskeleton to their final destination. One of the main characterized RBPs associated with mRNA transport is Staufen (Stau) [190]. Two distinct proteins exist, Stau1 and Stau2. The loss of Stau1 leads to impaired dendritic spine morphology in hippocampal pyramidal cells [191, 192]. In addition to mRNA transport, translation control is required to express proteins in a spatially restricted manner and it has been shown that different translation repressors such as Pumilio 2 (Pum2), the zipcoding binding protein 1 (ZIP1), the fragile X mental retardation protein (FMRP) and other RBPs interact with the RNAs to inhibit protein synthesis during transport. Pum2 is a repressor of local protein translation and its downregulation results in dendritic spine reduction in rat hippocampal primary neurons and knockdown of Pum2 in mice results in epilepsy [192, 193]. Moreover, reduced Pum2 expression was observed in patients with temporal lobe epilepsy [194]. Another RNA-binding protein found in RNP is ZBP1, which has been described to be crucial for cellular β-actin mRNA localization and proper spine growth [195, 196]. Knockdown and overexpression of ZBP1 in developing rat hippocampal neurons in culture result in dendritic arbor simplification and β-actin mislocalization [197]. Several studies have indicated the relevance of translational repressors in neurological diseases. Thus, fragile X syndrome (FXS), the most-frequently inherited form of intellectual disability and the most-prevalent single-gene cause of autism, results from mutations in the gene coding for the ribonucleoprotein FMRP [198]. Beside mRNA transport and translation inhibition, there is evidence indicating that synaptic proteome acts by mediating local degradation of translation suppressors [199, 200]. Upon stimulation, RBPs are recruited to specific synaptic sites. Recent evidence suggests that the mammalian target of rapamycin (mTOR) recruits target mRNAs through the RNA-binding protein HuD [201]. RNA granules became unpacked and released from translation suppression. In agreement with a crucial role of local translation in dendrite remodeling, it has been demonstrated that mTOR is crucial for proper dendritic arbor morphology of hippocampal neurons [202].

Growing evidence indicates that defects in RNA localization and translation are associated with molecular pathologies of neurodevelopmental disorders and neurodegenerative diseases [203, 204].

Control of dendrite patterning by regulatory RNAs

In addition to the coding RNA localized in dendrites, small non-coding RNAs have been detected in this cellular compartment. A small group of non-coding RNAs, micro RNAs (miRNAs), has been recently shown to be involved in translational control during the nervous system development. miRNAs are endogenous short (typically 21 nucleotides long) non-coding single-stranded RNAs that are involved in regulating protein expression post-transcriptionally by binding to the target messenger-RNAs (mRNA) and interfering with mRNA translation [205]. Functional studies of miRNA in the mammalian nervous system have emerged during the last years. These miRNAs have been implicated in different steps of neuronal maturation, including dendritic and axonal growth, and spine development. Since 2006, different miRNAs have been detected in dendrites of primary rat hippocampal neurons using highly sensitive fluorescent in situ hybridization (FISH) protocols [206]. Here we discuss some examples of miRNAs that play crucial roles in dendrite development (see Table 1).

miR-9 is one of the most abundant miRNA described in dendrites. Recently, Giusti and colleagues demonstrated a novel developmental role of this miRNA in the post-mitotic neuronal differentiation controlling dendrite growth and synaptic transmission in vivo [207]. In this work, the authors showed that miR-9 promotes these dendritic effects, downregulating the transcriptional repressor REST, which is essential for proper dendritic growth. Important functions in dendrite development were also assigned to other miRNA molecules such as miR-137. It was described that overexpression of miR-137 inhibits dendrite morphogenesis, phenotypic maturation and spine development in brain and cultured primary neurons by targeting the ubiquitin ligase Mib1 (Mind bomb-1), which is abundantly expressed in the adult brain and plays an important role in neuronal morphogenesis [208, 209]. Another miRNA involved in the correct elaboration of the dendritic tree is the activity-regulated miR-134. This miRNA is included in the gene cluster miRNA-379-410 regulated by the transcription factor MEF2. Specifically, miR-134 regulates activity-dependent dendritogenesis in cultures of hippocampal neurons by regulating the RNA-binding protein and translational repressor Pum2 [210], and negatively modulates spine growth by controlling the cytoskeletal protein LimK1, a serine/threonine kinase that regulates actin polymerization via phosphorylation of the actin-binding factor cofilin [206]. miR-138 is another miRNA that has been involved in dendrite plasticity, and was implicated as a potential regulator of memory performance in humans [211]. CREB target, miRNA-132 [150] has also been implicated in dendrite development. Overexpression of this miRNA in cortical neurons results in an increase in neurite number, and blocking its function leads to a decrease in neurite outgrowth. This miRNA controls dendrite development by regulating p250GAP, a factor involved in cytoskeletal remodeling [151, 212].

Further studies are required to elucidate the underlying mechanisms through which miRNA regulate dendrite patterns in the vertebrate nervous system. Many questions require further analysis including: How are miRNAs transported to and maintained in dendrite compartments? Which is the physiological relevance of the different miRNAs for dendrite development? How is miRNA-dependent translation regulated by neuronal activity?

A large proportion of the mammalian genome comprised long non-coding RNAs (lncRNAs) that have little or no coding capacity, and have emerged during the last years as critical regulators of various cellular processes. A significant fraction of these lncRNAs is expressed in rodent brain, in an activity-dependent manner, and with a specific temporal pattern [213–215]. Circular RNAs (circRNAs) subfamily of lncRNAs, can be distinguished from their linear counterparts by their continuous closed loop structure generated by an unconventional head-to-tail splicing event [216–218]. Interestingly, there is a much higher diversity of circRNA species in the brain compared to other tissues. Different studies have revealed that circRNAs are regulated during neuronal differentiation and nervous system development [218, 219]. The physiological role of most circRNAs remains unknown. It has been proposed that binding of specific miRNAs by circRNAs can regulate miRNA expression levels competitively suppressing their function by acting as miRNA sponges [220]. CircRNAs have a preferential subcellular distribution in neurons and are enriched in dendritic preparations [221], suggesting an important contribution of these molecules for dendrite development. Interestingly, circRNAs from genes with synaptic functions, such as Dscam and Homer, have been observed in dendritic structures of hippocampal neurons, indicating an active transport of these molecules to specific neuronal locations [219, 221]. It is not clear what the exact role of circRNA in dendrite development is, but loss-of-function approaches targeting specific circRNAs would be important to understand their physiological relevance for dendritic morphology and function.

Control of dendrite development by cytoskeletal remodeling molecules

Cytoskeletal regulators

Correct development of dendrites requires coordinated organization of cytoskeletal components such as actin and tubulin. Different extracellular signals can act on surface molecules and exert their effects by signaling to the

cytoskeleton. The Ras-related small GTPases such as RhoA, Rac1 (Ras-related C4 botulinum toxin substrate 1) and Cdc42 (Cell division control proteins 42 homologue) regulate growth dynamics of the cytoskeleton to control dendrite growth, branching and spine formation in mammalian neurons [222–224]. These molecules cycle between an inactive GDP-bound state and an active GTP-bound state. The activation state of GTPases is regulated by the action of guanine-nucleotide exchange factors (GEFs), which enhance the exchange of bound GDP for GTP; and GTPases activating proteins (GAPs), which increase the intrinsic rate of hydrolysis of bound GTP. Many pieces of evidence indicate that these molecules are involved in different steps of dendrite maturation. In different neuronal systems, Rac1 has been associated with dendrite elaboration and maturation. The expression of a dominant-negative Rac1 in hippocampal pyramidal neurons leads to a reduction in the number of primary dendrites and progressive spine loss, reflecting a requirement for Rac1 in dendritic development and long-term spine stability [225, 226]. Similarly, the expression of a dominant-negative Cdc42 results in a reduction of dendritic development in cortical neurons. Conversely, Rac1 or Cdc42 overexpression in these neurons leads to an increase in the number of primary dendrites [226]. In contrast to the role of Rac1 and Cdc42 in dendrite formation, expression of activated RhoA mutants results in a dramatic simplification of dendritic branching [225, 227, 228]. Moreover, Rac1, Cdc42 and RhoA have been shown to play essential roles in spine morphogenesis. While Rac1 promotes the formation and stabilization of spines, RhoA inhibits spine formation and maturation [227, 229]. Consistent with this concept, mutants of genes that regulate small Ras-GTPAses, such as GAPs and GEFs present altered dendritic phenotypes. Thus, genetic ablation of the RhoA activator GEF1 resulted in increased spine density [227, 230]. Studies in hippocampal neurons have identified the Rac1 guanine nucleotide exchange factor Tiam1 as a critical mediator of NMDAR-dependent dendritic spine development [231]. Tiam1 has also been shown to cooperate with the polarity protein PAR-3 to modulate dendritic spine morphogenesis [232] and to mediate EphB receptor-dependent dendritic spine formation in hippocampal neurons [233]. On the other hand, it has been reported that loss of the Rho-GEF, Ephexin1 in cultured hippocampal neurons or in vivo perturbs the ability of ephrinA to induce EphA4-dependent spine retraction [234]. In agreement with the role of small Ras-GTPases in the control of dendrite arborization, branching and spine formation, molecules that are downstream of them have been involved on dendrite development. Thus, the overexpression of the Rac1 downstream effector Pak1 (serine/threonine kinase p21 activated kinase) in cortical neurons increases the number of dendrites and the branching of the apical dendrites, while the introduction of a dominant-negative form of Pak1 causes a reduction of these morphological features [235]. On the other hand, inhibition of the major RhoA target, ROCK, blocks spine loss [228, 236], while overexpression of a constitutively active version of ROCK in hippocampal cultured neurons results in the reduction of dendritic complexity to an extent similar to that of activated RhoA [225].

The actin cytoskeleton is a structural element underlying the proper development and morphology of dendrites and dendritic spines. The rapid modification of the three-dimensional structure and dynamics of actin filament networks in response to extracellular cues allows the neuron to respond appropriately to the external factors. The different conformations of actin filament networks are regulated by actin-binding proteins (ABPs), which have different functions regulating actin polymerization and stabilization [237]. One of the most important regulators of dendrite spine growth is the Arp2/3 complex. This molecular complex binds to the sides of existing actin filaments and drives nucleation of a new filament, generating a dense network of branched actin. The Arp2/3 complex is concentrated in dendritic spines, and depletion of its activators such as WAVE-1 and N-WAPS leads to aberrations in spine morphology and behavioral abnormalities [238–241]. Another actin assembly protein important in dendritic spine development is the Formin, which belongs to a family of ABPs, and which is involved in polymerization of linear actin filaments. Several members of this family of proteins, such as FMN2 and mDia2, have been demonstrated to be important for the actin-dependent formation of dendritic filopodia during the initial stages of spine formation [242, 243]. Finally, it is interesting to mention that Profilin, a G-actin-binding protein that allows actin to polymerize, is recruited to dendritic spines in an activity-dependent fashion, promoting spine stabilization [244].

Dendritic patterning is also controlled by microtubule (MT) bundles, which are required for dendritic arbor growth, maintenance and trafficking of cargos including organelles, neurotransmitter receptors, postsynaptic density (PSD)-structural proteins, and specific mRNAs for local protein synthesis within dendrites. While axonal microtubules are polarized (with the plus ends facing the end of the axon), dendritic microtubules present a mixed polarity that facilitates bidirectional cargo transport by MT-based motors. The formation and dynamics of MTs are regulated by different molecules including assembly and stabilizing factors as well as posttranslational modifications.

Structural microtubule-associated proteins (MAPs), such as MAP2 and MAP1A, are enriched in dendrites and have been shown to be involved in dendrite development. Inhibition of MAP2 production by the addition of MAP2 antisense oligonucleotides in the culture medium of cerebellar neurons results in the inhibition of the initial dendritic

formation and growth [245, 246], indicating that MAP2 is essential for dendritic growth by selectively stabilizing dendritic MTs. In agreement with this, genetic ablation of MAP2 results in a reduction in MT density in dendrites and leads to significant reduction in dendrite elongation. Interestingly, MAP1A has also been described to be required for activity-dependent growth, branching and stabilization of the developing dendritic arbors [247–249].

Several evidences indicate that the interaction between microtubules and actin filaments are essential for dendrite development and dendritic spine formation. Microtubule plus-end tracking protein CLIP-170 and the actin-binding protein IQGAP1 have been involved in the regulation of dendrite morphology of rat neurons by coordinating the interaction between microtubules and actin cytoskeleton [250].

Although for a long time MTs were considered to be distributed along the dendritic shaft in mature neurons but absent from dendritic spines, current evidence indicates that neuronal MTs enter to dendritic spines [251, 252]. MT spine entry has been associated with transient morphological changes, such as the formation of spine head protrusions and rapid spine growth. It has been reported that growing microtubule plus ends decorated by the microtubule tip-tracking protein EB3 enter spines and regulate the assembly of actin filaments modulating spine morphology [252]. Moreover, depletion of EB3 results in a reduction of spine density [253]. Other proteins have also been described to be involved in this process. It has been shown that IQGAP1 mutant lacking the domain involved in CLIP-170 interaction results in a reduction in the number of mushroom-type spines [254]. MT invasion into spines is regulated by both neuronal activity and BDNF. While NMDA-dependent long-term depression in hippocampal neurons resulted in a rapid loss of MT dynamics in dendrites and spines [255], BDNF treatment prolongs MT invasion into dendritic spines [251].

Motor proteins

Dendritic transport of neurotransmitters, cytoskeletal proteins, membrane lipids, mRNAs as well as of organelles, is essential for correct dendrite development and function. Molecular motors from the kinesin, dynein and myosin superfamilies have been identified as transporters of different cargos that are essential for proper maturation of dendritic structures. Along axons and dendrites, microtubules and actin microfilaments represent the major longitudinal cytoskeletal structures. Kinesin and dyneins transport different cargos along microtubules. At the synaptic regions, actin filaments are the mayor cytoskeletal structures and myosins convey the cargos. In dendrites, various cargos are transported by kinesins. It has been described that the kinesin family motor KIF5 plays a critical role in dendrite development, as it is required for transport of different neurotransmitter receptors. By interacting with the scaffold protein GRIP, KIF5 transports the AMPA receptor subunit GLuA2 to dendrites, while $GABA_A$ receptors are transported to dendrites by KIF5 via Huntingtin-associated protein 1 (HAP1) [256]. Interestingly, recent studies have indicated that KIF5 binds to mRNA-containing protein complexes in dendrites [257] and fragile X mental retardation protein (FMRP) has been implicated in the association of mRNAs to KIF5 [258]. Another kinesin family motor, KIF17 (also known as OSM3), is localized mainly in the cell bodies and dendrites of neurons [259, 260] and transports vesicles containing NMDA receptor GluN2B to dendrites through the scaffold complex LIN10–LIN2–LIN7 [260, 261]. Moreover, KIF17 has also been involved in the distribution of glutamate receptor subunit, GLuK1, and the voltage-sensitive channel Kv4.2 to dendrites [262, 263]. In agreement with this, transgenic mice overexpressing KIF17 showed enhanced spatial and working memory [264]. Finally, the kinesin KIFC2, which is abundantly expressed in the adult brain and localized in cell bodies and dendrites, has been associated with the transport of multivesicular body-like organelles in dendrites [260, 265].

Cytoplasmic dynein is a multisubunit complex that transports diverse cellular cargo towards the minus ends of microtubules. In dendrites, cargo carried by cytoplasmic dynein includes molecules such as glycine receptor vesicles, and messenger ribonucleoprotein complexes, such as the LSm-1/CBP80-mRNPs complex, as well as Rab5 and Rab7 containing endosomes and organelles such as mitochondrias [266–268]. Dynactin is a multiprotein complex of more than 20 subunits that interacts with the dynein and mediates dynein-cargo interaction. The TRAK family adaptor protein TRK2 predominantly interacts with dynein/dynactin and mediates mitochondria dendritic targeting. TRK2 knockdown reduces dendritic outgrowth and branching [269].

The myosin superfamily of motor proteins also plays an essential role in dendrite development. Myosin II was detected in the postsynaptic dendrites of the mature brain, and it has been involved in the organization of actin bundles [270]. It was demonstrated that myosin II motors regulate neuronal plasticity by imparting mechanical forces onto the spine actin cytoskeleton in response to synaptic stimulation [271]. Another member of the myosin superfamily, Myosin-Va has been associated with the dendritic transport of mRNP complexes [272]. By lost of function assays performed in hippocampal neurons, it was shown that myosin-Va facilitates the transport of mRNP complexes in dendritic spines [273, 274]. Recently, it was shown that Myosin-Va mediates BDNF-dependent recycling of its receptor TrkB and its translocation into dendritic spines [275], which is

important for the maintenance of prolonged BDNF downstream signaling during LTP. Myosin VI has also been associated with dendrite development and dendritic spine maturation. Mice deficient in Myosin VI ($Myo6^{-/-}$) have fewer synapses and the dendritic spines of hippocampal neurons are smaller [276]. It was shown that myosin VI regulates the stimulation-dependent internalization of AMPARs [277] and is required for internalization of the activated TrkB in response to BDNF [278], essential for BDNF/TrkB signaling during LTP. During the last years, it has become increasingly evident that molecular motors are essential for the establishment of correct dendritic development and deficiencies in these molecules have been associated with different neuronal diseases [279].

Interestingly, different genes coding for motor proteins with important roles in dendrite development have been associated with developmental and degenerative diseases. Thus, mutations in human homolog dynein cytoplasmic 1 heavy chain (DYNC1Ha) have been linked to spinal muscular atrophy, Charcot–Marie–Tooth disease and mental retardation. Mutations in human kinesin KIF5 is associated with cortical dysplasias [280].

Secretory pathways and dendrite morphology

Finally, it is important to mention the role of dendrite specific membrane systems in the elaboration of dendritic arbors. In neurons, two separate secretory pathways have been described. In the canonical pathway, proteins are synthesized and post-translationally modified in the somatic endoplasmic reticulum (ER), transported to a perinuclear Golgi for additional modifications, and targeted distally via post-Golgi vesicles. Besides this canonical pathway, it has been suggested that another local secretory pathway also exists in dendrites, as they contain a continuous ER [281, 282] and satellite Golgi cisternae, known as Golgi outposts (GOPs) [283–285]. This alternative secretory pathway has emerged over the past several years as an essential player in dendritic morphogenesis. Dendritic GOPs are developmentally regulated and they are evident during periods of dendritic outgrowth and synapse formation [286]. In hippocampal neurons, GOPs have been found in main dendrites and concentrated at branching points [21]. Manipulations that selectively block Golgi trafficking result in the disruption of dendrite growth in developing neurons and shrinkage of dendrites in mature pyramidal neurons [21, 22]. Studies over the past several years indicate that ER that extends as a continuous network in dendrites also plays an important role in the localization of essential proteins in dendrites. Additional recent studies indicate that dendritic endoplasmic reticulum might play a role in the dendritic localization of relevant proteins such as AMPA and the GABA type B metabotropic receptors [287, 288]. Proteins that control secretory trafficking have been implicated in the control of dendrite morphology. In particular, knockdown of Sar1, a GTP binding protein that functions in trafficking from ER to Golgi, reduces the total dendritic, but not axonal length of cultured hippocampal neurons, indicating that the secretory trafficking from ER to Golgi affecting membrane supply from soma to dendrites [285]. Understanding how these secretory mechanisms are controlled in different neuronal types to generate characteristic dendrite morphologies, represent a new and exciting area of research.

Conclusions

Investigations of dendrite development have led to the identification of a hugely complex set of extrinsic factors and intracellular signaling pathways that regulate different aspects of dendrite patterning. Here, we have discussed the main categories of regulators including extrinsic factors, represented by secreted signals, contact-mediated cues and neuronal activity as well as cell-intrinsic molecules that without strictly depend on external factors can mediate or regulate intracellular responses to them.

Proper development of neuronal type-specific dendrite patterns is essential for the correct function of the nervous system. Although we have begun to identify molecular determinants of dendrite patterning, these molecular mechanisms have been studied in a relatively small number of vertebrate neuronal types. Future efforts using time-inducible neuronal type-restricted knockout mice or transgenic mice engineered to express optogenetic tools in a cell-specific manner [289] represent powerful approaches that should allow us to understand how different types of neurons achieve their dendrite patterns in vivo.

The extrinsic signals that regulate dendrite morphology are not unique to this process, since they also control various aspects of neuronal development, such as axonal growth and guidance. It is therefore relevant to understand how these factors can generate specificity in their response. The location of key downstream signaling mediators in specific neuronal compartments generating opposite responses between axons and dendrites in response to the same guidance cue, represents a strategy to obtain specificity. For example, the specific localization of soluble guanylate cyclase (sGC) in cortical pyramidal neurons only in the dendritic compartment appears to mediate the attraction of apical dendrites and the repulsion of the axons in response to the same gradient of the guidance cue Sema3A [82].

Besides location, the developmental stage at which an extracellular factor participates also appears to contribute to specificity. Thus, in developing cerebellar granule neurons, at early stages calcium influx appears to promote

dendritic growth, whereas at later developmental stages calcium triggers dendrite pruning and retraction [129, 130].

It has been well established that several different classes of proteins and regulatory RNAs play crucial roles in determining the formation, maintenance and refinement of dendritic arbors. Due to the broad array of molecules regulating dendrite arborization there is enough evidence to assume that dendrite development requires the coordinated action of different classes of proteins.

During development, different dendritic domains encounter similar environmental cues. It is now evident that cell-intrinsic modulators, located within specific domains of the dendrites (for example, proximal vs. distal and apical vs. basal domains), control the cellular interpretation of the extrinsic cues, thereby allowing that different neuronal types generate distinctive morphologies. Thus, in the future it will be essential to determine how these cell-intrinsic drivers, located in selected dendritic domains, can promote specificity during dendrite morphogenesis.

Alterations in dendrite complexity and in the number and morphology of dendritic spines have been detected in postmortem brains of individuals with neurodevelopmental and neurodegenerative disorders, such as autism spectrum disorders (ASD), Down syndrome, Rett syndrome and Alzheimer disease. Although in some cases these abnormalities may be consequences of the disorder, they could also be important contributors of disease pathogenesis, since human genetic studies of these disorders have implicated genes involved in processes underlying the control of neuronal connectivity such as neurite growth and synapse formation [280, 290].

Certainly, future studies identifying genes critically involved in the induction of dendritic abnormalities, leading to circuit deficits, may provide a link between dendritic phenotypes and neuronal dysfunction.

Acknowledgements We thank Carly McCarthy for comments on the manuscript. Work in the author's laboratory is funded by Grants from the Argentine Agency for Promotion of Science and Technology (ANPCyT) PICT2013-0914, PICT2014-2155 and UBACyT 2013-2016GC (20020120100026BA), and UBACyT 2014-2017GC (20020130100779BA). FL and GP are supported by an independent research career position from the Argentine Medical Research Council (CONICET), Argentina.

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