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Molecular basis of dendritic arborization

Malgorzata Urbanska[1,2], Magdalena Blazejczyk[1,3], and Jacek Jaworski[1]*

[1]International Institute of Molecular and Cell Biology, Warsaw, Poland, *Email: jaworski@iimcb.gov.pl; [2]Warsaw University of Life Sciences, Warsaw, Poland; [3]Laboratory of Molecular Neurobiology, Nencki Institute, Warsaw, Poland

The pattern of dendritic branching along with the receptor and channel composition and density of synapses regulate the electrical properties of neurons. Abnormalities in dendritic tree development lead to serious dysfunction of neuronal circuits and, consequently, the whole nervous system. Not surprisingly, the complicated and multi-step process of dendritic arbor development is highly regulated and controlled at every stage by both extrinsic signals and intrinsic molecular mechanisms. In this review, we analyze the molecular mechanisms that contribute to cellular processes that are crucial for the proper formation and stability of dendritic arbors, in such distant organisms as insects (e.g. *Drosophila melanogaster*), amphibians (*Xenopus laevis*), and mammals.

Key words: dendritic arbor, signal transduction, cytoskeleton dynamics, protein synthesis, membrane trafficking

INTRODUCTION

Dendrites are the main site of information input into neurons, and different type of neurons have distinctive and characteristic dendrite branching patterns. Advances in electrophysiology and computational modeling have clearly shown that dendritic arbor shape is one of the crucial factors determining how signals coming from individual synapses are integrated (Segev and London 2000, Gulledge et al. 2005). Several neuropathologic conditions are characterized by abnormalities in dendritic tree structure, including a number of mental retardation syndromes (such as Down's, Rett's as well as Fragile X syndrome; for review see: Kaufmann and Moser 2000), schizophrenia (Harrison 1999), and neurodegenerative diseases (for review see Anderton et al. 1998). In addition, animal studies reveal that even mild, prolonged stress can induce the shrinkage of hippocampal dendritic fields, dendritic regression and loss of dendritic spines (Wood et al. 2004, Chen et al. 2008).

Dendritic arbor development is a complex, multistep process (Fig. 1), which generally can be divided, into several different, although partially overlapping, stages: (i) neurite initiation, outgrowth and guidance; (ii) branching and synapse formation, and (iii) stabilization (Kossel et al. 1997, Wu et al. 1999, Portera-Cailliau et al. 2003, Williams and Truman 2004; for review see: Scott and Luo 2001). Although the time scale of these steps differs between species, the sequence of events seems to be very similar. Initial dendrite growth is relatively slow, and a very fast period of dendritic extension follows. For example, total dendritic length increased from ~50 to 100 μm during first 24 h of *X. laevis* tectal neurons dendritic arbor development but almost 4-fold increase was observed during the next 48 hours (Wu et al. 1999). Subsequently, dynamic dendritic branching occurs, which combined with neuronal activity and synapse formation, leads to the establishment of a well-developed dendritic arbor. Stabilization of the dendritic arbor occurs over a long period of time (Wu et al. 1999, Williams and Truman 2004). While the development of dendritic tree associates with high rates of branch additions and retractions, the mature dendritic arbor is less plastic with a very low branch turnover under basal conditions (Wu et al. 1999). Nevertheless, dendritic arbors in the mature nervous system preserve some degree of plasticity. Increased branching was observed in the nucleus

Correspondence should be addressed to J. Jaworski, Email: jaworski@iimcb.gov.pl

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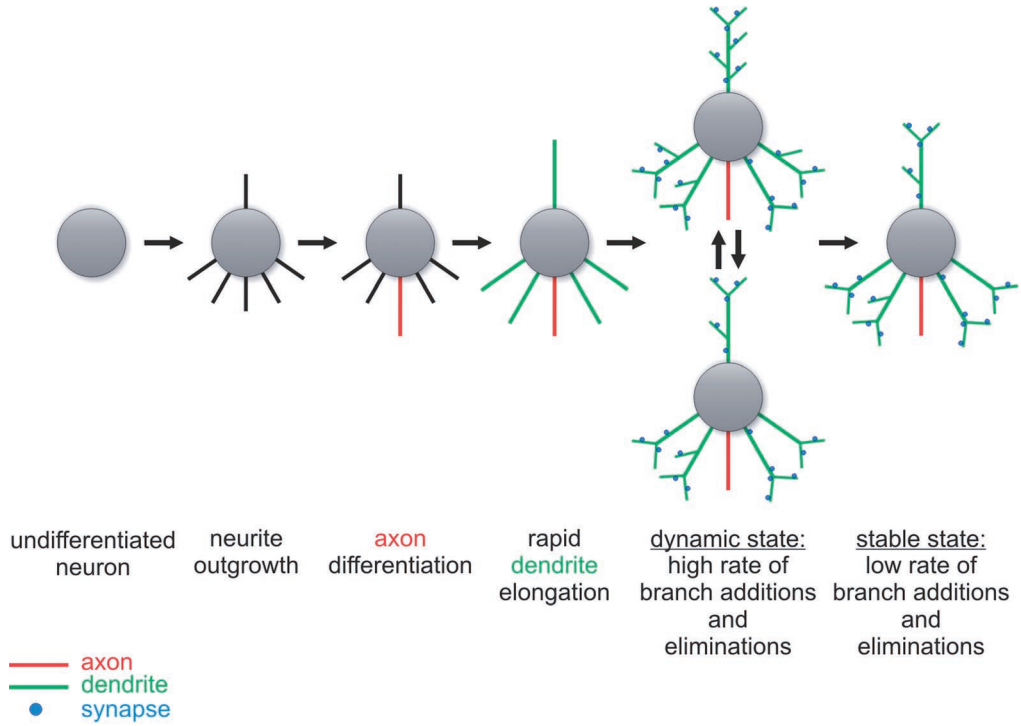

Fig. 1. Development of dendritic arbor consists of several overlapping stages

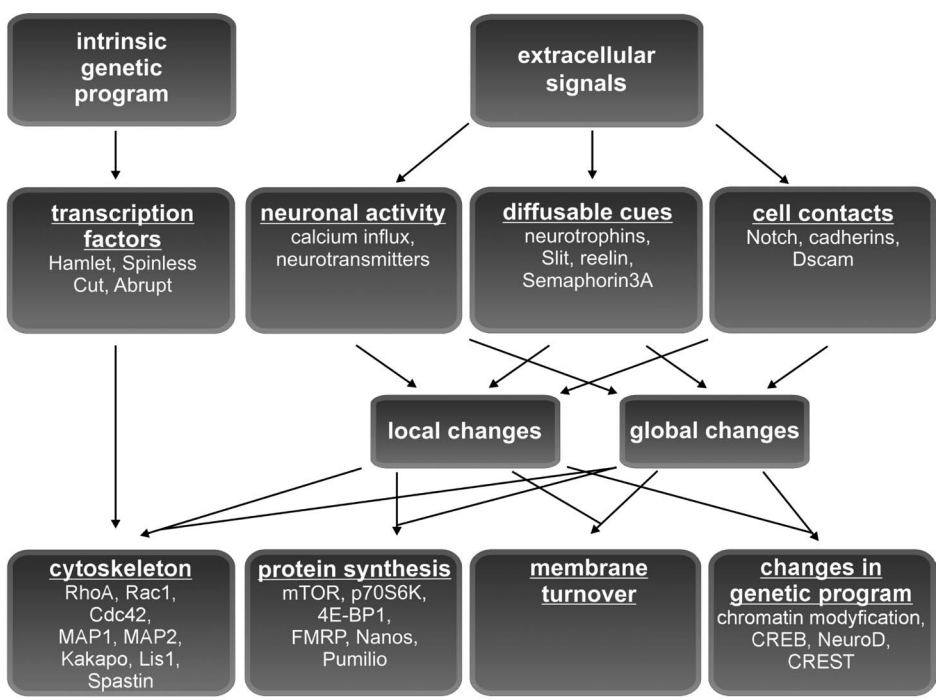

Fig. 2. Dendritogenesis is a process strictly controlled by the combination of an intrinsic genetic program and extracellular signals causing changes in the cytoskeleton, macromolecule synthesis and membrane turnover. Several changes occur either globally or only locally in dendrites.

accumbens and the caudate-putamen upon repeated cocaine administration (Zhang et al. 2006), and in the spinal cord in response to a long-term locomotor training accompanying recovery after spinal cord injury (Gazula et al. 2004).

The complex processes of dendritic arbor development and stabilization must be highly orchestrated at the molecular level. Recent advances in genetic manipulations of neuronal cells helped to reveal a complicated interacting network of dozens, if not hundreds, of proteins involved in signal transduction, macromolecule synthesis, cytoskeleton rearrangements and intracellular trafficking of proteins and membranes (Fig. 2). These processes are regulated by both an intrinsic genetic program and a wide variety of extracellular signals, either globally at the whole-cell level or locally in dendrites.

The aim of this review is to present readers, especially those not familiar with topics of neuronal development and morphology, selected aspects of the molecular biology underlying the complex process of dendritic arbor formation. First, we discuss the impact of a genetic program and signals from the extracellular environment on a dendritic arborization. Second, we describe a role for intracellular events such as signal transduction, cytoskeleton dynamics, transcription, translation, and cellular membrane turnover in translating genetic and environmental instructions to the final shape of a dendritic arbor.

GENETIC PROGRAM AND EXTRINSIC CUES IN DENDRITIC ARBOR DEVELOPMENT

Genetic program – role of transcription factors in dendritogenesis

The genetic program is executed by transcription factors (TFs), several of which determine dendritic patterning independently from extracellular cues. The best examples come from developmental studies of the *Drosophila melanogaster* neurons. Hamlet is a TF expressed during development in the external sensory neurons (es) of the *Drosophila* peripheral nervous system (Moore et al. 2002). Neurons belonging to this particular class develop only a single dendrite and Hamlet expression prevents the es neurons from acquiring a morphology characteristic of multiple dendrite (md) neurons. Knockdown of *hamlet* in precursors of the es neurons results in transformation of these cells to the md neurons with complex dendritic trees. Conversely, overexpression of Hamlet in the md neurons causes growth of only a single dendrite. Hamlet can act alone, but the complex pattern of the dendritic arborization (da) subclass of the md *Drosophila* neurons requires the concerted action of several TFs. Combinatorial expression of Cut, Abrupt, and Spineless define dendritic arbor complexity in the da neuron subclasses. Class I neurons, with relatively simple dendritic arbors, express high levels of Abrupt and Spineless but no Cut. Highly-branched Class IV neurons express intermediate levels of Cut, high levels of Spineless, and lack expression of Abrupt (Parrish et al. 2007). Recent work by Parish and coauthors (2006) identified dozens of TFs that are critical for proper dendritic arborization of the Class I da neurons; however, it is difficult to distinguish which of them act autonomously, executing the intrinsic genetic program independently from extracellular cues, and which respond to extracellular instructions. For example, BAP55, Brm, BAP60 and Snr1, proteins identified during this screen are elements of Brg/Brm associated factor complex that regulates transcription and dendritic branching in an activity-dependent manner (Wu et al. 2007).

Despite examples of autonomously acting TFs in *Drosophila* during specification of dendritic arbor morphology, less is known about similar proteins in the mammalian nervous system. One example is Neurogenin 2 (Ngn2), a basic helix-loop-helix factor that defines a specific pattern of dendritic arborization in pyramidal neurons in cerebral cortex (Hand et al. 2005). Cobos et al. (2005, 2007) showed that Dlx homeobox transcription factors regulate, cell autonomously, dendritic arborization of cortical interneurons. Interneuron precursors, derived from the Dlx1 knockout mice, grafted to the brains of wild-type mice, developed about 40% less dendritic branches, which suggests that even in a normal environment the *Dlx1 -/-* interneurons do not develop properly (Cobos et al. 2005). In double Dlx1/2 mutants, long and poorly branched dendrites and axons develop prematurely, disturbing migration and proper positioning of the interneurons (Cobos et al. 2007).

Table I

Extracellular signals controlling shape of dendritic arbor

Protein/Protein complex	Effect on dendrites	Nervous system structure /Species	Reference
	Neuronal activity related		
AMPAR	DN-Ox – decreased TDL, TDBTN and dendritic arbor (ShA) simplification Inh - decreased branch addition after light exposure	optic tectum /*X. laevis*	Haas et al. 2006 Sin et al. 2002
NMDAR	Inh - decreased branch addition after light exposure	optic tectum /*X. laevis*	Sin et al. 2002
VGCC	KCl application – increased TDL, TDBTN, complexity	hippocampus, cortex, cerebellum/rat, mouse	Redmond et al. 2002, Yu and Malenka 2003, Gaudilliere et al. 2004, Chen et al. 2005, Wayman et al. 2006, Wu et al. 2007
GABAR	GABA application – increased TDL and number of primary dendrites Inh – decreased TDL and number of primary dendrites	cortical subventricular zone-derived, olfactory bulb /rat	Gascon et al. 2006
CaSR	DN-Ox – decreased TDL, dendritic arbor simplification (ShA)	hippocampus /mouse	Vizard et al. 2008
	Diffusable cues		
agrin	Agrin application – increased TDL and number of 2nd order dendrites	hippocampus /rat	Mantych and Ferreira 2001
BDNF	BDNF application – increased TDL WT-Ox – increased dendritic arbor complexity (ShA)	hippocampus, cortex/rat	Wirth et al. 2003, Dijkhuizen and Ghosh 2005, Jaworski et al. 2005, Takemoto-Kimura et al. 2007
BMP	BMP7 application – increased TDL, number of dendrites, TDBTN	SCG, hippocampus /rat	Withers et al. 2000, Guo et al. 2001, Lein et al. 2007
cpg15	WT-Ox – increased TDL, complexity (ShA), growth rate	optic tectum /*X. laevis*	Nedivi et al. 1998
Semaphorin3a	Sema3A application – increased DBPN	cortex/mouse	Morita et al. 2006

Slit	Slit1 application – increased TDL, number of dendrites, DBPN	cortex /rat, mouse	Whitford et al. 2002
Reelin	Reelin application – increased TDL and number of branches	hippocampus /mouse	Jossin and Goffinet 2007
	Cell contacts		
Celsr-2	KnD - dendritic arbor simplification (ShA)	cortex, hippocampus /rat	Shima 2007
Celsr-3	KnD – increased dendritic arbor complexity (ShA)	cortex, hippocampus /rat	Shima et al. 2007
Delta-Notch	DN-Ox - decreased DBPN, increased average dendrite length CA-Ox - decreased average dendrite length KnD – decreased DBPN, increased average dendrite length	cortex/rat	Redmond et al. 2000
Dscam	KO – lost self-avoidance	da /*D. melanogaster*	Hughes et al. 2007, Matthews et al. 2007, Soba et al. 2007
EphrinB-EphB	KO – decreased TDL, number of primary dendrites and complexity Inh – reduced number of primary dendrites	hippocampus /rat, mouse	Hoogenraad et al. 2005
N-cadherin	WT-Ox - increased TDBTN DN-Ox – decreased TDBTN	hippocampus /rat	Yu and Malenka 2003

(ADL) average dendrite length; (CA-Ox) overexpression of constitutively active mutant; (DBPN) dendritic branching points number; (DN-Ox) overexpression of dominant negative mutant; (Inh) non genetic inhibition; (KO) knockout; (Knd) knockdown; (SCG) superior cervical ganglion; (ShA) Sholl analysis; (TDBTN) total dendritic branch tip number; (TDL) total dendritic length; (WT-Ox) overexpression of wild type protein

Role of extracellular signals in the control of dendritic arborization

Evidence for the importance of extracellular guidance for dendritic arborization is overwhelming. Depending on the developmental stage, combinations of (i) diffusible cues, (ii) cell contacts, and (iii) neuronal activity were shown to control dendritic arborization, plasticity and stability (for review see: McAllister 2000, Wong and Ghosh 2002, Jan and Jan 2003, Parrish et al. 2006) (Table I).

Diffusible cues are numerous and a few examples are agrin (Mantych and Ferreira 2001), brain-derived neurotrophic factor (BDNF) (McAllister et al. 1995, Horch and Katz 2002, Tolwani et al. 2002, Wirth et al. 2003, Jaworski et al. 2005), bone morphogenetic protein family members (Withers et al. 2000, Beck et al. 2001, Guo et al. 2001, Lein et al. 2007), cpg15 (Nedivi et al. 1998), reelin (Jossin and Goffinet 2007), semaphorins (Polleux et al. 2000) and Slits (Whitford et al. 2002) (Table I).

Interactions of cell surface proteins like contactin (Berglund et al. 1999), Delta and Notch (Sestan et al.

1999, Redmond et al. 2000), ephrinB and EphB (Hoogenraad et al. 2005), cell adhesion molecule L1 (Demyanenko et al. 1999), N-cadherins (Yu and Malenka 2003, Zhu and Luo 2004) and seven-pass transmembrane cadherins (Flamingo, Celsr2 and Celsr3) (Gao et al. 2000, Shima et al. 2007) are additional important factors, which can accelerate or inhibit dendrite growth and branching (Table 1). For example, Notch and Celsr3 suppress growth and branching of dendrites of cortical pyramidal neurons (Sestan et al. 1999, Redmond et al. 2000, Shima et al. 2007). On the other hand, N-cadherin, Celsr2 and EphrinB-EphB enhance dendritic arborization of hippocampal, as well as, cortical (Celsr2) neurons (Yu and Malenka 2003, Hoogenraad et al. 2005, Shima et al. 2007).

In addition to defining dendrite length and complexity, cell surface proteins ensure proper dendrite-axon contacts and suppress dendrite crossing (Parrish et al. 2007). Recently, Down's syndrome-related cell adhesion molecule (Dscam) attracted attention due to revealed participation in dendrite self-avoidance, a mechanism by which dendrites of a particular neuron avoid contact with one another, which presumably ensures proper coverage of a dendritic field (Zhu et al. 2006, Hughes et al. 2007, Matthews et al. 2007, Soba et al. 2007). Dscam is especially well-suited for this job because of the enormous variability of its isoforms. In *Drosophila*, the alternative splicing of *Dscam* may result in over 35 000 various isoforms. Indeed, it was shown for several types of *Drosophila* neurons that neighboring dendrites expressing the same isoform of Dscam repulse based on a homophilic Dscam isoform interaction (Zhu et al. 2006, Hughes et al. 2007, Matthews et al. 2007, Soba et al. 2007).

In addition to interneuronal interactions, interactions between neurons and glial cells ensure proper dendritic arborization. Yamamoto and colleagues (2006) presented evidence that a neuro-glial interaction *via* Neuroglian (Nrg), a member of the Ig superfamily, is important for the proper dendritic arbor shaping of selected da neurons (ddaE) of *Drosophila*. Nrg knockdown resulted in formation of ectopic dendrites by ddaE neurons, the process that could be reversed only by expression of Nrg in both the ddaE neurons and the accompanying glial cells (Yamamoto et al. 2006).

Neuronal activity is the third category of the extracellular signals important for dendritic arbor development. Neuronal transmission can either increase or decrease dendritic arborization (for more thorough review see McAllister 2000). A very elegant example demonstrating the neuronal activity-dependent positive effects on dendrite growth comes from time-lapse *in vivo* imaging of dendritic arbors of developing neurons in the optic tectum of *Xenopus laevis*. Sin and colleagues (2002) showed that dendritic arbors of the developing tectal neurons are regulated by visual input. A four-hour light exposure resulted in substantial increases in dendrite growth dynamics and total dendritic length. This dendritic arbor reaction to the light was blocked by inhibition of the alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and N-methyl-D-aspartic acid (NMDA) receptor-mediated glutamatergic transmission. Indeed, Ewald and coworkers (2008) showed that precise subunit composition of NMDA receptors (NMDARs) is important for proper dendritic architecture in tectal neurons. Furthermore, overexpression of peptides interfering with AMPAR function led to decreased dendritic branch lifetime and an overall decrease in dendritic arbor complexity (Haas et al. 2006).

In addition to glutamatergic transmission, voltage-gated calcium channels (VGCCs) play a role in dendritic arbor development. Numerous examples from hippocampal, cortical and cerebellar *in vitro* cultures show that depolarization of neurons by an application of KCl leads to increased dendritic growth that can be inhibited by nimodipine, an L-type calcium channel blocker (Redmond et al. 2002, Yu and Malenka 2003, Gaudilliere et al. 2004, Chen et al. 2005, Wayman et al. 2006, Wu et al. 2007). Furthermore, the γ-aminobutyric acid (GABA)-based transmission increased dendritic growth of young interneurons (in which GABA application results in neuronal depolarization and consequent activation of VGCCs) (Gascon et al. 2006). Application of a GABA-A receptor antagonist, bicuculline, caused decreases in dendrite length and in the number of primary dendrites on subventricular zone-derived neurons. Time-lapse imaging experiments showed that GABA acts by stabilizing newly formed dendritic branches. Nevertheless, there are also reports of increased dendritic growth under conditions of neuronal activity inhibition. It was shown that inhibition of the glutamatergic transmission or blockade of the VGCCs led to increased dendritic growth in slices from ferret visual cortex (McAllister et al. 1996, Baker et al. 1997).

It is now widely accepted that the effects of neuronal activity on dendritic arborization are due to elevated cellular concentrations of calcium (for review see: Konur and Ghosh 2005, Redmond and Ghosh 2005). Lohman and coworkers (2002) showed that Ca^{2+}-induced Ca^{2+} release (CICR), locally in dendrites, prevented retraction of dendrites of the chick retinal ganglion neurons. Gascon and others (2006) presented evidence that application of BAPTA-AM, a calcium chelator, resulted in dendritic growth cone destabilization.

But not only intracellular calcium concentration regulates dendritic arbor development. Recent studies showed that extracellular calcium can directly influence dendritic morphology by activating extracellular calcium sensing receptors (CaSR) (Vizard et al. 2008). Overexpression of a dominant negative mutant of CaSR, in hippocampal neurons led to decreased dendritic arbor complexity.

INTRACELLULAR MECHANISMS UNDERLYING DENDRITIC ARBOR FORMATION AND STABILITY

Extracellular factors need intracellular messengers to affect dendritic arbor development. In the second part of this review we present recent developments in our understanding of the molecular mechanisms underlying a conversion of those extracellular signals to changes in a dendritic arbor morphology. We focus on four crucial aspects: signal transduction, cytoskeleton dynamics, gene expression and membrane trafficking.

Major signal transduction pathways in the control of dendritic branching

Extracellular signals activate a myriad of intracellular signaling pathways. Major players in cellular signaling include small G-proteins of the Ras family, protein kinases and protein phosphatases (Table II). In what follows, we will focus on signaling proteins that are among the most well-documented.

The Ras family of small GTPases

Small GTPases of the Ras family play a central role in a neuronal signal transduction and are crucial for several aspects of neuronal development, synaptic plasticity, and learning and memory (Mazzucchelli and Brambilla 2000, Tada and Sheng 2006). Dendritic arbor growth is also heavily regulated by the Ras family proteins, particularly Ras, Rap, and Rit (Table II). Jaworski and coauthors (2005) and Kumar and others (2005) investigated signaling pathways involved in neurotrophic factor-dependent dendritic branching and dendritic spine development, and showed that increased Ras activity led to an increase in the total number of dendrites and the overall complexity of dendritic arbors of hippocampal neurons in culture. Inhibition of an endogenous Ras by overexpression of a dominant negative (DN) mutant, RasN17, blocked dendritic growth induced by both BDNF and calcium/calmodulin-dependent protein kinase I (CaMKI), which is regulated by neuronal activity (Kumar et al. 2005, Wayman et al. 2006). Looking for signaling cascade members acting downstream of Ras, Jaworski and colleagues (2005) showed that the Ras effect on dendritic arbor depended on phosphoinositdide-3' kinase (PI3K), extracellular signal-regulated kinases (ERKs), phospholipase D, and mammalian target of rapamycin (mTOR) kinase. Ras is also important for dendritic development *in vivo* as mice overproducing a constitutively active (CA) mutant of Ras, RasV12, had more elaborated dendritic arbors (Alpar et al. 2003). Although most of the work published so far documents the positive effects of Ras activation on dendritic arborization, recently Huang and others (2007) presented evidence that overexpression of v-KIND, a Ras guanine exchange factor (GEF) leading to Ras activation, inhibited dendritic arbor growth. The potential of v-KIND to decrease dendritic growth and arborization depended on its ability to bind to and increase threonine phosphorylation of microtubule associated protein 2 (MAP2). This behavior may suggest that, under certain conditions, Ras is involved in protein complexes that can have either permissive and inhibitory effects on dendritic arbor development and/or stability.

Additional members of the Ras family, Rap1, Rap2 and Rit, are involved in shaping the dendritic arbor (Table II). Overexpression of a constitutively active form of Rap1 (Rap1V12) in cortical neurons *in vitro* increased the number of dendritic branches, especially those in close proximity to the cell soma (Chen et al. 2005). Overexpression of Rap1N17, a dominant negative mutant of Rap1 resulted in opposite effects, both in dissociated and organotypic neuronal preparations. Moreover, overexpression of either Rap1N17 or

Table II

Proteins involved in intracellular processes underlying dendritic arborization

Protein/ Protein complex	Effect on dendrites	Nervous system structure/Species	Reference
	Signal transduction		
Ras	CA Ox – increased complexity (ShA) Tg – increased total dendritic tree surface	hippocampus, cortex /rat, mouse	Jaworski et al. 2005, Kumar et al. 2005, Alpar et al. 2003
Rap1	DN-Ox – decreased complexity; prevented KCl-induced complexity increase CA-Ox – increased number of proximal branches	cortex/rat	Chen et al. 2005
Rap2	DN-Ox – increased TDL CA-Ox – decreased TDL	hippocampus/rat	Fu et al. 2007
Rit	DN-Ox - increased TDL CA-Ox - decreased TDL	hippocampus/rat	Lein et al. 2007
CaMKI	CA-Ox – increased TDL DN-Ox – prevents KCl-induced TDL increase KnD - prevents Bic-induced TDL increase	hippocampus/rat, mouse	Wayman et al. 2006
CL3/CaMKIγ	WT-Ox – increased TDL KnD, KO – decreased TDL and TDBTN	cortex/rat	Takemoto-Kimura et al. 2007
CaMKIIα	KnD - decreased TDL	cerebellum/rat	Gaudilliere et al. 2004
CaMKIIβ	KnD – decreased dendritic arbor perimeter	hippocampus/rat	Fink et al. 2003
CaMKIV	CA-Ox – increased TDL, TDBTN	cortex, hippocampus /mouse, rat	Redmond et al. 2002, Yu and Malenka 2003
ERK1/2	Inh. - prevents BDNF-induced primary dendrites growth	cortex/rat	Dijkhuizen and Ghosh 2005
JNK1	DN-Ox; KO – increased DBPN and ADL	cerebellum/mouse	
PI3K	WT-Ox – increased TDL DN-OX & Inh. - decreased TDBTN CA-Ox – increased TDL, TDBTN, complexity (ShA) Inh. - BDNF-induced primary dendrites growth inhibition	hippocampus, cortex /rat	Jaworski et al. 2005, Kumar et al. 2005, Dijkhuizen and Ghosh 2005

Akt	DN-OX & Inb - decreased TDBTN and dendritc arbor simplification (ShA) CA-Ox – increased TDBTN, complexity (ShA)	hippocampus/rat	Jaworski et al. 2005, Kumar et al. 2005
mTOR	KnD, Inb - decreased TDBTN and dendritic arbor simplification (ShA)	hippocampus/rat	Jaworski et al. 2005, Kumar et al. 2005
p70S6K	KnD – decreased TDBTN and dendritic arbor simplification (ShA)	hippocampus/rat	Jaworski et al. 2005
GSK3β	Inh. – increased number of dendrites, TDL and dendritic arbor complexity (ShA)	SCG, hippocampus, cortex/rat	Naska et al. 2006
Fyn	KO – decreased DBPN	cortex/rat	Morita et al. 2006
Abl	CA-Ox – increased number of primary dendrites and length Inh. – decreased number of primary and secondary dendrites and length	hippocampus/rat	Jones et al. 2004
Par1b/MARK2	WT-Ox – decreased TDL and TDBTN KnD - increased TDL and TDBTN	hippocampus/rat	Terabayashi et al. 2007
	Cytoskeleton		
RhoA	CA-Ox – decreased number of dendritic segments, TDBTN, dendritic arbor simplification (ShA) CA-Ox – decreased branch additions after light exposure	hippocampus/rat, optic tectum/*X. laevis*	Nakayama et al. 2000, Sin et al. 2002, Yu and Malenka 2003
Rac1	DN-Ox - decreased number of primary dendrites, decreased TDL, TDBTN CA-Ox – increased number of primary dendritesKO – decreased number of terminal branches	cortex/rat, da/*D. melanogaster*	Threadgill et al. 1997, Lee et al. 2003, Rosso et al. 2005
Cdc42	DN-Ox - decreased number of primary dendrites CA-Ox – increased primary dendrites number	cortex/rat	Threadgill et al. 1997
Tiam-1	KnD – dendritic arbor simplification (ShA)	hippocampus/rat	Tolias et al. 2005
Kalirin-7	KnD – decreased TDL and dendritic arbor simplification (ShA)	hippocampus/rat	Ma et al. 2003
Lfc	WT-Ox – decreased number of dendritic segments	hippocampus/rat	Ryan et al. 2005

N-WASP	WT-Ox – increased number of neurites and DBPN	hippocampus/rat	Pinyol et al. 2007
Cobl	WT-Ox – increased DBPN, number of dendrites, decreased dendrite length KnD - decreased DBPN	hippocampus/rat	Ahuja et al. 2007
Pak1	DN-Ox - decreased number of dendrites CA-Ox – increased number of dendrites	cortex/mouse	Hayashi et al. 2002
ROCK	CA-Ox - decreased number of dendritic segments CA-Ox - decreased branch additions after light exposure	hippocampus/rat optic tectum/*X. laevis*	Nakayama et al. 2000, Sin et al. 2002
MAP1 & MAP2	KO – decreased length of dendrites	hippocampus/mouse	Teng et al. 2001
CHO1/MLKP1	KnD – increased dendrite length; dendrite straightening	hippocampus/mouse	Yu et al. 2000
CRMP3	KO – decreased DBPN and TDL	hippocampus/mouse	Quach et al. 2008
Lis1	KO – decreased total number of segments	mushroom body /*D. melanogaster*	Liu et al. 2000
Kakapo	KO – reduced lateral branches	md/*D. melanogaster*	Prokop et al. 1998, Gao et al. 1999
Septin-7	WT-Ox – increased TDBTN and complexity (ShA) KnD – decreased TDBTN and complexity (ShA)	hippocampus/rat	Tada et al. 2007, Xie et al. 2007
	Transcription, mRNA transport, translation		
BAF53	KO - decreased number of dendrites and TDL	hippocampus, cortex, cerebellum/mouse	Wu et al. 2007
CREST	KO – decreased TDL (hippocampus, cortex) and DBPN (cortex)	cortex, hippocampus /rat	Aizawa et al. 2004
MECP2	WT-Ox - dendritic arbor simplification (ShA) KnD – dendritic arbor simplification (ShA)	hippocampus/rat	Zhou et al. 2006
CBP	Inh - decreased TDL and KCl-induced growth	cortex/rat	Redmond et al. 2002
CREB	CA-Ox – increased TDL DN-Ox – decreased complexity, KCl-induced growth inhibition, KnD - KCl-induced growth inhibition	cortex, hippocampus /rat	Redmond et al. 2002, Wayman et al. 2006

NeuroD	KnD - decreased TDL and KCl-induced growth inhibition	cerebellum/rat	Gaudilliere et al. 2004
c-Fos	KO – cocaine induced TDBTN increase inhibition	nucleus accumbens, caudate putamen/ mouse	Zhang et al. 2006
Pumilio	WT-Ox – decreased number of higher order branches KO – higher order branch number reduction of class IV da neurons	da/*D. melanogaster*	Ye et al. 2004
Nanos	WT-Ox - decreased number of higher order branches KO – higher order branch number reduction of class IV da neurons	da/*D. melanogaster*	Ye et al. 2004
FMR1	WT-Ox – decreased number of dendritic ends per 1000 μm2 KO - increased number of dendritic ends per 1000 μm2	da/*D. melanogaster*	Lee et al. 2003
Me31B	WT-Ox – decreased number of higher order branches KO – increased number of higher order branches	da/*D. melanogaster*	Barbee et al. 2007
4E-BP1	WT, CA-Ox – decreased TDBTN and complexity (ShA)	hippocampus/rat	Jaworski et al. 2005
	Membrane turnover		
Protein kinase D	DN-Ox – decreased TDL, TDBTN and complexity (ShA)	hippocampus, cortex /rat	Horton et al. 2005
GRASP65	WT-Ox – disruption of polarized dendrite growth	hippocampus/rat	Horton et al. 2005
SNAP-25	Botulinum neurotoxin A application – decreased TDL	hippocampus/mouse	Grosse et al. 1999
TI-VAMP	WT-Ox – decreased dendrites length and number	hippocampus/rat	Martinez-Acra et al. 1999
Sar1	KO – decreased TDL KnD - decreased TDL	da/*D. melanogaster* hippocampus/rat	Ye et al. 2007

(ADL) average dendrite length; (Bic) bicucculline; (CA-Ox) overexpression of constitutively active mutant; (DBPN) number of branching points; (DN-Ox) overexpression of dominant negative mutant; (Inh) non genetic inhibition; (KO) knockout; (Knd) knockdown; (SCG) superior cervical ganglion; (ShA) Sholl analysis; (Tg) transgenic animal; (TDBTN) total dendritic branch tip number; (TDL) total dendritic length; (WT-Ox) overexpression of wild type protein

Rap1GAP (a GTPase-activating protein for Rap1, a natural inhibitor of Rap1 activity) blocked induction of dendritic arbor growth caused by activation of voltage-gated calcium channels (Chen et al. 2005). In terms of downstream cellular mechanisms, more detailed analyses suggest that Rap1 acts via ERK kinases and activation of CREB-dependent transcription (Chen et al. 2005). Work by Ghosh group, performed on neurons transfected at relatively early stages of development, led to a conclusion that Rap1 is permissive for dendritic growth. Opposite results were obtained by Fu and coauthors (2007) in a study of the role of Rap1 and Rap2 in more mature (DIV10-15) hippocampal neurons. Overexpression of the Rap1-DN mutant resulted in increased total dendritic length (Fu et al. 2007). Moreover, in more mature neurons, overexpression of Rap2V12 resulted in a substantial decrease in the total length of dendritic branches due to dendrite retraction (Fu et al. 2007). On the other hand, overexpression of Rap2-DN as well as Rap1-DN increased total dendrite length. The authors concluded that, in mature neurons, Rap2 restricts dendritic growth (Fu et al. 2007). Taken together, the data suggest that Rap proteins can act differently during development to stabilize the dendritic arbor. Apart from Ras and Rap, Rit, another member of the Ras family, influences dendritic growth. Its activation in hippocampal and sympathetic neurons promotes dendrite growth (Lein et al. 2007).

Protein kinases

All major protein kinases known to be active in neurons influence dendritic arbor development (Table II). These enzymes include CaMK (Wu and Cline 1998, Redmond et al. 2002, Fink et al. 2003, Yu and Malenka 2003, Gaudilliere et al. 2004, Wayman et al. 2006, Hoogenraad et al. 2007, Takemoto-Kimura et al. 2007), mitogen-activated protein kinases (MAPK) (Bjorkblom et al. 2005, Dijkhuizen and Ghosh 2005), protein kinase A (PKA) (Leemhuis et al. 2004), PI3K (Dijkhuizen and Ghosh 2005, Jaworski et al. 2005, Kumar et al. 2005), mTOR (Jaworski et al. 2005, Kumar et al. 2005, Brandt et al. 2007, Jossin and Goffinet 2007), glycogen synthase kinase 3 beta (GSK3β) (Naska et al. 2006), and non-receptor (Fyn, Abl) (Jones et al. 2004, Morita et al. 2006) and receptor tyrosine kinases (TrkB) (Yacoubian and Lo 2000).

CaMK

CaMKs are serine/threonine protein kinases, primarily regulated by the Ca^{2+}/calmodulin complex, that have many functions in neuronal morphogenesis and plasticity. In 1998, Wu and Cline, presented evidence that, in developing tectal neurons of *X. laevis,* CaMKII is expressed only in more mature neurons with elaborated and stable dendritic arbors *in vivo* (Wu and Cline 1998). Younger neurons, characterized by very dynamic dendritic growth, high rates of dendritic branch additions and retractions, did not express that enzyme. Consequently, overexpression of CaMKII in the younger neurons led to premature stabilization of the dendritic arbors (longer branch life time) and a lower net increase of total dendritic length. Application of a CaMK inhibitor, KN93, resulted in increased dynamics of dendritic arbor of neurons already expressing CaMKII and having established complex dendritic arbors (Wu and Cline 1998). CaMKII was shown to control processes of dendritic arbor growth in several different ways. Gaudilliere and others (2004) showed that CaMKIIα controls neuronal activity-dependent growth of dendrites of cerebellar neurons by phosphorylation of NeuroD at S336. Fink and colleagues (2003) revealed that CaMKII is important for dendritic arborization of hippocampal neurons; however, their results point to CaMKIIβ as a major regulator of this process. Only overexpressed wild-type CaMKIIβ was able to bind to and regulate the actin cytoskeleton and increase dendritic arborization. Finally, Hoogenraad and coworkers (2007) showed that CaMKII controls dendritic arborization through degradation of liprin1, a protein critical for cellular localization and activity of a tyrosine phosphatase LAR1.

In addition to CaMKII, CaMKIV and CaMKI were shown to control dendritic growth and arborization induced by either BDNF or neuronal activity (Redmond et al. 2002, Yu and Malenka 2003, Wayman et al. 2006, Takemoto-Kimura et al. 2007). Both CaMKs control dendritic arbor growth at a transcriptional level (Redmond et al. 2002, Wayman et al. 2006) (see below). Yu and Malenka (2003) additionally showed that CaMKIV required N-cadherin and non-nuclear functions of β-catenin to promote dendritic arbor growth. Recently, Takemoto-Kimura and colleagues (2007) presented evidence that the membrane-anchored neuronal CLICK-III(CL3)/CaMKIγ promoted BDNF-induced dendrite extension of young (1–3 days *in vitro*)

cortical neurons, by acting upstream of SIF and Tiam 1-like exchange factor (STEF), a Rac1 GEF. CL3 knockdown using RNAi led to decreased length and number of dendrites of both BDNF-treated and control cells, probably due to downregulation of Rac1 activity and changes in the actin cytoskeleton (Takemoto-Kimura et al. 2007).

Class I PI3K

Recently several reports addressing the role of PI3K in dendritic arbor development have been published. Class I PI3K is a lipid kinase that phosphorylates phosphatidylinositol 4,5-bisphosphate (PIP2) to phosphatidylinositol 3,4,5-trisphosphate (PIP3). Increased levels of PIP3 results in activation of several PI3K effectors, including Akt kinase, several GEFs and GAPs for small GTPases (RhoA, Rac1 and Arf6) (Rodgers and Theibert 2002). Jaworski and others (2005) and Kumar and colleagues (2005) showed that overexpression of a constitutively active form of PI3K led to increased dendritic arbor complexity and expansion of dendritic fields of hippocampal neurons *in vitro*. Inhibition of PI3K activity, either genetically or pharmacologically, had opposite effects (Jaworski et al. 2005, Kumar et al. 2005). Dijkhuizen and Ghosh (2005) used preparations of cortical neurons and showed that PI3K, along with ERK and phospolipase Cγ1, are crucial for BDNF-induced growth of primary dendrites. Moreover, overexpression of PI3K-CA alone was sufficient to induce growth of primary dendrites (Dijkhuizen and Ghosh 2005). Leemhuis and coworkers (2004) studied the effects of PI3K inhibition by wortmanin on the dynamics of dendritic arbor growth of hippocampal neurons in *in vitro* culture. Time-lapse microscopy, over a period of 8 h, revealed that PI3K inhibition completely abolished retractions of existing branches and decreased additions of new branches by 50%.

Molecular mechanisms downstream of PI3K, involved in dendritic arbor development and stability, are diverse and involve both *de novo* protein synthesis and the regulation of actin cytoskeleton dynamics. Work by Jaworski and coauthors (2005) and Kumar and others (2005) showed that a constitutively active Akt mutant mimicked the dendritic branching effects of increased PI3K activity. Both, PI3K-CA- and Akt-CA-dependent dendritic branching were blocked by inhibition of mTOR kinase. mTOR kinase is a well known regulator of protein synthesis via its downstream targets p70S6 kinase (p70S6K) and eIF-4E binding protein 1 (4E-BP1) (Burnett et al. 1998). Importantly, knockdown of p70S6K by means of RNAi, like mTOR knockdown, led to a severe simplification of dendritic arbors in hippocampal neurons (Jaworski et al. 2005). Overexpression of a constitutively active form of 4E-BP1 (activity of which could not be turned off by the PI3K-Akt-mTOR pathway) completely blocked dendritic growth and arborization induced by PI3K-CA (Jaworski et al. 2005). These results suggest that, at certain stages of dendritic arbor development PI3K regulates this process by controlling protein translation.

Nevertheless, the effects of PI3K on the dendritic arbor cannot be solely attributed to protein synthesis. Dijkhuizen and Ghosh (2005) showed that BDNF-induced growth of primary dendrites is insensitive to cycloheximide, a general protein translation inhibitor. PI3K can also regulate actin cytoskeleton dynamics by enhancing Rac1 activity, probably via recruitment of PI3K to the Rac1-activating molecular complex Eps8–Abi1–Sos-1 (Innocenti et al. 2003). But it is important to stress that overexpression of Abi-1 results in a decrease, and its knock down by RNAi in an increase, of dendritic arbor complexity of hippocampal neurons (Proepper et al. 2007). That suggests a more complex role of Abi-1 during dendritic arbor development, potentially due to additional nuclear functions of this protein. Another possibility is that PI3K can exert positive effects on dendritic growth by suppressing inhibitory effects of RhoA on branch formation and extension (Leemhuis et al. 2004) (see also below).

Protein kinases regulating MAP2 phosphorylation

Although particular kinases regulate dendritic arbor growth influencing several cellular processes, various protein kinases may also converge on a common downstream effector protein. MAP2, a protein marker for dendrites, can serve as a good example. MAP2 is a microtubule-stabilizing protein; its phosphorylation by different kinases can exert opposite effects on dendritic arborization. For example, phosphorylation of MAP2 in a C-terminal proline-rich region by c-Jun N-terminal kinase 1 (JNK1) contributes positively to dendrite elongation (Bjorkblom et al. 2005). Lack of JNK1 in cerebellar granular neurons results in dephosphorylation of MAP2, shortening of dendrites, and increased dendritic branching. Coexpression of a JNK

activator, δMEKK1, with MAP2 resulted in elongation of dendrites.

Another kinase capable of phosphorylating MAP2 is Polarity-regulating kinase partitioning defective 1/ Microtubule affinity-regulating kinase 2 (Par1b/ MARK2) (Terabayashi et al. 2007). Overexpression of this kinase, leading to phosphorylation of a KXGS motif in MAP2, had opposite effects on hippocampal neuron dendritic arbor development, causing a decrease of total dendritc length and dendritic branching. Knockdown of Par1b/MARK2 by RNAi increased both dendritic length and branching.

Role of actin and microtubule cytoskeleton in dendritic arbor development and stabilization

A very tight control of actin and microtubule cytoskeleton organization is indispensable for the formation of proper cell morphology (Table II). The best known regulators in this context are RhoA, Rac1, Cdc42 (cell division cycle 42), regulators of cytoskeleton dynamics that belong to the Rho family of small GTPases (Burridge and Wennerberg 2004, Jaffe and Hall 2005).

In most studies published thus far, increased activity of RhoA and inhibition of Rac1 or Cdc42 resulted in significant simplification of the dendritic trees in many neuron types (Threadgill et al. 1997, Nakayama et al. 2000, Hayashi et al. 2002). In contrast, activation of Rac1 or Cdc42 caused an increase in the number of dendrite branches (Threadgill et al. 1997, Nakayama et al. 2000, Hayashi et al. 2002).

Several extracellular signals are involved in the regulation of the Rho GTPases during dendritic arbor formation. Li and coauthors (2002), developed a method for the detection of Rho GTPase activity *in situ* in the optic tectum of *Xenopus* and showed that electrical stimulation of an optic nerve led to increased activity of Rac1 and decreased activity of RhoA, in an NMDAR- and AMPAR-dependent manner. Studies by Sin and colleagues (2002), indicated that accelerated dendritic arbor development of the *Xenopus* optic tectum neurons induced by 4h light exposure depended on the Rho GTPases. Overexpression of RhoA-CA in tectal neurons blocked light-induced development, as did a genetic decrease of Rac1 and Cdc42 activity. Inhibition of RhoA occluded the effect of light on dendritic arbor growth. Li and coworkers (2002) also presented evidence for an extensive cross-talk between the Rho GTPases during dendritic branching. For example, activation of RhoA blocked dendritic growth induced by Rac1-CA overexpression. In addition to electrical and neurotransmitter stimuli, other extracellular signals such as BDNF, Wnt-7 and EphrinB-EphB interaction, control dendritic growth employing the Rho GTPases (Penzes et al. 2003, Rosso et al. 2005, Takemoto-Kimura et al. 2007).

Guanine nucleotide exchange factors and GTPase-activating proteins for Rho GTPases

How is the activity of Rho GTPases regulated during dendritogenesis? Small GTPases cycle between an active (GTP-bound) and an inactive (GDP-bound) states (for review see Etienne-Manneville and Hall 2002). In the GTP-bound form, active GTPases bind to and regulate the activity of several downstream effectors. Activation of small GTPases depends on the balance between guanine nucleotide exchange factors (GEFs) and GTPase-activating proteins (GAPs), which is regulated by extracellular signals important for dendritic arbor development and stabilization.

Some mammalian Rac1 GEFs, such as Tiam-1 and Kalirin-7, interact with glutamate receptors or/and postsynaptic density proteins involved in glutamate receptor anchoring and turnover, linking glutamatergic neurotransmission to Rac1 activation. Both Kalirin-7 and Tiam-1 were shown to be necessary for NMDA-induced Rac1 activation (Tolias et al. 2005, Xie et al. 2007b). Kalirin-7 is a multidomain protein that interacts with multiple Rho proteins, and is predominantly expressed in the brain, localizing to dendritic spines where it was shown to interact with several postsynaptic density scaffold proteins including PSD-95 (Penzes et al. 2000, 2001). RNAi-mediated knockdown of Kalirin-7 led to a simplification of hippocampal neuron dendrites in both dissociated and organotypic cultures (Ma et al. 2003). Tiam-1, like Kalirin-7, is widely expressed in the brain and localizes to dendritic spines where it interacts with the NMDA receptor subunit NR1 (Tolias et al. 2005). Transfection of hippocampal neurons with siRNA against Tiam-1 resulted in decreased dendritic complexity. BDNF regulates Rac1 activity, recruiting GEFs. Recently, Rac1 GEF, SIF and Tiam 1-like exchange factor (STEF), has been described to act downstream of BDNF and CLICK-III(CL3)/CaMKIγ during dendritic growth (see above). For example,

application of either a dominant interfering fragment (PHnTSS) of STEF or Rac1-DN blocked the positive effect of CL3 overexpression on dendrite length (Takemoto-Kimura et al. 2007). Lee and colleagues (2003) revealed that Rac1 protein levels can be controlled during dendritic arbor development by translational inhibition by *Drosophila* Fragile X-related protein (FMR1). mRNA encoding Rac1 was found in FMR1-containing ribonucleoprotein particles (RNPs, see also below) and overexpression of Rac1 partially rescued detrimental effects of FMR1 overexpression on the da neurons dendritic arbor complexity (Lee et al. 2003). All of these observations show that both the expression level and activity of Rac1 are under strict and local control in dendrites.

Rho GEFs also regulate dendritic arbor growth. Lfc is a Rho-GEF abundantly expressed in the brain that localizes to dendrites (Ryan et al. 2005). Lfc redistributes from a dendritic shaft to dendritic spines upon NMDAR and VGCC stimulation, and Ca^{2+} influx into cells. Consistent with the role of activated RhoA in dendritic growth, long-term overexpression of Lfc in hippocampal neurons *in vitro* caused a significant decrease of the number of dendritic segments, in a Rho-GEF activity-dependent manner (Ryan et al. 2005). Certain signaling pathways impinge their effects on dendritic arbor growth by inhibiting RhoA activity. For example, Abl, a non-receptor tyrosine kinase, stimulates extension and branching of dendrites *via* inhibition of RhoA. Inhibition of Abl kinase leads to increased RhoA activity and significant simplification of dendritic arbors in hippocampal neurons (Jones et al. 2004). On the other hand, Abl-CA expression results in new dendrite formation and branching, which can be suppressed by RhoA-CA (Jones et al. 2004).

Regulation of the actin cytoskeleton during dendritic arborization is dependent on Rho GTPases

The Rho GTPases are regulators of actin polymerization rates and spatial organization (Etienne-Manneville and Hall 2002, Burridge and Wennerberg 2004, Jaffe and Hall 2005). In eukaryotic cells, downstream effectors of the Rho GTPases, Arp2/3 and mDia, are two major factors involved in actin polymerization. The activity of cofilin, an actin severing factor which increases the number of uncapped, barbed ends, can promote both filament assembly and disassembly.

Rac1 and cdc42 activate Arp2/3 (and consequently actin polymerization) indirectly *via* Wiskott-Aldrich syndrome (WASP) family proteins, WAVE and N-WASP, respectively, leading to formation of a branched filament network (for review see Etienne-Manneville and Hall 2002, Burridge and Wennerberg 2004, Jaffe and Hall 2005). Both N-WASP and Arp2/3 play important roles in the proper shaping of the dendritic arbor (Pinyol et al. 2007, Rocca et al. 2008). Overexpression of N-WASP increased the number of neurites and branch points in developing hippocampal neurons *in vitro*; these effects depended on cdc42 activity (Pinyol et al. 2007). Recently, Rocca and coauthors (2008) showed that Arp2/3 actin nucleation activity is important for proper dendritic branching patterns in developing hippocampal neurons. A synaptic protein that binds Arp2/3, PICK1, disrupts Arp2/3 binding to N-WASP and inhibits Arp2/3-mediated actin polymerization. *PICK-1* knockdown caused increases in proximal dendrite branching and decreases in distal arborization. The effects of the *PICK-1* knockdown were reversed by overexpression of PICK-1 resistant to siRNA. Taken together, these data emphasize the importance of actin nucleation for proper dendritic arborization.

RhoA regulates actin polimerization, directly binding a formin, mDia, and inducing the linear elongation of actin filaments. A role for this formin has not been studied in the context of dendritic development, but mDia activation *via* RhoA was found important for neurite elongation in PC12 cells upon NGF exposure (Nusser et al. 2006).

Recently, Cordon-Bleu (Cobl) protein was identified as a new actin nucleation factor enriched in the brain (Ahuja et al. 2007), which acts independently from the Arp2/3 complex. Cobl promotes formation of long, unbundled and unbranched filaments, gives rise to plus-end (barbed–end) growth and localizes to sites of high actin dynamics. In primary hippocampal neurons, overexpression of the Cobl C-terminal domain, containing all WASP homology 2 domains necessary for its activity, induced formation of highly branched dendritic arbors built of short dendrites whereas RNAi-mediated knockdown of *Cobl* resulted in a significant reduction in the length and branching of dendrites.

The Rho GTPases also influence the dendritic arborization activating proteins that are not directly

involved in actin nucleation. p21-activated kinase (Pak1) acts downstream of Rac1, and through effector proteins, such as filamin or LIM kinase (LIMK), to stabilize actin filaments. A constitutively active form of Pak1, when expressed in immature cortical neurons, increased the number of apical and basal dendrites. Disruption of endogenous Pak1 activity by a dominant negative mutant had an opposite effect (Hayashi et al. 2002). In cultures of hippocampal neurons, either hyperactivation or loss of Pak1 lead to disruption of neuronal morphology and neurite differentiation to an axon and dendrites (Jacobs et al. 2007).

Rho kinase (ROCK) is a downstream target for RhoA. Activation of ROCK has complex cellular consequences, including a myosin contraction of actin filaments and an activation of LIMK. Overexpression of ROCK-CA (ROCKΔ3), in rat hippocampal neurons in organotypic culture, caused simplification of dendritic trees (Nakayama et al. 2000). Consequently, inhibition of ROCK by a specific inhibitor, Y-27632, prevented dendritic arbor simplification caused by RhoA-CA overexpression or by suppression of Abl kinase which leads to RhoA activation (Nakayama et al. 2000, Jones et al. 2004). Overexpression of ROCK-CA *in vivo* in the *Xenopus* optic tectum neurons prevented changes in dendritic arbor triggered by light exposure (Sin et al. 2002; see also above).

Microtubule cytoskeleton

Besides involvement in the control of actin cytoskeleton, Rho GTPases regulate microtubule dynamics and interactions of actin and microtubules (for review see Jaffe and Hall 2005). Rac1 stabilizes microtubules *via* JNK1-dependent phosphorylation of MAP2 (see above). RhoA alters the microtubule cytoskeleton by decreasing levels of cypin (Chen and Firestein 2007). Since, cypin binds to tubulin heterodimers and promotes the assembly of microtubules (Akum et al. 2004), a decreased cypin levels, resulting from RhoA activation, results in a decreased dendrite number (Chen and Firestein 2007). The development and stability of a proper dendritic arbor morphology depend on several, non-Rho GTPase-related microtubule binding proteins, including MAPs, microtubule plus-end tracking proteins, and motor proteins. CHO1/MKLP1, CRMP3, Lis1, MAP1b, kakapo are a few examples (Prokop et al. 1998, Liu et al. 2000, Yu et al. 2000, Teng et al. 2001; Quach et al. 2008).

Septins

Septins are another cytoskeletal component identified to play a role in dendritic branching. They are evolutionary conserved proteins with essential functions in cytokinesis, membrane trafficking, and scaffolding for the assembly of cellular factors (Kinoshita 2006). In the rat brain, expression patterns of members of the septin family are cell-type specific and change during development (Tada et al. 2007). Overexpression of neuron specific isoforms, Septin2, Septin6 or Septin7 increase dendritic arbor complexity (Tada et al. 2007, Xie et al. 2007a), and RNAi-mediated knockdown reduces dendritic branching. In cultured hippocampal neurons, Septin7 is localized at dendritic branch points and at the base of dendritic protrusions (Tada et al. 2007).

Transcription and translation

Transcription

Transcription plays an important part in intrinsically driven genetic program-based dendritic arborization (see above). Nevertheless, in mammalian neurons, transcription factors, cofactors and chromatin-modifying proteins are studied mostly in the context of dendrite development induced by extracellular factors. A general necessity for transcription during neuronal activity-dependent dendritic arbor growth is well-exemplified in the recent work of Wu and others (2007) on chromatin remodeling complexes in neurons. They showed that BAF53b is a crucial protein for ATP-dependent remodeling of chromatin, a process that makes promoters of certain genes accessible to transcriptional machinery. Hippocampal neuronal cultures derived from mice lacking BAF53b had deficits in KCl-induced dendritic arbor growth. BAF53b acts in concert with transcriptional coactivator CREST, which was previously identified as a calcium-responsive transcription coactivator important for neuronal activity-induced dendritic arbor growth in hippocampal and cortical neurons (Aizawa et al. 2004).

Methyl-CpG-binding protein 2 (MECP2) is a protein that binds to methylated DNA and functions as a transcription repressor. Overexpression of MECP2 in organotypic hippocampal cultures, as well as knockdown of MECP2 by RNAi, resulted in simplification

of the dendritic arbor (Zhou et al. 2006). These findings suggest that proper neuronal development requires a very precise set point for MECP2 expression. Indeed, overexpression of an siRNA-resistant form of MECP2 that could be phosphorylated by CaMKII reversed the detrimental effects of RNAi.

CREB-binding protein (CBP) is another general chromatin modifier and transcription coactivator shown to play a pivotal role in dendritic arborization. Overexpression of a mutant form of adenoviral E1A protein, which inhibits CBP, blocked CaMKIV-dependent and KCl-induced dendritic growth of cortical neurons *in vitro* (Redmond et al. 2002). CBP is crucial for CREB transcriptional activity. Overexpression of various forms of dominant negative mutants of CREB or siRNA also prevented KCl-, CaMKIV- and CaMKI-induced dendritic growth in cortical and hippocampal neurons (Redmond et al. 2002, Wayman et al. 2006). Overexpression of a constitutively active CREB mutant was sufficient to increase total dendritic length (Wayman et al. 2006).

Other transcription factors control neuronal activity-driven dendritic arbor growth. Gaudilliere and colleagues (2004) showed that removal of NeuroD by RNAi from cerebellar granular neurons inhibited dendritic growth induced by both neuronal activity (KCl, biccuculine) and CaMKIIα. c-Fos, a product of an immediate early gene *c-fos*, is a TF induced by exposure of animals to cocaine (Zhang et al. 2006). One of the morphological effects of repeated cocaine administrations is increased dendritic branching of the caudate putamen and the nucleus accumbens neurons (Zhang et al. 2006). This particular morphological change is missing in *c-fos* knockout mice, demonstrating the role for transcription in neuronal plasticity-dependent dendritic arbor remodeling *in vivo* (Zhang et al. 2006).

Although the participation of TFs in dendritic arbor growth is well-documented, only a few downstream genes important for dendritogenesis have been identified. Recent examination of BAF53b target genes by a chromatin precipitation method revealed several genes important for neurite outgrowth. In neurons from BAF53b knockout mice, transcription of ephexin-1, GAP43, Stathmin, Gelsolin and Rap1A were downregulated while RacGAP1 was upregulated (Wu et al. 2007). More detailed analysis revealed that overexpression of ephexin-1 in neurons lacking BAF53b restored responsiveness of the dendritic arbor to depolarization (Wu et al. 2007).

Wnt-2, expression of which depends on CREB, is another important gene for activity-driven dendritic growth (Wayman et al. 2006). Overexpression of Wnt-2 in neurons in organotypic cultures is sufficient to increase both total dendritic length and number of branches. On the other hand, expression of Wnt antagonist, Wif, led to inhibition of KCl-, bicuculline- and CaMKI-induced dendritic growth.

Lastly, analysis of target genes for the *Drosophila* transcription factor Knot/Collier revealed a gene encoding a microtubule severing protein, Spastin (Jinushi-Nakao et al. 2007). In the class IV da sensory neurons of *Drosophila*, overexpression of Knot/Collier increased expression of Spastin and promoted dendrite arborization that was inhibited by knockdown of Spastin (Jinushi-Nakao et al. 2007).

mRNA dendritic transport and local protein translation

Given that transcription is crucial for dendritic arbor growth, protein translation must be also involved. We already mentioned the importance of mTOR, p70S6K, and 4E-BP1 in the translational control of dendritic branching (Jaworski et al. 2005). Moreover, recently Chihara et al. (2007) defined a crucial role of protein translation in proper dendritic arborization of the *Drosophila* olfactory projection neurons and the mushroom body γ neurons. This was done by knocking down genes encoding various aminoacyl-tRNA synthetases, enzymes catalyzing attachment of amino-acids to their corresponding tRNAs, which is indispensible for translation.

The discovery of the requirement for protein translation in dendritic arbor development raises questions about the specific locations of protein translation in neuronal cells. It is worth stressing that translation in neurons can take place at various locations and therefore can be divided to general and local (Kindler et al. 2005, Skup et al. 2008, this issue). The latter one occurs at several discrete locations along dendrites, in proximity to synapses and in the growth cones of axons, and is independent from the general translation in the cell soma (Kindler et al. 2005, Skup et al. 2008, this issue). mRNAs transported to dendrites and axons as ribonucleoprotein particles and their translation are activated by extracellular signals such as BDNF or specific patterns of neuronal activity (Kindler et al. 2005). mTOR, p70S6K and 4E-BP1 were shown

to control translation locally in dendrites and axons during long-lasting long-term potentiation (L-LTP) and axon guidance, respectively (for review see: Jaworski and Sheng 2006, Swiech et al. 2008), but direct evidence is missing for local translation in the process of dendritic arbor development. Nevertheless, several indirect findings suggest such a possibility.

There is compelling evidence from *Drosophila* models that translational repressors that are components of dendritic RNPs such as Pumilio, Nanos, FMR1 and Me31B regulate proper dendrite growth (Lee et al. 2003, Ye et al. 2004, Barbee et al. 2006). Overexpression of Pumilio, Nanos, FMR1 and Me31B in the class IV da sensory neurons, reduces higher order dendrite complexity (Lee et al. 2003, Ye et al. 2004, Barbee et al. 2006). Overexpression of RNP-related translation repressors has consistent inhibitory effects on dendritic branching, but knockdown of those proteins led to diverse effects on dendritic arbors. Inhibition of Nanos and Pumilio resulted in reduced higher order branches in the class IV da neurons and incomplete coverage of epidermis by the dendritic arbors by 15% and 20% in neurons lacking Nanos and Pumilio, respectively (Ye et al. 2004). Knockdown of *fmr1* increased the number of higher order branches (Lee et al. 2003). Inhibition of Me31B, by RNAi, substantially increased higher order branch complexity similarly to effects of *fmr1* knockdown (Barbee et al. 2006). Nevertheless, the more branched dendritic arbors of class IV da neurons showed incomplete dendritic field coverage as in the case of removing Nanos and Pumilio (Barbee et al. 2006). There are several unclear issues remaining: (i) where do the differences in observed phenotypes arise from, (ii) why do dendritic arbor phenotypes of different classes of the da neurons vary substantially in response to the same genetic manipulations, and (iii) how does the morphology of mammalian neurons depend on RNP components? The role for local protein synthesis in mammalian neurons is supported by several lines of evidence, including those discussed above. Some experiments designed to identify dendritic mRNAs showed that several proteins important for control of dendritic branching, for example CaMKIIα, glutamate receptor subunits, BDNF, TrkB, GRIP1 and PSD95, are translated locally in dendrites, often in a neurotrophic factor-, neuronal activity- and mTOR-dependent fashion (see review by Swiech et al., 2008, for more detailed discussion).

Organellar protein translation may also contribute to dendritic arbor development and stability. Chihara and coauthors (2007) showed subtle differences between the effect of translation taking place in cytoplasm and mitochondria on dendritic arbor. They took advantage of the existence of cytoplasmic- and mitochondria-specific isoforms of several aminoacyl-tRNA synthetases (see above). When genes encoding the cytoplasmic forms of either tryptophanyl-tRNA synthetase or glutaminyl-tRNA-synthetsase were knocked down in the *Drosophila* olfactory projection neurons or the mushroom body γ neurons, dendritic and axonal terminal arborization was impaired (Chihara et al. 2007). When mitochondrial protein synthesis was impaired by removal of the gene encoding mitochondrial ribosomal protein S12, dendrites of DL1 projection neurons reached their target (DL1 glomerulus) but dendritic density was decreased and this effect was increasing with age. Based on these data, Chihara and others (2007) concluded that cytoplasmic protein translation is crucial for dendritic arbor development, and the mitochondrial protein translation controls the stability of mature dendrites.

Membrane trafficking

Extensive dendritic growth during development requires constant additions of membrane to the cell surface. Moreover, activity-dependent branching depends on the presence and activity of neurotransmitter receptors that need to be delivered to and removed from the cell surface. Quite surprisingly, membrane trafficking only recently took a central stage in research directed at understanding dendritic arborization mechanisms. Dendrites are endowed with membranous organelles, including both rough and smooth endoplasmic reticulum (ER), the ER–Golgi intermediate compartment, and Golgi outposts that have no membranous connections with the somatic Golgi. Golgi outposts presumably serve both general and specific local trafficking needs, and could mediate membrane trafficking required for polarized dendritic growth during neuronal differentiation (Horton and Ehlers 2003, Horton et al. 2005). Disruption of the Golgi apparatus by GRASP65 overexpression (Barr et al. 1997) abolishes the asymmetry in Golgi orientation observed during dendritic growth, which results in a marked reduction in dendritic polarity. Moreover, selectively blocking Golgi outpost trafficking halts

dendrite growth in developing neurons and causes shrinkage of dendrites in mature pyramidal neurons (Liljedahl et al. 2001, Horton et al. 2005).

Recent findings suggest that dendritic growth heavily relies on classical exocytic traffic. Membrane proteins and secretory cargo are targeted to the ER of the exocytic pathway extending from the soma, and are then routed to the cell surface through multiple rounds of vesicle budding and fusion. These processes are mediated by an evolutionarily conserved set of coat proteins such as the SNARE complex (soluble N-ethylmaleimide sensitive factor (NSF), SNAP-25, syntaxins, TI-VAMP, etc.) (Cai et al. 2007, Tang 2008) and the Rab family GTPases (Bonifacino and Lippincott-Schwartz 2003). There is evidence for Rab8 (Huber et al. 1995), SNAP-25 (Grosse et al. 1999), TI-VAMP (Martinez-Arca et al. 2001) and the SNARE complex (Vega and Hsu 2001) being involved in exocytosis-mediated dendritic extension. Moreover, Jan and colleagues (Ye et al. 2007) isolated *Drosophila* mutants with defects in dendritic, but not axonal, growth in a genetic screen. Isolated mutations were present in genes encoding *Drosophila* homologues of *Sec23*, *Sar1* and *Rab1*, all of which function in the early secretory pathway, (ie, in ER–Golgi transport).

Another way whereby membrane materials can be incorporated into the cell surface is through the recycling of internalized proteins via recycling endosomes (Maxfield and McGraw 2004, van Ijzendoorn 2006). The requirement of Rab11 (Shirane and Nakayama 2006), NSF (Guo et al. 2001, Isaac et al. 2007) and syntaxin (Simonsen et al. 1998, Hirling et al. 2000) mediated-processes have implicated recycling endosome function in neurite outgrowth. For example, overexpression of Syntaxin 16, a protein involved in Golgi-endosomal trafficking, moderately stimulates neurite outgrowth in primary mouse cortical neurons (Mallard et al. 2002, Chua and Tang 2008).

CONCLUSIONS

Although enormous progress has been made over the last decade in revealing the molecular basis of dendritic arbor development and its stability, many questions remain. For example, what are the exact differences, at the molecular level, between development, stabilization and further remodeling of dendritic arbors? The existence of such differences is obvious from several studies, including our own work showing that PI3K can induce dendritic growth only in a certain timeframe during development, but is constantly needed for preservation of the already formed tree (Jaworski et al. 2005). Another problem that emerges from the use of such distant organisms as flies and rodents, which have very different spatial organization of dendritic arbors, is inaccurate generalizations of experimental observation. Another issue is the identification of executor proteins, the expression of which is controlled during dendritic development by transcription factors and local translation. Finally, much more work needs to be done in mammalian *in vivo* models to extend our understanding of the molecular mechanisms of dendritic arbor dysfunctions that may contribute to human nervous system disorders. Hopefully with growing interest in molecular biology of neuronal development these issues can be solved in a reasonable time scale.

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REFERENCES

Ahuja R, Pinyol R, Reichenbach N, Custer L, Klingensmith J, Kessels MM, Qualmann B (2007) Cordon-bleu is an actin nucleation factor and controls neuronal morphology. Cell 131: 337–350.

Aizawa H, Hu SC, Bobb K, Balakrishnan K, Ince G, Gurevich I, Cowan M, Ghosh A (2004) Dendrite development regulated by CREST, a calcium-regulated transcriptional activator. Science 303: 197–202.

Akum BF, Chen M, Gunderson SI, Riefler GM, Scerri-Hansen MM, Firestein BL (2004) Cypin regulates dendrite patterning in hippocampal neurons by promoting microtubule assembly. Nat Neurosci 7: 145–152.

Alpar A, Palm K, Schierwagen A, Arendt T, Gartner U (2003) Expression of constitutively active p21H-rasval12 in postmitotic pyramidal neurons results in increased dendritic size and complexity. J Comp Neurol 467: 119–133.

Anderton BH, Callahan L, Coleman P, Davies P, Flood D, Jicha GA, Ohm T, Weaver C (1998) Dendritic changes in Alzheimer's disease and factors that may underlie these changes. Prog Neurobiol 55: 595–609.

Baker RE, Wolters P, van Pelt J (1997) Chronic blockade of glutamate-mediated bioelectric activity in long-term organotypic neocortical explants differentially effects pyramidal/non-pyramidal dendritic morphology. Brain Res Dev Brain Res 104: 31–39.

Barbee SA, Estes PS, Cziko AM, Hillebrand J, Luedeman RA, Coller JM, Johnson N, Howlett IC, Geng C, Ueda R, Brand AH, Newbury SF, Wilhelm JE, Levine RB, Nakamura A, Parker R, Ramaswami M (2006) Staufen- and FMRP-containing neuronal RNPs are structurally and functionally related to somatic P bodies. Neuron 52: 997–1009.

Barr FA, Puype M, Vandekerckhove J, Warren G (1997) GRASP65, a protein involved in the stacking of Golgi cisternae. Cell 91: 253–262.

Beck HN, Drahushuk K, Jacoby DB, Higgins D, Lein PJ (2001) Bone morphogenetic protein-5 (BMP-5) promotes dendritic growth in cultured sympathetic neurons. BMC Neurosci 2: 12.

Berglund EO, Murai KK, Fredette B, Sekerkova G, Marturano B, Weber L, Mugnaini E, Ranscht B (1999) Ataxia and abnormal cerebellar microorganization in mice with ablated contactin gene expression. Neuron 24: 739–750.

Bjorkblom B, Ostman N, Hongisto V, Komarovski V, Filen JJ, Nyman TA, Kallunki T, Courtney MJ, Coffey ET (2005) Constitutively active cytoplasmic c-Jun N-terminal kinase 1 is a dominant regulator of dendritic architecture: role of microtubule-associated protein 2 as an effector. J Neurosci 25: 6350–6361.

Bonifacino JS, Lippincott-Schwartz J (2003) Coat proteins: shaping membrane transport. Nat Rev Mol Cell Biol 4: 409–414.

Brandt N, Franke K, Rasin MR, Baumgart J, Vogt J, Khrulev S, Hassel B, Pohl EE, Sestan N, Nitsch R, Schumacher S (2007) The neural EGF family member CALEB/NGC mediates dendritic tree and spine complexity. Embo J 26: 2371–2386.

Burnett PE, Barrow RK, Cohen NA, Snyder SH, Sabatini DM (1998) RAFT1 phosphorylation of the translational regulators p70 S6 kinase and 4E-BP1. Proc Natl Acad Sci U S A 95: 1432–1437.

Burridge K, Wennerberg K (2004) Rho and Rac take center stage. Cell 116: 167–179.

Cai H, Reinisch K, Ferro-Novick S (2007) Coats, tethers, Rabs, and SNAREs work together to mediate the intracellular destination of a transport vesicle. Dev Cell 12: 671–682.

Chen H, Firestein BL (2007) RhoA regulates dendrite branching in hippocampal neurons by decreasing cypin protein levels. J Neurosci 27: 8378–8386.

Chen Y, Wang PY, Ghosh A (2005) Regulation of cortical dendrite development by Rap1 signaling. Mol Cell Neurosci 28: 215–228.

Chen Y, Dube CM, Rice CJ, Baram TZ (2008) Rapid loss of dendritic spines after stress involves derangement of spine dynamics by corticotropin-releasing hormone. J Neurosci 28: 2903–2911.

Chihara T, Luginbuhl D, Luo L (2007) Cytoplasmic and mitochondrial protein translation in axonal and dendritic terminal arborization. Nat Neurosci 10: 828–837.

Chua CE, Tang BL (2008) Syntaxin 16 is enriched in neuronal dendrites and may have a role in neurite outgrowth. Mol Membr Biol 25: 35–45.

Cobos I, Borello U, Rubenstein JL (2007) Dlx transcription factors promote migration through repression of axon and dendrite growth. Neuron 54: 873–888.

Cobos I, Calcagnotto ME, Vilaythong AJ, Thwin MT, Noebels JL, Baraban SC, Rubenstein JL (2005) Mice lacking Dlx1 show subtype-specific loss of interneurons, reduced inhibition and epilepsy. Nat Neurosci 8: 1059–1068.

Demyanenko GP, Tsai AY, Maness PF (1999) Abnormalities in neuronal process extension, hippocampal development, and the ventricular system of L1 knockout mice. J Neurosci 19: 4907–4920.

Dijkhuizen PA, Ghosh A (2005) BDNF regulates primary dendrite formation in cortical neurons via the PI3-kinase and MAP kinase signaling pathways. J Neurobiol 62: 278–288.

Etienne-Manneville S, Hall A (2002) Rho GTPases in cell biology. Nature 420: 629–635.

Ewald RC, Van Keuren-Jensen KR, Aizenman CD, Cline HT (2008) Roles of NR2A and NR2B in the development of dendritic arbor morphology in vivo. J Neurosci 28: 850–861.

Fink CC, Bayer KU, Myers JW, Ferrell JE, Jr., Schulman H, Meyer T (2003) Selective regulation of neurite extension and synapse formation by the beta but not the alpha isoform of CaMKII. Neuron 39: 283–297.

Fu Z, Lee SH, Simonetta A, Hansen J, Sheng M, Pak DT (2007) Differential roles of Rap1 and Rap2 small GTPases in neurite retraction and synapse elimination in hippocampal spiny neurons. J Neurochem 100: 118–131.

Gao FB, Kohwi M, Brenman JE, Jan LY, Jan YN (2000) Control of dendritic field formation in Drosophila: the roles of flamingo and competition between homologous neurons. Neuron 28: 91–101.

Gascon E, Dayer AG, Sauvain MO, Potter G, Jenny B, De Roo M, Zgraggen E, Demaurex N, Muller D, Kiss JZ (2006) GABA regulates dendritic growth by stabilizing lamellipodia in newly generated interneurons of the olfactory bulb. J Neurosci 26: 12956–12966.

Gaudilliere B, Konishi Y, de la Iglesia N, Yao G, Bonni A (2004) A CaMKII-NeuroD Signaling Pathway Specifies Dendritic Morphogenesis. Neuron 41: 229–241.

Gazula VR, Roberts M, Luzzio C, Jawad AF, Kalb RG (2004) Effects of limb exercise after spinal cord injury on motor neuron dendrite structure. J Comp Neurol 476: 130–145.

Grosse G, Grosse J, Tapp R, Kuchinke J, Gorsleben M, Fetter I, Hohne-Zell B, Gratzl M, Bergmann M (1999) SNAP-25 requirement for dendritic growth of hippocampal neurons. J Neurosci Res 56: 539–546.

Gulledge AT, Kampa BM, Stuart GJ (2005) Synaptic integration in dendritic trees. J Neurobiol 64: 75–90.

Guo X, Lin Y, Horbinski C, Drahushuk KM, Kim IJ, Kaplan PL, Lein P, Wang T, Higgins D (2001) Dendritic growth induced by BMP-7 requires Smad1 and proteasome activity. J Neurobiol 48: 120–130.

Haas K, Li J, Cline HT (2006) AMPA receptors regulate experience-dependent dendritic arbor growth in vivo. Proc Natl Acad Sci U S A 103: 12127–12131.

Hand R, Bortone D, Mattar P, Nguyen L, Heng JI, Guerrier S, Boutt E, Peters E, Barnes AP, Parras C, Schuurmans C, Guillemot F, Polleux F (2005) Phosphorylation of Neurogenin2 specifies the migration properties and the dendritic morphology of pyramidal neurons in the neocortex. Neuron 48: 45–62.

Harrison PJ (1999) The neuropathology of schizophrenia. A critical review of the data and their interpretation. Brain 122 (Pt 4): 593–624.

Hayashi K, Ohshima T, Mikoshiba K (2002) Pak1 is involved in dendrite initiation as a downstream effector of Rac1 in cortical neurons. Mol Cell Neurosci 20: 579–594.

Hirling H, Steiner P, Chaperon C, Marsault R, Regazzi R, Catsicas S (2000) Syntaxin 13 is a developmentally regulated SNARE involved in neurite outgrowth and endosomal trafficking. Eur J Neurosci 12: 1913–1923.

Hoogenraad CC, Milstein AD, Ethell IM, Henkemeyer M, Sheng M (2005) GRIP1 controls dendrite morphogenesis by regulating EphB receptor trafficking. Nat Neurosci.

Hoogenraad CC, Feliu-Mojer MI, Spangler SA, Milstein AD, Dunah AW, Hung AY, Sheng M (2007) Liprinalpha1 degradation by calcium/calmodulin-dependent protein kinase II regulates LAR receptor tyrosine phosphatase distribution and dendrite development. Dev Cell 12: 587–602.

Horch HW, Katz LC (2002) BDNF release from single cells elicits local dendritic growth in nearby neurons. Nat Neurosci 5: 1177–1184.

Horton AC, Ehlers MD (2003) Dual modes of endoplasmic reticulum-to-Golgi transport in dendrites revealed by live-cell imaging. J Neurosci 23: 6188–6199.

Horton AC, Racz B, Monson EE, Lin AL, Weinberg RJ, Ehlers MD (2005) Polarized secretory trafficking directs cargo for asymmetric dendrite growth and morphogenesis. Neuron 48: 757–771.

Huang J, Furuya A, Furuichi T (2007) Very-KIND, a KIND domain containing RasGEF, controls dendrite growth by linking Ras small GTPases and MAP2. J Cell Biol 179: 539–552.

Huber LA, Dupree P, Dotti CG (1995) A deficiency of the small GTPase rab8 inhibits membrane traffic in developing neurons. Mol Cell Biol 15: 918–924.

Hughes ME, Bortnick R, Tsubouchi A, Baumer P, Kondo M, Uemura T, Schmucker D (2007) Homophilic Dscam interactions control complex dendrite morphogenesis. Neuron 54: 417–427.

Innocenti M, Frittoli E, Ponzanelli I, Falck JR, Brachmann SM, Di Fiore PP, Scita G (2003) Phosphoinositide 3-kinase activates Rac by entering in a complex with Eps8, Abi1, and Sos-1. J Cell Biol 160: 17–23.

Isaac JT, Ashby M, McBain CJ (2007) The role of the GluR2 subunit in AMPA receptor function and synaptic plasticity. Neuron 54: 859–871.

Jacobs T, Causeret F, Nishimura YV, Terao M, Norman A, Hoshino M, Nikolic M (2007) Localized activation of p21-activated kinase controls neuronal polarity and morphology. J Neurosci 27: 8604–8615.

Jaffe AB, Hall A (2005) Rho GTPases: biochemistry and biology. Annu Rev Cell Dev Biol 21: 247–269.

Jan YN, Jan LY (2003) The control of dendrite development. Neuron 40: 229–242.

Jaworski J, Sheng M (2006) The growing role of mTOR in neuronal development and plasticity. Mol Neurobiol 34: 205–219.

Jaworski J, Spangler S, Seeburg DP, Hoogenraad CC, Sheng M (2005) Control of dendritic arborization by the phosphoinositide-3'-kinase-Akt-mammalian target of rapamycin pathway. J Neurosci 25: 11300–11312.

Jinushi-Nakao S, Arvind R, Amikura R, Kinameri E, Liu AW, Moore AW (2007) Knot/Collier and cut control different aspects of dendrite cytoskeleton and synergize to define final arbor shape. Neuron 56: 963–978.

Jones SB, Lu HY, Lu Q (2004) Abl tyrosine kinase promotes dendrogenesis by inducing actin cytoskeletal rearrangements in cooperation with Rho family small GTPases in hippocampal neurons. J Neurosci 24: 8510–8521.

Jossin Y, Goffinet AM (2007) Reelin signals through phosphatidylinositol 3-kinase and Akt to control cortical development and through mTor to regulate dendritic growth. Mol Cell Biol 27: 7113–7124.

Kaufmann WE, Moser HW (2000) Dendritic anomalies in disorders associated with mental retardation. Cereb Cortex 10: 981–991.

Kindler S, Wang H, Richter D, Tiedge H (2005) RNA transport and local control of translation. Annu Rev Cell Dev Biol 21: 223–245.

Kinoshita M (2006) Diversity of septin scaffolds. Curr Opin Cell Biol 18: 54–60.

Konur S, Ghosh A (2005) Calcium signaling and the control of dendritic development. Neuron 46: 401–405.

Kossel AH, Williams CV, Schweizer M, Kater SB (1997) Afferent innervation influences the development of dendritic branches and spines via both activity-dependent and non-activity-dependent mechanisms. J Neurosci 17: 6314–6324.

Kumar V, Zhang MX, Swank MW, Kunz J, Wu GY (2005) Regulation of dendritic morphogenesis by Ras-PI3K-Akt-mTOR and Ras-MAPK signaling pathways. J Neurosci 25: 11288–11299.

Lee A, Li W, Xu K, Bogert BA, Su K, Gao FB (2003) Control of dendritic development by the Drosophila fragile X-related gene involves the small GTPase Rac1. Development 130: 5543–5552.

Leemhuis J, Boutillier S, Barth H, Feuerstein TJ, Brock C, Nurnberg B, Aktories K, Meyer DK (2004) Rho GTPases and phosphoinositide 3-kinase organize formation of branched dendrites. J Biol Chem 279: 585–596.

Lein PJ, Guo X, Shi GX, Moholt-Siebert M, Bruun D, Andres DA (2007) The novel GTPase Rit differentially regulates axonal and dendritic growth. J Neurosci 27: 4725–4736.

Li Z, Aizenman CD, Cline HT (2002) Regulation of rho GTPases by crosstalk and neuronal activity in vivo. Neuron 33: 741–750.

Liljedahl M, Maeda Y, Colanzi A, Ayala I, Van Lint J, Malhotra V (2001) Protein kinase D regulates the fission of cell surface destined transport carriers from the trans-Golgi network. Cell 104: 409–420.

Liu Z, Steward R, Luo L (2000) Drosophila Lis1 is required for neuroblast proliferation, dendritic elaboration and axonal transport. Nat Cell Biol 2: 776–783.

Lohmann C, Myhr KL, Wong RO (2002) Transmitter-evoked local calcium release stabilizes developing dendrites. Nature 418: 177–181.

Ma XM, Huang J, Wang Y, Eipper BA, Mains RE (2003) Kalirin, a multifunctional Rho guanine nucleotide exchange factor, is necessary for maintenance of hippocampal pyramidal neuron dendrites and dendritic spines. J Neurosci 23: 10593–10603.

Mallard F, Tang BL, Galli T, Tenza D, Saint-Pol A, Yue X, Antony C, Hong W, Goud B, Johannes L (2002) Early/recycling endosomes-to-TGN transport involves two SNARE complexes and a Rab6 isoform. J Cell Biol 156: 653–664.

Mantych KB, Ferreira A (2001) Agrin differentially regulates the rates of axonal and dendritic elongation in cultured hippocampal neurons. J Neurosci 21: 6802–6809.

Martinez-Arca S, Coco S, Mainguy G, Schenk U, Alberts P, Bouille P, Mezzina M, Prochiantz A, Matteoli M, Louvard D, Galli T (2001) A common exocytotic mechanism mediates axonal and dendritic outgrowth. J Neurosci 21: 3830–3838.

Matthews BJ, Kim ME, Flanagan JJ, Hattori D, Clemens JC, Zipursky SL, Grueber WB (2007) Dendrite self-avoidance is controlled by Dscam. Cell 129: 593–604.

Maxfield FR, McGraw TE (2004) Endocytic recycling. Nat Rev Mol Cell Biol 5: 121–132.

Mazzucchelli C, Brambilla R (2000) Ras-related and MAPK signalling in neuronal plasticity and memory formation. Cell Mol Life Sci 57: 604–611.

McAllister AK (2000) Cellular and molecular mechanisms of dendrite growth. Cereb Cortex 10: 963–973.

McAllister AK, Lo DC, Katz LC (1995) Neurotrophins regulate dendritic growth in developing visual cortex. Neuron 15: 791–803.

McAllister AK, Katz LC, Lo DC (1996) Neurotrophin regulation of cortical dendritic growth requires activity. Neuron 17: 1057–1064.

Moore AW, Jan LY, Jan YN (2002) hamlet, a binary genetic switch between single- and multiple- dendrite neuron morphology. Science 297: 1355–1358.

Morita A, Yamashita N, Sasaki Y, Uchida Y, Nakajima O, Nakamura F, Yagi T, Taniguchi M, Usui H, Katoh-Semba R, Takei K, Goshima Y (2006) Regulation of dendritic branching and spine maturation by semaphorin3A-Fyn signaling. J Neurosci 26: 2971–2980.

Nakayama AY, Harms MB, Luo L (2000) Small GTPases Rac and Rho in the maintenance of dendritic spines and branches in hippocampal pyramidal neurons. J Neurosci 20: 5329–5338.

Naska S, Park KJ, Hannigan GE, Dedhar S, Miller FD, Kaplan DR (2006) An essential role for the integrin-linked kinase-glycogen synthase kinase-3 beta pathway during dendrite initiation and growth. J Neurosci 26: 13344–13356.

Nedivi E, Wu GY, Cline HT (1998) Promotion of dendritic growth by CPG15, an activity-induced signaling molecule. Science 281: 1863–1866.

Nusser N, Gosmanova E, Makarova N, Fujiwara Y, Yang L, Guo F, Luo Y, Zheng Y, Tigyi G (2006) Serine phosphorylation differentially affects RhoA binding to effectors: implications to NGF-induced neurite outgrowth. Cell Signal 18: 704–714.

Parrish JZ, Kim MD, Jan LY, Jan YN (2006) Genome-wide analyses identify transcription factors required for proper morphogenesis of Drosophila sensory neuron dendrites. Genes Dev 20: 820–835.

Parrish JZ, Emoto K, Kim MD, Jan YN (2007) Mechanisms that regulate establishment, maintenance, and remodeling of dendritic fields. Annu Rev Neurosci 30: 399–423.

Penzes P, Johnson RC, Alam MR, Kambampati V, Mains RE, Eipper BA (2000) An isoform of kalirin, a brain-specific GDP/GTP exchange factor, is enriched in the postsynaptic density fraction. J Biol Chem 275: 6395–6403.

Penzes P, Beeser A, Chernoff J, Schiller MR, Eipper BA, Mains RE, Huganir RL (2003) Rapid induction of dendritic spine morphogenesis by trans-synaptic ephrinB-EphB receptor activation of the Rho-GEF kalirin. Neuron 37: 263–274.

Penzes P, Johnson RC, Sattler R, Zhang X, Huganir RL, Kambampati V, Mains RE, Eipper BA (2001) The neuronal Rho-GEF Kalirin-7 interacts with PDZ domain-containing proteins and regulates dendritic morphogenesis. Neuron 29: 229–242.

Pinyol R, Haeckel A, Ritter A, Qualmann B, Kessels MM (2007) Regulation of N-WASP and the Arp2/3 complex by Abp1 controls neuronal morphology. PLoS ONE 2:e400.

Polleux F, Morrow T, Ghosh A (2000) Semaphorin 3A is a chemoattractant for cortical apical dendrites. Nature 404: 567–573.

Portera-Cailliau C, Pan DT, Yuste R (2003) Activity-regulated dynamic behavior of early dendritic protrusions: evidence for different types of dendritic filopodia. J Neurosci 23: 7129–7142.

Proepper C, Johannsen S, Liebau S, Dahl J, Vaida B, Bockmann J, Kreutz MR, Gundelfinger ED, Boeckers TM (2007) Abelson interacting protein 1 (Abi-1) is essential for dendrite morphogenesis and synapse formation. Embo J 26: 1397–1409.

Prokop A, Uhler J, Roote J, Bate M (1998) The kakapo mutation affects terminal arborization and central dendritic sprouting of Drosophila motorneurons. J Cell Biol 143: 1283–1294.

Quach TT, Massicotte G, Belin MF, Honnorat J, Glasper ER, Devries AC, Jakeman LB, Baudry M, Duchemin AM, Kolattukudy PE (2008) CRMP3 is required for hippocampal CA1 dendritic organization and plasticity. Faseb J 22: 401–409.

Redmond L, Ghosh A (2005) Regulation of dendritic development by calcium signaling. Cell Calcium 37: 411–416.

Redmond L, Kashani AH, Ghosh A (2002) Calcium regulation of dendritic growth via CaM kinase IV and CREB-mediated transcription. Neuron 34: 999–1010.

Redmond L, Oh SR, Hicks C, Weinmaster G, Ghosh A (2000) Nuclear Notch1 signaling and the regulation of dendritic development. Nat Neurosci 3: 30–40.

Rocca DL, Martin S, Jenkins EL, Hanley JG (2008) Inhibition of Arp2/3-mediated actin polymerization by PICK1 regulates neuronal morphology and AMPA receptor endocytosis. Nat Cell Biol 10: 259–271.

Rodgers EE, Theibert AB (2002) Functions of PI 3-kinase in development of the nervous system. Int J Dev Neurosci 20: 187–197.

Rosso SB, Sussman D, Wynshaw-Boris A, Salinas PC (2005) Wnt signaling through Dishevelled, Rac and JNK regulates dendritic development. Nat Neurosci 8: 34–42.

Ryan XP, Alldritt J, Svenningsson P, Allen PB, Wu GY, Nairn AC, Greengard P (2005) The Rho-specific GEF Lfc interacts with neurabin and spinophilin to regulate dendritic spine morphology. Neuron 47: 85–100.

Scott EK, Luo L (2001) How do dendrites take their shape? Nat Neurosci 4: 359–365.

Segev I, London M (2000) Untangling dendrites with quantitative models. Science 290: 744–750.

Sestan N, Artavanis-Tsakonas S, Rakic P (1999) Contact-dependent inhibition of cortical neurite growth mediated by notch signaling. Science 286: 741–746.

Shima Y, Kawaguchi SY, Kosaka K, Nakayama M, Hoshino M, Nabeshima Y, Hirano T, Uemura T (2007) Opposing roles in neurite growth control by two seven-pass transmembrane cadherins. Nat Neurosci 10: 963–969.

Shirane M, Nakayama KI (2006) Protrudin induces neurite formation by directional membrane trafficking. Science 314: 818–821.

Simonsen A, Bremnes B, Ronning E, Aasland R, Stenmark H (1998) Syntaxin-16, a putative Golgi t-SNARE. Eur J Cell Biol 75: 223–231.

Sin WC, Haas K, Ruthazer ES, Cline HT (2002) Dendrite growth increased by visual activity requires NMDA receptor and Rho GTPases. Nature 419: 475–480.

Skup M (2008) Dendrites as separate compartment – local protein synthesis. Acta Neurobiol Exp (Wars) 68: 305–321.

Soba P, Zhu S, Emoto K, Younger S, Yang SJ, Yu HH, Lee T, Jan LY, Jan YN (2007) Drosophila sensory neurons require Dscam for dendritic self-avoidance and proper dendritic field organization. Neuron 54: 403–416.

Swiech L, Perycz M, Malik A, Jaworski J (2008) Role of mTOR in physiology and pathology of the nervous system. Biochim Biophys Acta 1784: 116–132.

Tada T, Sheng M (2006) Molecular mechanisms of dendritic spine morphogenesis. Curr Opin Neurobiol 16: 95–101.

Tada T, Simonetta A, Batterton M, Kinoshita M, Edbauer D, Sheng M (2007) Role of Septin cytoskeleton in spine morphogenesis and dendrite development in neurons. Curr Biol 17: 1752–1758.

Takemoto-Kimura S, Ageta-Ishihara N, Nonaka M, Adachi-Morishima A, Mano T, Okamura M, Fujii H, Fuse T, Hoshino M, Suzuki S, Kojima M, Mishina M, Okuno H, Bito H (2007) Regulation of dendritogenesis via a lipid-raft-associated Ca2+/calmodulin-dependent protein kinase CLICK-III/CaMKIgamma. Neuron 54: 755–770.

Tang BL (2008) Emerging aspects of membrane traffic in neuronal dendrite growth. Biochim Biophys Acta 1783: 169–176.

Teng J, Takei Y, Harada A, Nakata T, Chen J, Hirokawa N (2001) Synergistic effects of MAP2 and MAP1B knockout in neuronal migration, dendritic outgrowth, and microtubule organization. J Cell Biol 155: 65–76.

Terabayashi T, Itoh TJ, Yamaguchi H, Yoshimura Y, Funato Y, Ohno S, Miki H (2007) Polarity-regulating kinase partitioning-defective 1/microtubule affinity-regulating kinase 2 negatively regulates development of dendrites on hippocampal neurons. J Neurosci 27: 13098–13107.

Threadgill R, Bobb K, Ghosh A (1997) Regulation of dendritic growth and remodeling by Rho, Rac, and Cdc42. Neuron 19: 625–634.

Tolias KF, Bikoff JB, Burette A, Paradis S, Harrar D, Tavazoie S, Weinberg RJ, Greenberg ME (2005) The Rac1-GEF Tiam1 couples the NMDA receptor to the activity-dependent development of dendritic arbors and spines. Neuron 45: 525–538.

Tolwani RJ, Buckmaster PS, Varma S, Cosgaya JM, Wu Y, Suri C, Shooter EM (2002) BDNF overexpression increases dendrite complexity in hippocampal dentate gyrus. Neuroscience 114: 795–805.

van Ijzendoorn SC (2006) Recycling endosomes. J Cell Sci 119: 1679–1681.

Vega IE, Hsu SC (2001) The exocyst complex associates with microtubules to mediate vesicle targeting and neurite outgrowth. J Neurosci 21: 3839–3848.

Vizard TN, O'Keeffe GW, Gutierrez H, Kos CH, Riccardi D, Davies AM (2008) Regulation of axonal and dendritic growth by the extracellular calcium-sensing receptor. Nat Neurosci 11: 285–291.

Wayman GA, Impey S, Marks D, Saneyoshi T, Grant WF, Derkach V, Soderling TR (2006) Activity-dependent dendritic arborization mediated by CaM-kinase I activation and enhanced CREB-dependent transcription of Wnt-2. Neuron 50: 897–909.

Whitford KL, Marillat V, Stein E, Goodman CS, Tessier-Lavigne M, Chedotal A, Ghosh A (2002) Regulation of cortical dendrite development by Slit-Robo interactions. Neuron 33: 47–61.

Williams DW, Truman JW (2004) Mechanisms of dendritic elaboration of sensory neurons in Drosophila: insights from in vivo time lapse. J Neurosci 24: 1541–1550.

Wirth MJ, Brun A, Grabert J, Patz S, Wahle P (2003) Accelerated dendritic development of rat cortical pyramidal cells and interneurons after biolistic transfection with BDNF and NT4/5. Development 130: 5827–5838.

Withers GS, Higgins D, Charette M, Banker G (2000) Bone morphogenetic protein-7 enhances dendritic growth and receptivity to innervation in cultured hippocampal neurons. Eur J Neurosci 12: 106–116.

Wong RO, Ghosh A (2002) Activity-dependent regulation of dendritic growth and patterning. Nat Rev Neurosci 3: 803–812.

Wood GE, Young LT, Reagan LP, Chen B, McEwen BS (2004) Stress-induced structural remodeling in hippocampus: prevention by lithium treatment. Proc Natl Acad Sci U S A 101: 3973–3978.

Wu GY, Cline HT (1998) Stabilization of dendritic arbor structure in vivo by CaMKII. Science 279: 222–226.

Wu GY, Zou DJ, Rajan I, Cline H (1999) Dendritic dynamics in vivo change during neuronal maturation. J Neurosci 19: 4472–4483.

Wu JI, Lessard J, Olave IA, Qiu Z, Ghosh A, Graef IA, Crabtree GR (2007) Regulation of dendritic development by neuron-specific chromatin remodeling complexes. Neuron 56: 94–108.

Xie Y, Vessey JP, Konecna A, Dahm R, Macchi P, Kiebler MA (2007a) The GTP-binding protein Septin 7 is critical for dendrite branching and dendritic-spine morphology. Curr Biol 17: 1746–1751.

Xie Z, Srivastava DP, Photowala H, Kai L, Cahill ME, Woolfrey KM, Shum CY, Surmeier DJ, Penzes P (2007b) Kalirin-7 controls activity-dependent structural and functional plasticity of dendritic spines. Neuron 56: 640–656.

Yacoubian TA, Lo DC (2000) Truncated and full-length TrkB receptors regulate distinct modes of dendritic growth. Nat Neurosci 3: 342–349.

Yamamoto M, Ueda R, Takahashi K, Saigo K, Uemura T (2006) Control of axonal sprouting and dendrite branching by the Nrg-Ank complex at the neuron-glia interface. Curr Biol 16: 1678–1683.

Ye B, Petritsch C, Clark IE, Gavis ER, Jan LY, Jan YN (2004) Nanos and Pumilio are essential for dendrite morphogenesis in Drosophila peripheral neurons. Curr Biol 14: 314–321.

Ye B, Zhang Y, Song W, Younger SH, Jan LY, Jan YN (2007) Growing dendrites and axons differ in their reliance on the secretory pathway. Cell 130: 717–729.

Yu W, Cook C, Sauter C, Kuriyama R, Kaplan PL, Baas PW (2000) Depletion of a microtubule-associated motor protein induces the loss of dendritic identity. J Neurosci 20: 5782-5791.

Yu X, Malenka RC (2003) Beta-catenin is critical for dendritic morphogenesis. Nat Neurosci 6: 1169–1177.

Zhang J, Zhang L, Jiao H, Zhang Q, Zhang D, Lou D, Katz JL, Xu M (2006) c-Fos facilitates the acquisition and extinction of cocaine-induced persistent changes. J Neurosci 26: 13287–13296.

Zhou Z, Hong EJ, Cohen S, Zhao WN, Ho HY, Schmidt L, Chen WG, Lin Y, Savner E, Griffith EC, Hu L, Steen JA, Weitz CJ, Greenberg ME (2006) Brain-specific phosphorylation of MeCP2 regulates activity-dependent Bdnf transcription, dendritic growth, and spine maturation. Neuron 52: 255–269.

Zhu H, Luo L (2004) Diverse functions of N-cadherin in dendritic and axonal terminal arborization of olfactory projection neurons. Neuron 42: 63–75.

Zhu H, Hummel T, Clemens JC, Berdnik D, Zipursky SL, Luo L (2006) Dendritic patterning by Dscam and synaptic partner matching in the Drosophila antennal lobe. Nat Neurosci 9: 349–355.