PERSPECTIVE

Regulation of dendritic branching by Cdc42 GAPs

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Nerve cells form elaborate, highly branched dendritic trees that are optimized for the receipt of synaptic signals. Recent work published in this issue of *Genes & Development* by Rosario and colleagues (pp. 1743–1757) shows that a Cdc42-specific GTPase-activating protein (NOMA-GAP) regulates the branching of dendrites by neurons in the top layers of the mouse cortex. The results raise interesting questions regarding the specification of arbors in different cortical layers and the mechanisms of dendrite branching.

Early neuroanatomists distinguished many different types of neurons based solely on the morphology of the cell body and the patterning and targeting of their information-carrying processes: axons and dendrites (Ramon y Cajal 1990). We now know that neurons also differ in their developmental origins, gene expression patterns, and electrophysiology, but morphology remains a useful basis for neuron identification. Dendrites are particularly distinctive. The branching patterns of dendrites, known as arbors because of their tree-like form, range from the nearly two-dimensional vertical espaliers of cerebellar Purkinje cells to the freely branching bushes of basket cells and the horizontal disc arbors of retinal ganglion cells (Ramon y Cajal 1990). The arbor takes shape before neural networks are established, so it is presumably determined by autonomous developmental programs and exogenous nonsynaptic signals that together regulate the number, direction, and growth rate of primary dendrites and the positions and lengths of branches (Scott and Luo 2001; Urbanska et al. 2008). Later, new branches may sprout or old branches may be pruned in response to synaptic inputs on the “use it or lose it” principle. However, the regulation of the initial branching pattern remains poorly understood.

Dendritogenesis in the neocortex

The neocortex—the “thinking” part of the mammalian brain—is composed of layers of morphologically distinct neurons. More than three-quarters of cortical neurons are

projection neurons that extend long axons to other parts of the brain and deliver excitatory signals, while the remainder are interneurons, making local, inhibitory connections. The projection neurons are born below the cortex proper and migrate upward to the top of the cortex (Ayala et al. 2007). Successive neurons migrate beyond their predecessors, so early-born neurons move short distances and end up deep in the neocortex, below late-born neurons at the top (Fig. 1A).

The genesis of axons and dendrites by cortical projection neurons is temporally and spatially regulated. Axonogenesis starts soon after a neuron is born and committed, during the time that the neuron itself is still migrating from its birthplace to the growing cortical plate. On the other hand, dendrites form after migration ends. Many projection neurons are “pyramids,” with a prominent apical dendrite. This may derive from the leading process that explores the environment ahead of the neuron during its migratory phase (Hatanaka and Murakami 2002). When an early-born neuron reaches its layer and stops moving, the leading process must lengthen in order to maintain its connections with the top of the growing cortical plate (Fig. 1A, blue neuron in layer 5). Other primary dendrites extending from the cell body are presumably formed *de novo* after migration stops. Late-born neurons in layers 2 and 3 also have an apical dendrite that may derive from the leading process and basal dendrites that form *de novo* (Fig. 1A, red neuron).

Dendrite branching

We can imagine two ways that dendrites may branch (Fig. 1B). (1) The leading tip of a growing primary dendrite may fork, and both tines of the fork may extend simultaneously. (2) Side branches may form at some distance behind the growth tip. Distinguishing these possibilities requires sequential imaging of individual cells over time. Such studies have not been reported in the neocortex but have been done using hippocampal slices *ex vivo* and the optic tectum of live tadpoles and zebrafish (Dailey and Smith 1996; Wu et al. 1999; Niell et al. 2004; Urbanska et al. 2008). In these experiments, primary dendrites form first, and side branches emerge later. The side branches start out as transient slender projections, or filopodia, that emerge along the shaft of a primary dendrite at some

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Figure 1. Dendrite development in the neocortex. (A) Development of normal and NOMA-GAP mutant cortex. Time course of development with approximate embryo ages. (E14.5 [embryonic day 14.5]) Layer 5 cells (blue) arrive below layer 1, trailing an axon (orange) behind. (E16.5) The leading processes of layer 5 cells extend as the cortex grows, with layer 4 cells (not shown) inserting between layer 5 and layer 1. Layer 2/3 cells are entering from below. (E18.5) Layer 2/3 cells (red) arrive between layer 4 and layer 1. Primary dendrites have formed layer 5 cells. (Birth) Primary dendrites have formed layer 2/3 cells. Branches forming on layer 5 cells. (P5 [postnatal day 5]) Branches forming on layer 2/3 dendrites. Dendrites continue to remodel in response to activity. (NOMA-GAP^{-/-}) Layer 2/3 is reduced in size because the cells have normal primary dendrites but few branches. Layer 5 cells have normal dendritic branching close to the cell body (i.e., in layer 5). The extent of branching of layer 5 cell dendrites in layer 2/3 is not known (pale blue). (B) Possible mechanisms of dendrite branching by either branching of the growth tip or stabilization of filopodia on the dendrite shaft. (*) Lamellipodia; (arrowheads) filopodia; (arrows) direction of growth. (C) Signaling pathways that regulate dendrite branching in layer 2/3. Steps established by Rosario et al. 2012 are highlighted in red.

distance behind the growth tip. Filopodia are highly dynamic actin structures and can retract or grow. A filopodium can become a dendrite branch if it is stabilized. Stabilization coincides with, and may be caused by, the formation of synapses on the incipient branch. The stabilization of side branches by postsynaptic signaling presumably occurs by a process similar to the stabilization of dendritic spines, most likely involving calcium signaling (Konur and Ghosh 2005). Side branch formation thus requires dynamic actin assembly and disassembly for the formation and remodeling of filopodia, followed by stabilization of the actin cytoskeleton as the branching pattern develops.

RhoGTPases and the actin cytoskeleton

RhoGTPases are guanine nucleotide-binding proteins that function as molecular switches by cycling between an active GTP-bound state and an inactive GDP-bound state (Etienne-Manneville and Hall 2002). The GTP-bound state binds effector molecules that regulate actin assembly and disassembly processes.

The most intensively studied members of this large family are RhoA, Rac1, and Cdc42 (Etienne-Manneville and Hall 2002). They bind distinct effectors and are targeted to different subcellular membrane compartments by characteristic lipid modifications. Their activities are constantly regulated by at least three different sets of regulators; namely, GEFs (guanine nucleotide exchange factors), GAPs (GTPase-activating proteins), and GDIs (guanine nucleotide dissociation inhibitors). GEFs activate a RhoGTPase by stimulating the exchange of GTP for GDP, while GAPs enhance the intrinsic rate of GTP hydrolysis of the RhoGTPase, causing inactivation. GDIs interfere with GEF activity and sequester inactive RhoGTPases in specific areas of the cell. Notably, there are many more GAPs and GEFs than there are RhoGTPases, which makes for a bewildering variety of possible control points.

As a broad generalization, Rho family GTPases regulate the actin cytoskeleton. In many cell types, Cdc42 stimulates filopodia (Fig. 1B, arrowheads), Rac1 stimulates lamellipodia (Fig. 1B, asterisks), and RhoA stimulates contractile stress fibers (Hall 1998). Accordingly, RhoA, Rac1, and Cdc42 play key roles in the growth and branching of axons and dendrites (Govek et al. 2005; Urbanska et al. 2008). The first evidence came from studies using neuronal cell lines (Govek et al. 2005). Commonly used neuronal lines can undergo the initial steps of neuronal differentiation and extend neurites, which are the uncommitted precursors of dendrites and axons. In these *in vitro* systems, Cdc42 and Rac1 induce neurite growth and branching, while Rho inhibits (Govek et al. 2005). Further work in several *in vivo* systems has confirmed that Rac1 stimulates and Rho inhibits dendrite growth and branching, but the role of Cdc42 is less clear (Ruchhoeft et al. 1999; Ng et al. 2002). Expression of activated mutant Cdc42 inhibits dendrite growth in the *Drosophila* peripheral nervous system (Luo et al. 1994) but induces dendrites in *Xenopus* optic tectal neurons (Li et al. 2000). Loss of Cdc42 increased the length but did not alter the complexity of dendrites of specific neurons in the *Drosophila* CNS (Scott et al. 2003). These apparently contradictory results suggest that the role of Cdc42 is more complex and may vary in different types of neurons. In addition, the function of Cdc42, and possibly other Rho GTPases, may not depend on the permanent activation or inhibition state, but on the rate and localization of cycling between the GDP- and GTP-bound states. As a consequence, GEFs, GAPs, and GDIs acquire key roles in deciding where within the cell, when, and for how long Cdc42 is active or inactive.

NOMA-GAP regulates dendritic branching

In this issue of *Genes & Development*, Rosario et al. (2012) identified NOMA-GAP as a Cdc42-specific GAP

that is required for proper dendritic development in the upper layers of the neocortex. They found that homozygous deletion of the *NOMA-GAP* gene has little or no effect on neurogenesis, neuron fate specification, cell migration, axonogenesis, or the number of primary dendrites. However, when *NOMA-GAP* is absent, there is a marked reduction in the number of dendrite branches of layer 2/3 neurons, resulting in a simpler dendritic tree. *Cdc42* activity is increased in the mutant cortex. In an elegant and convincing series of experiments, Rosario et al. (2012) go on to show that the phenotype of a *NOMA-GAP* mutant is rescued by heterozygous deletion of *Cdc42*, thus showing genetically that the role of *NOMA-GAP* is to inhibit *Cdc42*. They show that downstream from *Cdc42*, a *Cdc42* effector, the protein kinase *PAK1*, is activated when *NOMA-GAP* is absent and that a *PAK1* substrate, another protein kinase, *LIMK*, is also activated. *LIMK* is known to phosphorylate and inhibit an actin severing/depolymerizing molecule, cofilin (Arber et al. 1998). Deletion of *NOMA-GAP* caused a significant increase in phosphorylated cofilin, particularly in the upper layers. In a final satisfying experiment, the investigators expressed a nonphosphorylatable mutant of cofilin in the *NOMA-GAP* mutant cortex and again rescued the phenotype. In sum, the study provides thorough documentation for a signaling pathway linking *NOMA-GAP* through *Cdc42*, *PAK1*, *LIMK*, and cofilin to dendrite branching (Fig. 1C).

Layer-specific dendritic complexity

One interesting aspect of the *NOMA-GAP* mutant phenotype is that the reduction in dendritic complexity is apparent in layer 2/3 neurons but not in layer 5 neurons, at least within 300 μm of the cell body, which was as far as the investigators could measure (Rosario et al. 2012). This raises the question of how *NOMA-GAP* regulates dendrite branching in layer 2/3 and not layer 5, given that *NOMA-GAP* is expressed in all layers. Here we consider that *NOMA-GAP* may be required more in one layer than another because (1) other *Cdc42*-GAPs are expressed in some layers and can substitute for *NOMA-GAP* or (2) *Cdc42* is activated more in some layers than others as a result of, for example, layer-specific environmental signals or differentially expressed *Cdc42*-GEFs.

Potential redundancy: overlap between *NOMA-GAP* and *RICS*

An obvious potential source of redundancy for *NOMA-GAP* is its close relative, *RICS*. Both proteins have been studied extensively under various names (*NOMA-GAP*/*ARHGAP33*/*SNX26*/*TCGAP* and *RICS*/*PX-RICS*/*ARHGAP32*/*Grit*/*p200RhoGAP*/*GC-GAP*). They are expressed in the same brain regions during development and are highly similar in structure and protein–protein interactions (Nakamura et al. 2002; Chiang et al. 2003; Hayashi et al. 2007; Rosario et al. 2007). Both *NOMA-GAP* and Phox homology (PX)-*RICS* (the main isoform in developing brains) contain an N-terminal phosphoinositide-binding PX domain, through which they localize to cell membranes.

After the PX domain, there is a SH3 domain, which typically binds to proline-rich peptides, followed by the RhoGAP domain, and finally, several proline-rich sequences localized in the C-terminal part of the protein. Many of the C-terminal proline sequences fit the consensus for binding to SH3 domains, suggesting that *NOMA-GAP* and *RICS* might autoregulate. Indeed, full-length *NOMA-GAP* and *RICS* are less active than their isolated GAP domains when overexpressed (Nakamura et al. 2002; Chiang et al. 2003). The proline sequences also bind to a large number of SH3 domain-containing signaling proteins. The neurotrophin receptor *TrkA* also binds to the C termini of both *NOMA-GAP* and *RICS*. These similarities suggest that *NOMA-GAP* and *RICS* may well have overlapping functions.

Genes with overlapping functions are typically redundant with each other. A *RICS* knockout mouse was made, but no phenotype was detected (Nasu-Nishimura et al. 2006). However, *RICS* knockout neurons had more active *Cdc42* and developed longer neurites when cultured in vitro, suggesting a role for *RICS* in dendritogenesis (Nasu-Nishimura et al. 2006). Very recently, RNAi was used to knock down *RICS* in developing rat cortex (Long et al. 2012). Intriguingly, *RICS* knockdown reduced the dendritic complexity of layer 2/3 neurons (Long et al. 2012), similar to the phenotype of *NOMA-GAP* knockout mice. Thus, it is possible that closer examination of *RICS* knockout mice might reveal defects in dendrite branching that were previously overlooked.

If *RICS* has functions similar to *NOMA-GAP* and is expressed in the same cells, why do the knockouts and knockdowns have any phenotypes at all? One possible explanation is that, despite their many similarities, the *NOMA-GAP* and *RICS* proteins may have different downstream effectors and upstream regulators. In this regard, differences in GAP activity and binding partners of *NOMA-GAP* and *RICS* have been reported, but unfortunately, the two proteins were not compared side by side by the same experimenters. For example, *NOMA-GAP* was reported to stimulate hydrolysis of *Cdc42*.GTP and *Rac1*.GTP faster than *RhoA*.GTP (Chiang et al. 2003), yet it binds more tightly to *Cdc42*.GTP than to *Rac1*.GTP or *RhoA*.GTP (Rosario et al. 2007). Different researchers reported that *RICS* stimulates GTP hydrolysis equally by *Cdc42*, *Rac1*, or *RhoA* (Moon et al. 2003) or that *RICS* prefers *Cdc42* over *Rac1* or *RhoA* as a substrate (Nakamura et al. 2002). In vivo, both *NOMA-GAP* and *RICS* are linked predominantly to *Cdc42* (Chiang et al. 2003; Okabe et al. 2003; Hayashi et al. 2007; Rosario et al. 2012). *RICS* binds to β -catenin, E-Cadherin, N-Cadherin, PSD-95/DLG4, and a variety of SH3 domain proteins (Okabe et al. 2003). However, these interactions may not be unique, since binding to *NOMA-GAP* has not been tested.

Both *NOMA-GAP* and *RICS* are under upstream control by tyrosine phosphorylation. *NOMA-GAP* can be phosphorylated in at least two regions; namely, the GAP domain by the Src-family kinase *Fyn*, and the C-terminal tail by *TrkA* (Liu et al. 2006; Rosario et al. 2007). In NGF-stimulated PC12 cells, *Fyn*-dependent phosphorylation of *NOMA-GAP* inhibited the GAP activity and promoted

neurite outgrowth in a Cdc42-dependent manner (Liu et al. 2006). NGF also stimulated TrkA-dependent phosphorylation of the C-terminal tail of NOMA-GAP. This recruited Shp2, activated Erk5, and stimulated neurite outgrowth (Rosario et al. 2007). Similarly, RICS can be phosphorylated by TrkA and Src kinases (Nakamura et al. 2002; Moon et al. 2003), although the functional significance for dendrite outgrowth or branching is less clear. RICS can also be phosphorylated by CaMKII and possibly by EGFR, although it is not clear whether the EGFR-dependent phosphorylation is direct or indirect through Src activation (Nakamura et al. 2002; Okabe et al. 2003).

Given this complexity, an important task for the future will be to systematically compare NOMA-GAP and RICS in the same binding and biochemical assays and to test the effects of single and double knockdown or knockout on dendrite branching *in vivo*.

Transcriptional regulation of the Cdc42 pathway

Differential expression of other Cdc42 GAPs or GDIs could suppress the requirement for NOMA-GAP in deep-layer neurons. In this regard, there are, of course, many differences in gene expression between neurons in different layers (Ayoub et al. 2011), and any of the large number of Cdc42 GAPs or GDIs could compensate when NOMA-GAP is absent from layer 5 neurons. However, recent results suggest candidate transcription factors that may regulate the layer-specific expression of Rho regulators.

In flies, the transcription factor Cut controls the dendrite morphology of post-mitotic neurons (Grueber et al. 2003). Interestingly, in mice, *Cux1* and *Cux2*, which are the vertebrate homologs of Cut, are specifically expressed in the top layers of the cortical plate. Moreover, analysis of single or double *Cux1/Cux2* mutant mouse brains showed reduced dendritic complexity just in the top layers of the cortical plate, similar to the NOMA-GAP mutant (Cubelos et al. 2010; Rosario et al. 2012). These data suggest a model in which *Cux1* and *Cux2* might regulate expression of Cdc42 regulators, giving a possible explanation for the layer-specific phenotype in NOMA-GAP mutant mice.

Another possible mechanism to generate diversity is through the specific expression of microRNAs (miRs). miR-132 is enriched in the brain and targets RICS in cultured hippocampal neurons, stimulating dendrite extension and branching (Vo et al. 2005). *In silico*, at least three different microRNAs may target NOMA-GAP (miR-544, miR-31, and miR-490). Analysis of their capacity to recognize and target NOMA-GAP mRNA as well as their layer distribution during late development might help to understand the highly restrictive phenotype in NOMA-GAP mice.

Input signals: layer-specific activation of Cdc42 in the developing cortex

It is self-evident that Cdc42 inactivation by GAPs is only necessary if Cdc42 is activated. Therefore, the increased requirement for NOMA-GAP in upper cortical layers could be a reflection of increased activation of Cdc42

GEFs in these neurons. Indeed, arborization is known to be regulated by diffusible cues, cell-cell contacts, and neuronal activity, which vary layer by layer (Urbanska et al. 2008). Three diffusible signals—Reelin, Sema3A, and neurotrophins—are of particular interest because their expression is layer-specific and they regulate tyrosine kinases that modify NOMA-GAP and RICS and also regulate GEFs for Cdc42.

Reelin is expressed primarily in layer 1 of the developing brain but diffuses down through the cortical plate (D'Arcangelo et al. 1995; Jossin et al. 2007). *In vitro*, Reelin stimulates dendrite growth, and dendritic complexity is reduced *in vivo* in Reelin heterozygous mutant mice (Niu et al. 2004). Reelin signals by activating Src family tyrosine kinases Src and Fyn, which are known regulators of NOMA-GAP and RICS (Arnaud et al. 2003; Moon et al. 2003; Liu et al. 2006; Rosario et al. 2007). Tyrosine kinases stimulate many Rho family GEFs by phosphorylation or membrane recruitment (Schiller 2006). The increased Reelin concentration near the top of the cortical plate could therefore stimulate Cdc42 GTP loading in layer 2/3 neurons more than in layer 5, necessitating increased NOMA-GAP activity to compensate.

Sema3A was identified as a chemoattractant for dendrites using assays in which dissociated cortical neurons were plated onto live cortical slices (Polleux et al. 2000). Sema3A is produced near the top of the cortical plate and forms a gradient from top to bottom. The gradient stimulates the growth of apical dendrites toward the source of Sema3A. Sema3A also stimulates dendritic branching, in part through Fyn (Morita et al. 2006). Curiously, Sema3A induces dendrite collapse in cultured neurons, seemingly the opposite of its main role *in vivo* (Sasaki et al. 2002). These results emphasize the importance of *in vivo* experiments to control for the artificial environment imposed by *in vitro* culture.

The neurotrophins BDNF, NT-3, and NT-4 have complicated combinatorial effects on dendrite growth and arborization. BDNF stimulates dendrite growth by layer 4 neurons and inhibits layer 6 neurons (McAllister et al. 1995, 1997). Reciprocally, NT-3 inhibits layer 4 neurons and stimulates layer 6 neurons. NT-4 stimulates layer 6 dendrites early in development and layer 2/3 neurons later (McAllister et al. 1995; Wirth et al. 2003). As discussed above, neurotrophin receptors (Trks) phosphorylate RICS and NOMA-GAP (Nakamura et al. 2002; Rosario et al. 2007) and also activate a variety of Rho family GEFs (Schiller 2006), so the effects of neurotrophins on dendritogenesis could be mediated by Cdc42 GEFs and GAPs. Interestingly, one mechanism for activation of Rac1, and potentially Cdc42, is through the WAVE complex (Pollard et al. 2000). One component of the WAVE complex, Nap1, is induced by BDNF in culture and is expressed *in vivo* when neurons stop migrating and start differentiation (Yokota et al. 2007). Like NOMA-GAP, Nap1 is needed for dendritic arborization. Taken together, these results suggest a variety of ways in which neurotrophins could interact with Cdc42 in determining the layer specificity of dendritic arborization.

Cdc42, actin dynamics, and dendrite branching

In principle, Cdc42 could impact dendrite branching through a number of different mechanisms. One is by regulating the polarity of growing dendrite processes. Cdc42 focuses actin polymerization to a restricted region of the cell membrane, thus regulating the polarity of cell migration and the site of axon emergence (Etienne-Manneville and Hall 2002). These processes are conceptually similar to maintaining a single point of growth at the tip of a dendrite, so high Cdc42 activity would inhibit branching, as observed in the NOMA-GAP mutant. However, these Cdc42 functions involve atypical protein kinase C and the Par complex, as opposed to the PAK1, LIMK, cofilin pathway used by NOMA-GAP (Rosario et al. 2012). Therefore, we need to understand how cofilin regulates branching.

Cofilin is an actin-severing protein. It interacts with actin filaments, breaks them, and associates with free ends (Pollard et al. 2000). In this way, it dismantles actin filaments. However, it also regenerates a pool of actin subunits for recycling, so cofilin actually promotes actin polymerization. The net effect is to stimulate actin dynamics. Thus, inhibition of cofilin by Cdc42–PAK–LIMK stabilizes existing filaments and inhibits the growth of new ones (Arber et al. 1998), and cofilin knockout interferes with neurite formation in vivo and in vitro (Bellenchi et al. 2007). In addition, Cdc42 binds to and activates N-WASP, which stimulates actin filament assembly, and diaphanous-related formin 3, which promotes the growth of parallel actin bundles (Pollard et al. 2000; Peng et al. 2003). Together, these Cdc42 effectors generate filopodia. The implication is that the activation of Cdc42 by NOMA-GAP deletion would induce filopodia via N-WASP and formins but, at the same time, reduce actin dynamics by inhibiting cofilin. The ability of non-phosphorylatable mutant cofilin to rescue the NOMA-GAP mutant implies that vigorous actin dynamics are critical for branching.

Clearly, understanding the exact mechanism by which NOMA-GAP, Cdc42, and cofilin regulate dendrite branching in vivo will require the development of techniques for following the differentiation of neocortical neurons in vivo or in slice culture over long periods of time. However, if we assume that the dendritic branches of cortical neurons arise from filopodia, as discussed above (Dailey and Smith 1996; Wu et al. 1999; Niell et al. 2004; Urbanska et al. 2008), then it seems probable that NOMA-GAP stimulates the initiation of dynamic filopodia. The conversion of transient filopodia into stable branches, however, would require inhibition of NOMA-GAP in order to slow down actin turnover. These considerations indicate that dynamic spatial and temporal regulation of Cdc42 GAPs and GEFs lies at the heart of dendrite arbor formation.

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