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The Yin–Yang of Dendrite Morphology: Unity of Actin and Microtubules

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Abstract Actin and microtubules (MT) are targets of numerous molecular pathways that control neurite outgrowth. To generate a neuronal protrusion, coordinated structural changes of the actin and MT cytoskeletons must occur. Neurite formation occurs when actin filaments (F-actin) are destabilized, filopodia are extended, and MTs invade filopodia. This process results in either axon or dendrite formation. Axonal branching involves interplay between F-actin and MTs, with F-actin and MTs influencing polymerization, stabilization, and maintenance of each other. Our knowledge of the mechanisms regulating development of the axon, however, far eclipses our understanding of dendritic development and branching. The two classes of neurites, while fundamentally similar in their ability to elongate and branch, dramatically differ in growth rate, orientation of polarized MT bundles, and mechanisms that initiate branching. In this review, we focus on how F-actin, MTs, and proteins that link the two cytoskeletons coordinate to specifically initiate dendritic events.

Keywords Dendrite · Actin · Microtubule · Neuronal morphology · Cytoskeleton

Introduction

Ancient Chinese philosophy focuses on the model of yin and yang, a complex notion used to explain the unity of opposites that dominates the natural world. In Western society, we have adopted and incorporated this idea into all aspects of thought, including our most basic understanding of cellular function [1–3]. While the actions of actin and microtubules (MT) do not oppose each other in the strictest sense, when functioning physiologically, they play distinct roles with the unified goal of establishing balanced dendrite morphology and cellular polarity. For many years, these two filament systems were viewed as functionally separate. However, more recent reports during the past three decades have provided clear evidence of both structural and functional interactions between the two [4–7]. Initial reports documented the indirect association between these two cytoskeletal elements in purified protein mixtures using biochemical methods and indicated that microtubule-associated proteins (MAPs) were essential for this interaction to occur [4, 8]. Later studies examined and confirmed these interactions in non-neuronal cell cultures [9, 10] and suggested a role for the coordination of actin and MTs in neuronal morphology and development [10, 11]. Currently, much of the evidence that supports an interaction between actin and MTs in the neuron has been reported either in axons or in non-specific neuronal projections, including growth cones and filopodia [12–14]. Although it is clear that careful synchronization of filamentous actin (F-actin) and MTs is necessary for dendrite branching to occur, a comprehensive description of the partnership between these

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two cytoskeletal elements has yet to be illuminated. In the following review, we focus on data which highlight the interactions between these elements in determining dendrite morphology. Specifically, we will examine the roles of intracellular proteins, motor proteins, Rho-GTPases, and extracellular signals/matrix proteins in producing coordinated cytoskeletal changes that affect dendrite patterning.

Determination of Neuronal Polarity: Axons vs. Dendrites

Significant progress has been made in our understanding of dendrite morphology and function since Santiago Ramón y Cajal's observation that the nervous system is not a continuous network of elements but is instead composed of distinct polarized nerve cells [15, 16]. Mature polarized neurons typically have a single long axon that is structurally and functionary distinct from several shorter dendrites [17, 18]. Dendrites and axons may be distinguished based on surface appearance, MT orientation and spacing, and the presence of specific protein markers (Fig. 1).

The first decision in establishing the identity of a neurite, becoming a dendrite rather than an axon, is dictated by the relationship between F-actin and MTs [19]. Various neurites branch from the cell body, and ultimately, a single neurite becomes the longest protrusion. The longest neurite becomes the future axon, and the cell polarity protein complex, PAR (*par*titioning defect), and active phosphoinositide 3-kinase (PI3K) accumulate at its tip [19]. The PAR protein complex, consisting of PAR3, PAR6, and atypical protein kinase C (aPKC), is vital for axon formation, and blocking the activity of these proteins will prevent one of the many neurites of a cell from becoming specified as an axon [20, 21]. Furthermore, the PAR complex regulates both MT and F-actin dynamics. While actin and MTs play separate roles in axon specification, enhanced MT polymerization and increased actin instability, which is less restraining to MT invasion, are both necessary for axon selection [22–25]. Most recently, Bradke and colleagues showed that stabilizing microtubules with taxol in cultures of mature neurons causes formation of multiple axons [26]. The transformation and growth of dendrites into axons continues after the drug has been washed out, suggesting that the initial stabilization of microtubules may be the critical signal for a neurite to become an axon rather than a dendrite.

Another mediator of neuronal polarity, and therefore neurite commitment to become a dendrite or an axon, is the strength of neuron-to-substrate adhesion [27]. All neurite initiation must be instigated by a reduction of actin-tensile forces. Decreasing actin tension in the cell, either by mechanically pulling on the neuron or via cytochalasin treatment, results in global neurite elongation [28]. In contrast, antagonizing MT polymerization with nocodazole specifically curtails dendritic outgrowth [29]. Axons and dendrites differ significantly in their requirements for initiation and elongation and use distinct approaches to reduce tensile forces, which are highly dependent on the relationship between MTs and F-actin. Typically, axons use compression from stable MTs oriented in a uniaxial configuration, while dendrites combat actin-mediated strain by relying heavily on cell-substrate adhesive forces [30, 27]. Dendrites have a different mechanistic requirement since their MTs are both less densely packed than in an

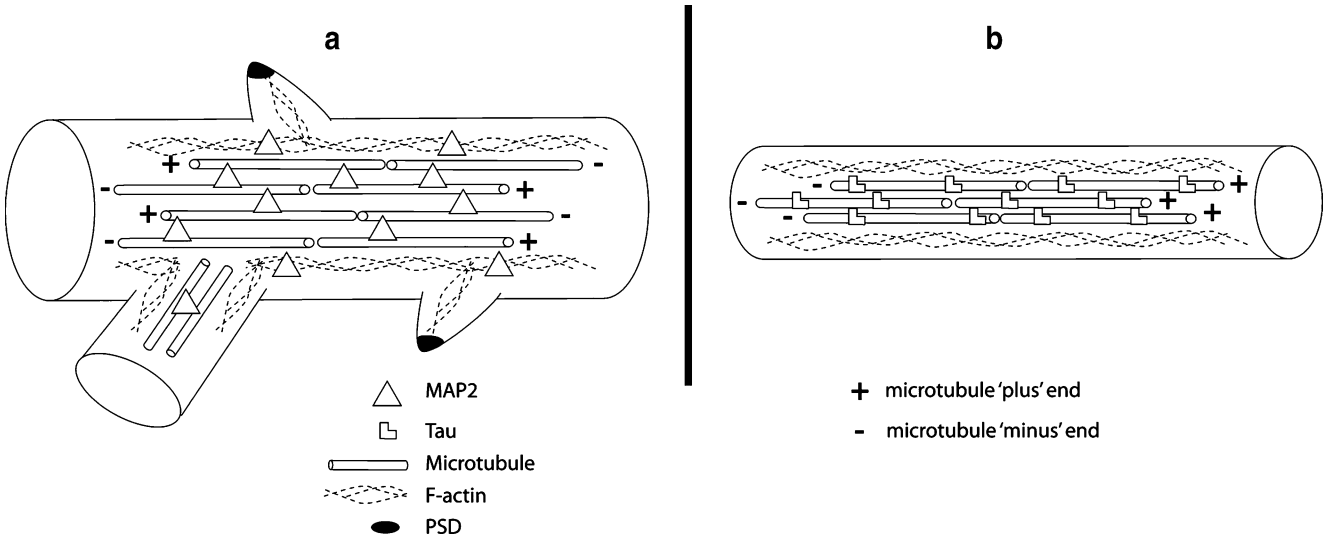

Fig. 1 Basic differences in axonal and dendritic structures. **a** Dendrites are characterized by rough surfaces, widely spaced microtubules, and the presence of MAP2 protein. Microtubule − and +ends are not aligned. PSD proteins are localized at actin-rich dendritic spines. **b** Axons are characterized by tightly packed microtubules and the presence of tau protein. Microtubules are aligned at − and +ends

axon and are biaxially oriented. Dendrites can only grow when the neuron is highly adhered to the substrate, while axons can extend when the cell is less tightly adhered to the substrate [31], suggesting that the concentration of polymerized MTs in a dendrite is not sufficient to antagonize actin-driven tensile forces on their own [27]. Thus, to achieve dendrite extension, compensation for the lower MT concentration is achieved by challenging actin-produced strain with a supplementary mechanical force imparted by a stronger cell-to-substrate interaction.

The Dendritic Cytoskeleton

The dendritic cytoskeleton, a dynamic structure composed of actin microfilaments, intermediate filaments, and MTs, plays roles in determining neuronal morphology, imparting physical protection for the cell and establishing cellular motility. While there are numerous signaling cascades that control neurite outgrowth, and specifically dendrite branching, many converge on controlling the activity and polymerization of the actin and MT cytoskeletons. At times, actin can either disrupt or promote dendrite initiation [32, 33]. On one hand, retrograde flow of actin may act as an obstacle to MTs [34], and on the other hand, actin bundles could advance MT bundles into the dendrite and serve as tracks for MT invasion [35]. Microtubule and F-actin networks collaborate in many cellular activities, including migration, organelle transport, and cell division. The means by which MTs and F-actin cooperate to mediate these different events, particularly cell migration via extension of cellular processes, is through the direct networking of MTs at cortical F-actin tips [36]. In the following section on components of the dendritic cytoskeleton, we will focus on the independent roles of actin and MTs in dendrites.

Actin

Structurally, actin microfilaments, intermediate filaments, and MTs make up the eukaryotic cytoskeleton. Actin microfilaments are formed from the helical twisting of two separate F-actin strands, each comprised of polymerized globular actin monomers [37]. The F-actin cytoskeleton is the framework for filopodia of the dendritic growth cone. Thus, it is primarily localized to the outer shell, or cortex, of dendrites as well as in dendritic spines [38, 39]. It is generally accepted that actin plays a key role in dendrite development, specifically in spine formation and dendritic filopodial protrusion [40]. It exhibits rapid turnover rates, thus imparting enhanced plasticity to dendrites [41, 37, 42]. In addition, actin plays an integral role in promoting synaptic efficiency via anchoring and proper trafficking of receptors in dendritic spines [37].

Microtubules

Tubulin is polymerized into MTs in the nucleating center located in the cell body, also known as the microtubule organizing center or the centrosome [43, 44]. MTs are further stabilized by MAP capping and are then ultimately transported into the growing dendrite via molecular motors [43, 44]. Unlike F-actin, MTs are enriched in the peripheral domain of dendrites. They are less densely packed in the dendrite than in the axon and are oriented biaxially or in non-uniform polarity [45]. MTs are generally dynamic and are in an equilibrium state of constant polymerization and depolymerization at stable dendrite branch points. Similar to actin, MTs provide structural support for dendrites. In addition, they play a major role in the targeting of dendritic proteins from the cell body [46]. MT depolymerization and subsequent invasion into filopodia are also necessary for the stabilization of filopodia that will become dendrite branches.

Intracellular Proteins that Link Actin and MTs in Dendrites

Intracellular proteins play a central role in the regulation of dendrite morphology via communication between the actin and MT cytoskeletons. These proteins participate in processes ranging from dendrite outgrowth, branching, and stabilization to spine morphogenesis and maturation. In the following section, we examine in detail the roles of selected intracellular proteins and how they initiate coordination of F-actin and MTs during dendrite patterning.

Microtubule-Associated Proteins

MAPs play a pivotal role in dendrite branching by directly linking MTs to the actin cytoskeleton. Proteins correlated with MAPs have properties that affect both MTs and F-actin. Many of the proteins involved were discovered for their ability to affect MT dynamics but have now been found to associate with other cytoskeletal proteins, specifically F-actin. Early MT research focused on proteins that stabilize or destabilize MTs. The MAPs (MAP1A, MAP1B, and MAP2) are examples of proteins known to stabilize MTs. The tau protein has related activity, but its action is axonal in nature and therefore will not be discussed here.

MAP1B is the earliest MAP to be expressed during neuronal development [47]. It plays a key role in neuritogenesis by promoting MT assembly and stabilization [48, 49]. Its phosphorylation state, which can be altered by glycogen synthase kinase-3 beta (GSK-3 beta), can dictate whether MTs are in a stable or dynamic state [50]. In addition, MAP1B has an actin-binding site that could serve

as a position at which MTs and F-actin are potentially cross-linked [51]. Whether or not MAP1B can bind both F-actin and MTs simultaneously is still unclear, but it is known that MAP1B interacts with both F-actin and MTs in the growth cone [52]. MAP1B has been implicated in controlling axon retraction following treatment with lysophosphatidic acid via contraction of F-actin followed by collapse of MTs [53]. Furthermore, reduction of MAP1B can alter actin dynamics and presumably modify dendrite branching [54].

The MT-associated protein MAP1A is also an actin-binding and cross-linking protein [11]. Addition of MAP1A to a solution of F-actin filaments increases the viscosity of the solution, indicating that MAP1A cross-links the filaments and hinting at its function in regulating neuronal morphology [11]. MAP1A expression is required for branching and stabilization of the dendritic arbor. Furthermore, actin and MAP1A co-localize in distal regions of the dendritic growth cone, specifically at filopodial extensions [55].

Another MAP, MAP2, is enriched in the cell body and in the dendrites of neurons [56]. MAP2 is critical for dendritogenesis. In fact, MAP2-deficient mice have shorter dendrites with a sparse MT cytoskeleton [57]. It has been known for almost two decades that MAP2 is not only a MT-associated protein, as its name would suggest, but also an actin-associated protein, and therefore, it confers dynamic activity to the actin microfilament network in dendrites [58]. MAP2 can bind F-actin at its MT binding site, which causes MT bundling [59]. The effect of MAP2 on dendrite branching is dependent on the phosphorylation state of MAP2. Dephosphorylated MAP2 promotes dendrite extension by inducing polymerizing MTs to bunch. In contrast, phosphorylated MAP2 promotes branching by changing the conformation of MT bundles and spacing the MTs further apart [60]. The phosphorylation state of MAP2 can be modified by the Ras guanine nucleotide exchange factor, which transports the kinase non-catalytic C-lobe domain, very-KIND (v-KIND). v-KIND is a negative regulator of dendritic branching and co-localizes with MAP2 and F-actin distally in dendrite tips [61].

Adenomatous Polyposis Coli Protein and End-Binding Proteins

Adenomatous polyposis coli protein (APC) binds cytoskeletal proteins and their associated proteins (for review, see [62]). Much of the information known about APC has been derived from other cells types or axons; however, APC may play a role in differentiating the axon from dendrites [63, 64].

APC can bundle actin fibers as well at MTs; however, MTs compete with actin for the binding of APC, depending on concentration [65]. In addition to the ability to bind and bundle MTs and actin separately, APC can cross-link MTs and actin to allow cytoskeletal interactions. Cross-linking of MTs and actin by APC is due, in part, to the link between APC and IQGAP1 and is regulated by cell division cycle 42 (Cdc42) and Rac1, signaling proteins involved in the cell cycle [66]. IQGAP1 can also bind to microtubule +ends, providing a link for APC to both actin and MTs [67].

APC can also interact with MT plus-end-binding (EB) protein family members. The EB family is part of a highly conserved group of *+TIP*s (plus-end-tracking proteins) which associate with the assembling plus-end of the MT. The mammalian EB family consists of EB1, 2, and 3. The EB proteins are thought to make up a "core" of MT +end tracking proteins. EB1 directly causes both catastrophic and rescue events in MTs assayed in vitro [68]. EB1 binds APC and is required to recruit APC to the +end of MTs [69, 70]. In fact, the ability of APC to bind actin is inhibited by the interaction of APC with EB1 [65]. In addition, EB1 is involved in transporting organelles via myosin from the MT to actin cytoskeletons [71]. EB1 is clearly a regulator of the role of APC in the regulation of the interaction between MTs and actin. Regulation of the association between APC and EB1 may play a critical role in influencing the interplay of MTs and F-actin, especially since dendrites are places of "unstable" MTs [29].

EB3, an EB family member that is preferentially expressed in the central nervous system, binds to a neuron-specific form of APC, called APCL [72]. This binding affects the ability of APC to interact with cytoskeletal components in a similar fashion to EB1. This association suggests that APC may be a major player in dendritic activity since EB3 is often used to track microtubule growth in axons and dendrites [73]

Shortstop

Shortstop (shot, kakapo) is a member of the spectraplakin protein family. This family of proteins is characterized by a plakin binding domain and MT and actin binding domains. Because of their diverse range of binding motifs, they are considered to be linker proteins between the actin and MT cytoskeletons in many cells types [74]. Among its many roles, shortstop regulates the highly ordered dendritic branching of *Drosophila* peripheral nervous system neurons [75]. Mutations in shortstop cause defects in a reduction in lateral dendrite branching as well as axonal outgrowth, and its mammalian homologs have similar functions [76].

While not a true cross-linker of MTs and actin, shortstop binds to MAPs and cooperatively regulates various aspects of actin and MT cytoskeletal interactions. For example, shortstop recruits EB1 and APC to MTs in muscle cells, indicating its relationship with proteins active in regulating MT and F-actin dynamics [77]. Shortstop can also coordinate the binding of APC and EB1 at cell–cell

junctions [78]. Thus, shortstop may play an important role in regulating EB1 and APC binding to MT bundles, causing MT instability and reduction in neurite outgrowth. Alternatively, along with APC, shortstop could direct MTs to the membrane where new neurites will form.

Abelson

The Abelson (Abl) family of non-receptor tyrosine kinases includes the ubiquitous c-Abl tyrosine kinase and Abl-related gene (Arg) proteins, which contribute to diverse signaling pathways, including cellular proliferation, apoptosis, and dendrite branching [79]. Both Ab1 and Arg co-localize at synaptic terminals in neurons [80]. Neurons from Abl or Arg knockout mice have reduced dendritic arbors, and it has been suggested that Arg may use binding domains for F-actin and MTs to reorganize the two at branch sites [81]. In addition, Abl binds to both MTs and F-actin and is another protein that regulates the coordination of MT and F-actin function in dendrite branching [81, 82]. Furthermore, signaling through Abl and Arg promotes dendrite branching in response to integrin adhesion to substrate and subsequent receptor activation [81, 82].

Neurabin

Neurabin was initially discovered as an F-actin binding protein. It is localized to growth cone lamellopodia during neuronal development and, specifically, to dendrites of primary rat hippocampal neurons following 10 days in culture [83]. Neurabin plays a crucial role in regulating dendritic spine morphogenesis and maturation [84], spine density [85, 86], and synaptogenesis [86]. Neurabin is also associated with the MT cytoskeleton via interactions with doublecortin [87] and Lfc [87, 88]. Lfc, a Rho-specific guanine nucleotide exchange factor (GEF), is associated with MTs in the dendritic shaft during basal conditions, but is rapidly translocated to spines following neuronal stimulation. Neurabin expression results in regulation of dendritic spine morphology via Rho-dependent recruitment of Lfc to the F-actin cytoskeleton in spines [88]. These studies provide support for a role for neurabin as an essential player in the regulation of dendritic spine morphology via interactions with both actin and MT cytoskeletons.

PSD Proteins

Postsynaptic density (PSD) proteins are specialized cytoskeletal proteins that assemble neurotransmitters and related receptors at the PSD to mediate mature synaptic function. The PSD contains intermediate filaments, MTs, and F-actin that anchor synaptic proteins, allowing them to be poised for stimulation when a presynaptic signal is present. For example, NMDA receptors and Ca(2+)/calmodulin-dependent protein kinase II alpha are localized at the PSD only when the actin cytoskeleton is intact [89]. In contrast, GABA receptors are properly localized only when the MT cytoskeleton is intact [89]. Furthermore, several scaffolding proteins of the PSD, specifically PSD-95, cypin, GRIP, and Shank, play roles in dendritic branching [90–92]. PSD-95, an essential component of the excitatory PSD that plays a role in learning and memory [93], exhibits a non-synaptic function early in dendritogenesis and acts as a signal to stop dendrite outgrowth and branching [91]. PSD-95 is also indirectly linked to MTs and actin via additional scaffolding proteins [94, 95]. The interaction between MTs and F-actin mediated by PSD-associated proteins is still largely unexplored, but it is likely that these proteins modulate cell and dendrite shape by influencing both cytoskeletons concurrently.

PSD-95: Linking the PSD and MT Cytoskeleton

It has been recently reported that overexpression of PSD-95 in a heterologous cell line results in disrupted MT organization [91]. Cypin, a guanine deaminase that binds to PSD-95 via its C-terminal PDZ-binding motif, functions as a positive regulator of dendrite branching [96]. Cypin binds to tubulin heterodimers and promotes microtubule assembly [97, 96, 91], and the binding of snapin to cypin negatively regulates the function of cypin [98]. Furthermore, although cypin functions as a negative regulator of PSD-95 localization [97], overexpression of PSD-95 blocks cypin-promoted increases in dendrite branching [91]. Thus, the ultimate shape of the dendritic arbor may be determined by the actions of cypin, snapin, and PSD-95 on the MT cytoskeleton (reviewed in [92]).

In addition, PSD-95 interacts with MAP1A via its guanylate kinase domain [94, 99]. It also associates with CRIPT via its third PDZ domain [100]. Like MAP1A, CRIPT links PSD-95 to MTs. Thus, these interactions act to link the PSD to the MT cytoskeleton.

PSD-95: Linking the PSD and Actin Cytoskeleton

Members of the Shank family of scaffolding PSD proteins bind indirectly to PSD-95 via guanylate kinase-associated protein (GKAP) and provide a link between the PSD and the actin cytoskeleton. Cortactin, an F-actin binding protein, is in a complex with Shank. Since Shank interacts with PSD-95 via association with GKAP and Shank interacts with cortactin, PSD-95 is indirectly linked to the actin cytoskeleton [101].

The Roles of Actin- and MT-Based Motor Proteins in Dendrite Branching

It is clear that molecular motors play an important role in the regulation and maintenance of dendrite morphology. Properly functioning motors are essential for accurate transport of cargo proteins to target sites via movement along specific cytoskeletal elements [102]. Actin- and MT-based motors work both together and in parallel to change dendrite morphology [103]. Motor proteins are categorized based on the cytoskeletal substrate they transverse. MT-based motors are further defined by the direction that they travel along MTs [104]. In the following section, we examine the differences between MT- and actin-based motor proteins and their roles in shaping dendrite morphology, both along the cytoskeletal element they transverse and in association with the other cytoskeletal element.

MT-Based Motors

Motor proteins from both the kinesin and dynein superfamilies move along MTs. Kinesin family members play a critical role in the transport of cargo proteins along MTs in the plus direction, while cytoplasmic dyneins allow retrograde transport of proteins from dendrites to the cell body [104]. Kinesin superfamily proteins (KIFs) transport PSD proteins, neurotransmitter receptors, ion channels, and specific messenger RNA (mRNAs) into the dendritic arbor [104]. KIF1Bα may regulate dendrite branching via its association with PSD-95 [105]. In addition, KIF5 regulates dendrite branching via its direct interaction with GRIP1, a scaffolding protein that contains PDZ domains, allowing for transport of ephrin receptors to dendrites [106, 107]. CHO1/MKLP1 is a kinesin-related motor protein that specifically transports minus-end distal MTs into the dendrite to allow for branching [108, 109]. When CHO1/MKLP1 is removed from a dendrite, minus-end distal MTs are shuttled out of the dendrite, leaving only plus-end distal MTs in place. These plus-end distal MTs are continuously transported by dynein to the existing actin cytoskeleton. Without the opposing drag of the CHO1/MKLP1 motor moving the oppositely polarized MTs, the oriented and polar MTs are able to bundle and continuously compress the actin cytoskeleton. Ultimately, the dendrite narrows in diameter resulting in similar morphology to that of an axon [108].

Microtubule dynein motors are also important for the proper shuttling of proteins associated with dendrite patterning. The PSD-95-associated protein GKAP interacts with the light chain subunit of cytoplasmic dynein, DLC. Interestingly, the actin-based motor, myosin-V, also contains the DLC subunit and interacts with GKAP as well [110, 111]. Taken together, these studies demonstrate the complexity of interactions between intracellular structural proteins, molecular motors, and the actin and MT cytoskeletons in shaping dendrite morphology.

Actin-Based Motors

Molecular motors of the myosin superfamily deliver cargo proteins to specific target locations within a cell by traveling along actin filaments. Myosin classes I, II, V, VI, and IX are present in neurons [103]. Myosin IIB has specifically been implicated as a regulatory motor in dendritic spine dynamics. Binding of actin by myosin IIB occurs via signaling pathways related to the PSD and Rho GTPases, thus providing an upstream link to changes in both actin and MTs [112–114]. Motors, traditionally considered to control either MT or actin dynamics, have also exhibited interactions with motors of the other cytoskeletal element during dendritic branching and development. Myosin-II-driven forces allow F-actin fibers to drift out of filopodia, resulting in neurite retraction, while dynein resists this trend and allows MTs to enter filopodia and the growth cone [115]. In addition, recent reports document the ability of a particular actin motor protein, myosin Va, to briefly diffuse along MTs via electrostatic interactions. Association of myosin Va with MTs allows for interaction with kinesin motors and possible handoff of cargo proteins for local delivery along actin filaments [116]. These reports highlight the indirect interactions between the actin and MT cytoskeletons with regards to molecular motors and provide a role for motor proteins in dendrite patterning.

Rho-GTPase Family Signaling and Cytoskeletal Coordination in Dendrite Morphology

Guanine nucleotide-binding proteins (G proteins), a subset of the GTPase family of proteins, play extensive roles in dendrite patterning. These proteins are activated by GEFs and switch between inactive GDP-bound and active GTP-bound states. Members of the Rho family of GTPases are known regulators of dendrite morphology. Signaling by one or more of these small GTPases regulates all aspects of dendrite patterning, including initiation, growth, branching, and spine formation [117]. Rac1, Cdc42, and RhoA are the main regulatory molecules in this family that regulate dendrite morphology [117]. Recently, however, additional members of the Rho GTPase family, including Rnd1 and Rnd2, have been implicated in the regulation of spine formation and dendrite branching, respectively [118]. In the following section, we examine the roles of Rac1, Cdc42, and RhoA and how these small GTPases regulate dendrite patterning via interactions with both actin and MT cytoskeletons.

Rac 1 and Cell Division Cycle 42 (Cdc42)

Rac 1 and Cdc42 have been studied for their vast roles in cellular processes, including cell cycle, adhesion, and motility. However, recent reports have focused on their novel roles in dendrite development [119–122]. Overexpression of Rac in neurons leads to increased dendrite sprouting and retraction events, while expression of dominant-negative Rac mutants stabilize filopodia and reduce basal dendrite number [120, 123]. Furthermore, the extracellular matrix molecule laminin acts to regulate the cytoskeleton in growth cones via a Rac1-dependent pathway [124]. Laminin causes MTs to bundle and move forward into the growth cone, upon which projecting F-actin foci form. Rac1 co-localizes with F-actin only in areas of the growth cone where it is also highly co-localized with dense MTs, such as the C-region or far into the peripheral region [124]. Thus, Rac1 mediates neurite outgrowth via MT-based accumulation of F-actin at growth cones. While these data have been reported nonspecifically in growth cones, they suggest that these pathways may be similarly occurring during dendritic development.

The Rac1 guanine nucleotide exchange factor, T-lymphoma invasion and metastasis 1 (Tiam1), plays an important role in transducing extracellular signals to the cytoskeleton for the regulation of dendrite patterning. Tiam1 regulates neurite outgrowth [125], and specifically, Tiam1 mediates this effect by activating Rac and inhibiting Rho [126]. In addition, Tiam1 is a common mediator of the regulation of dendrite morphology by interacting with ephrin-B1, EphB, EphA2, NMDA receptors, and TrkB [127–131].

Cdc42 also regulates dendrite patterning via interactions with both the actin and MT cytoskeletons. Expression of dominant-negative Cdc42 mutants reduces primary dendrite numbers in non-pyramidal neurons, thus implicating a role for these GTPases in dendrite initiation and growth [120]. In addition, functional Cdc42 is required for dendrite growth and spine formation in *Drosophila* visual system neurons [132]. The regulation of both actin and MT polymerization by Cdc42 may be integral to the role of Cdc42 in dendrite patterning [133]. The p21-activating kinases (Pak) are effector proteins that link Rac1 and Cdc42 to the cytoskeleton and modulate dendrite initiation, primary branching of apical dendrites, number of basal dendrites, and dendritic spines [134, 135]. The fact that Pak1 regulates both actin and MT dynamics provides a possible mechanism for Pak1-mediated regulation of dendrite patterning via Rho-GTPase signaling [136–138].

RhoA

Unlike Rac1 and Cdc42, RhoA acts as a negative regulator of dendrite growth and branching [139, 123]. RhoA destabilizes actin; furthermore, glutamate receptor-induced RhoA inactivation results in actin-rich dendritic spine collapse [140]. In addition, RhoA interacts with the actin cytoskeleton, causing inhibition of neuritogenesis via formation of a RhoA kinase/profilin IIa (ROCK/PIIa) complex. PIIa exerts its negative effects on neurite sprouting and growth via changes in the stability of the actin cytoskeleton. Furthermore, its physical association with ROCK, a RhoA effector kinase, provides a link between RhoA and the actin cytoskeleton and a possible mechanism for RhoA-mediated changes in dendrite morphology [141]

Additional studies also indicate a role for RhoA in MT dynamics. Activation of RhoA results in decreased cypin protein expression, providing a novel mechanism for RhoA action specifically in dendrite branching via changes in the MT cytoskeleton [142]. In addition, the RhoA effector protein, mDia, simultaneously modifies actin and MTs by aligning MTs in parallel to F-actin bundles along the cell axis. Mutations in particular regions of mDia1 cause F-actin to appear in a more disorganized configuration, therefore reducing MT alignment along the filaments [143]. These studies suggest that activation of RhoA may result in dynamic changes in the cytoskeleton and, thus, reported inhibition of dendrite branching.

The Role of Extracellular Signals and Adhesive Interactions with the Extracellular Matrix in Dendrite Morphology

A number of extracellular signaling proteins, including growth factors, matrix glycoproteins, and integrin receptors, influence dendrite patterning. The following section specifically focuses on those extracellular signal molecules that coordinate actin and MTs to regulate dendrite morphology.

Neurotrophic Growth Factors

Dendrite morphology is highly regulated by extracellular growth factors, such as nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), and neurotrophin-3 (NT-3; [144–148]. These neurotrophic growth factors play a role in numerous aspects of cell survival by initiating complicated signaling cascades via activation of receptor tyrosine kinases (Trk). Neurotrophins initiate coordination of actin and MTs to help regulate a number of processes, including cellular differentiation, proliferation, and dendrite patterning [149].

Nerve Growth Factor

NGF, a secreted growth factor that signals via TrkA, regulates dendrite arborization [150]. NGF enhances neurite

formation, specifically through the stabilization of tubulin mRNA [151, 152]. When treated with NGF for three weeks, PC12 cells, a model cell line for neurons, exhibit resistance to colchicine-mediated MT depolymerization [151]. NGF also mediates reorganization of the actin cytoskeleton [153]. Treatment with this neurotrophin results in enrichment of actin-associated proteins in both neurites and growth cones of PC12 cells [154]. While these data do not examine the role of NGF in dendrites specifically, these studies clearly indicate links between NGF treatment and changes in the cytoskeleton, thus providing possible mechanisms underlying reported NGF-induced dendrite outgrowth.

Brain-Derived Neurotrophic Factor

BDNF acts on various types of neurons in both the central and peripheral nervous systems and promotes functioning of existing neuronal connections, developing synapses, and neuronal morphology. BDNF increases the length and complexity [144, 146] and number [147] of pyramidal neuron dendrites. BDNF influences dendritic arborization in the visual cortex [145], retina [148], and cerebellum [155, 156]. Recent studies demonstrate that BDNF is a mediator of activity-dependent dendrite branching [157, 158]. Treatment with BDNF causes dendrites to be more active, that is, dendrites are both gained and lost more quickly than when no treatment is present [147]. This process of destabilizing dendrites by BDNF occurs via BDNF binding to and activating the high affinity catalytic receptor TrkB.

Both the phosphoinositide 3-kinase (PI3-K) and mitogen-activated protein kinase (MAPK) pathways are activated in response to BDNF [159]. These kinase pathways mediate BDNF-promoted modifications of dendrite morphology without new protein synthesis, suggesting that BDNF acts on the existing cytoskeletal framework to make changes [159]. MAPK regulates MT dynamics [160], while PI3K can regulate F-actin dynamics and, in some cases, MT dynamics [161, 162]. Simultaneous triggering of the PI3 and MAP kinase pathways by BDNF concurrently alters both F-actin and MT dynamics and changes downstream dendrite branching, although the exact mechanism of how this occurs is not yet clear.

Neurotrophin 3

NT-3, another neurotrophic growth factor, influences dendrite patterning via remodeling of the cytoskeleton. NT-3 enhances neurite outgrowth in cultures of dissociated hippocampal neurons [163] and increases dendrite length and number of branches in pyramidal neurons in organotypic explants [146, 164]. NT-3 signaling pathways lead to growth cone-localized cytoskeletal precursor mRNAs, thus promoting immediate assembly of crucial structural elements leading to neurite outgrowth [165, 166]. Colchichine-induced MT depolymerization results in inhibition of β-actin mRNA localization to growth cones and, notably, thin varicose neurites [166]. These results indicate a role for extracellular NT-3 in microtubule-dependent β-actin mRNA localization to neuronal processes via a cAMP signaling pathway, thus providing an additional link between the actin and MT cytoskeletons [166].

Reelin

Reelin is a large, secreted extracellular matrix glycoprotein named from its association with the *reeler* mouse. It signals through the very low-density lipoprotein receptor and the apolipoprotein E receptor 2 and regulates synaptic plasticity and dendrite branching [167]. Reelin triggers dendrite growth in hippocampal neurons via binding to its receptors, activation of an adaptor protein, and further activation of a downstream non-receptor tyrosine kinase-dependent signaling pathway [168]. In addition, Reelin induces phosphorylation of MAP1B via activation of GSK3β, thus linking its actions to both the actin and MT cytoskeletons [169, 170]. Furthermore, reelin directs actin organization in dendrite branching via the PI3K pathway and subsequent Akt activation, providing additional evidence for its regulatory actions on both the MT and actin cytoskeletons [171].

Agrin

Agrin, a multidomain glycoprotein of the extracellular matrix, regulates synaptogenesis by clustering acetylcholine receptors at neuromuscular junctions [172]. Recently, a positive regulatory role for agrin in dendrite patterning has been described [173, 174]. Agrin enhances neurite elongation and branching by upregulating expression of MAP1B, MAP2, and tau proteins [173] and simultaneous formation of acetylated tubulin-enriched MT loops [174]. In addition, agrin-mediated acetylcholine receptor clusters are dependent on actin polymerization [175]. Together, these studies indicate a role for this glycoprotein in positively shaping dendrite morphology via interactions with both actin and MT cytoskeletons.

Integrin Receptors

Integrins are a class of structural cell adhesion molecules which are heterodimeric and interact with both specific extracellular matrix ligands, such as laminin, fibronectin, and collagen, and the F-actin cytoskeleton. Integrin receptor binding by laminin recruits MT bundles to the edge of

Table 1 Table of key molecules that play roles in dendrite patterning via interactions with both actin and MT cytoskeletons

Type of molecule	Molecule	Effect on actin	Effect on microtubules	Effect on dendrite
Intracellular proteins	Microtubule-associated proteins (MAPs)			
	MAP1B	Binds actin and potentially cross-links MTs and actin	Promotes MT assembly and stabilization	
			GSK-3β alters phosphorylation state and affects whether MTs are stable or dynamic	
	MAP1A	Cross-links filaments		Is required for branching and stabilization of dendritic arbor
		Co-localizes with actin at dendritic growth cone		
	MAP2	Binds F-actin at MT binding site, causing MT bundling	Is phosphorylation-dependent	Is required for dendritogenesis
		v-KIND regulates MAP2 phosphorylation.	When dephosphorylated, bunches MTs	Promotes dendrite extension
		v-KIND colocalizes with F-actin and MAP2	when phosphorylated, spaces out MTs	Promotes dendrite branching
	APC	MTs compete with actin for binding	Binds MTs directly and stabilizes them	May determine future axon, leaving remaining neurites as dendrites
		Binds actin indirectly through IQGAP1	Binds to MT +ends indirectly through IQGAP1	
	End-binding proteins (EB)	Inhibit actin binding to APC	Bind to MT +ends and cause polymerization	
			EB1 is required for APC binding to MTs	
	Shortstop	Contains actin binding sites	Recruits APC and EB1 to MTs in muscle cells	Mutations cause reduced dendrite branching in *Drosophila* neurons
	Abelson	Binds to actin	Binds to MT	Promotes dendrite branching in response to integrins
	Neurabin	Binds to F-actin	Is associated with MTs via doublecortin and Lfc	Plays roles in spine morphogenesis, maturation, density, and synaptogenesis
	Postsynaptic density-95 (PSD-95)	Binds to MAP1A	Binds to cypin, which promotes dendritic branching	Plays a role in dendritogenesis
		Binds to Shank via GKAP, and Shank binds to cortactin, which binds to actin	Binds to CRIPT	Is a negative regulator of dendrite outgrowth and branching
MT- and actin-based motor proteins	MT based motors			
	Dyneins		Transport +end MTs to the actin cytoskeleton	Change dendrite to look more like the unipolar axon if unopposed by MT transported by kinesins
			Allow MTs to enter growth cones and filopodia to resist F-actin withdrawal	
	DLC	Interacts with GKAP (PSD-95 associated protein)		
	Kinesins			Carry cargo in +end direction
	KIF5			Transports ephrin receptors to dendrites
	CHO1/MAPK1		Transport −end distal MTs into dendrite	Increase dendrite branching
	Actin-based motors	Transport cargo along actin		

	Myosin-V	Interacts with MTs to allow transfer of cargo to actin cytoskeleton Interacts with GKAP (PSD-95 associated protein)		
	Myosin II	Bundles actin, which is regulated by PSD proteins and Rho-GTPases Allows F-actin to drift out of filopodia, resulting in retraction		Causes neurite retraction
Rho-GTPase family members	Rac1	Co-localizes with F-actin in growth cones		Is a positive regulator of dendrite branching
	Laminin	Causes actin foci to form on bundled MT	Causes MT bundling via activation of Rac1	
	Tiam1			Regulates neurite outgrowth by activating Rac and inhibiting Rho Mediates regulation of dendrite morphology by ephrins, Ephs, NMDA, and TrkB
	Cdc42		Is a positive regulator of dendrite branching Is required for dendrite growth and spine formation in *Drosophila* neurons	
	RhoA	Destabilizes actin Interacts with ROCK and PIIa Interacts with mDia	When activated, decreases cypin expression	Is a negative regulator of dendrite branching Inhibits neurite outgrowth and sprouting
		mDia organizes actin	mDia aligns MTs parallel to actin	
Extracellular signals and interactions with the ECM	Neurotrophic growth factors Nerve growth factor (NGF)	Enriches actin-associated proteins	Stabilizes tubulin mRNA increases resistance to colchicine MT depolymerization	Enhances neurite formation
	Brain-derived neurotrophic factor (BDNF)	Activates PI3K	Activates MAPK	Increases dendrite growth, branching, and arborization increases dendritic activity
	Neurotrophin 3 (NT-3)	Helps to localize β-actin in an MT-dependent manner	Enhances neurite outgrowth	
	Reelin	Induces phosphorylation of MAP1B Interacts with PI3K and activates Akt	Enhances dendrite growth	
	Agrin	Upregulates expression of MAP1B and MAP2 Clusters acetylcholine receptor, which interact with actin	Increases dendrite branching and growth enhances acetylated tubulin-enriched MT loops	Increases dendrite branching
	Integrin receptors	Induces MT bundle movement, causing increase in F-actin cores	Binds with laminin to recruit MT bundles to neurites	Promotes nonspecific neurite extension

Proteins are separated into four main categories: general intracellular proteins, molecular motor proteins, Rho-GTPase family members, and extracellular proteins. They are further described based on their effects on the actin and MT cytoskeletons and on dendrites. References supporting these roles are included in the text of the review

growing neurites in chick sympathetic ganglia, inducing development of F-actin cores, a process which is also Rac-dependent [124]. While these studies investigate the role of integrins in enhancing neurite growth nonspecifically in the growth cone, they suggest that this effect may specifically be observed during dendritic extension.

Conclusions

Dendrite initiation, growth, branching, and spine formation are highly organized processes that require the precise functioning of intricate signaling pathways. While we have presented the key players in these regulatory pathways, as summarized in Table 1, communication between these many proteins is critical for producing coordinated changes in the actin and microtubule cytoskeletons. The relationship between actin and MTs during dendrite development is, in some cases, opposing and, in others, cooperative; however, in all cases, the interplay between F-actin and MTs is essential for overall morphology, and hence function, of the neuron. Thus, the actin and MT cytoskeletons represent a model of how the abstract concept of yin and yang is incorporated into dendrite patterning.

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