CHAPTER 2

Branching Morphogenesis in Vertebrate Neurons

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Abstract

Within the developing vertebrate nervous system, strict control of branching morphogenesis is essential for establishing appropriate circuitry, since the geometry of neuronal arbors critically influences their functional properties. Thus, identification of the specific molecules and mechanisms involved in regulating neuronal branching morphogenesis has been the focus of intense study within recent decades, producing tremendous advances in the understanding of neuronal differentiation. Intrinsic regulation of branching morphogenesis arises through a combination of background gene expression, structural constraints imposed by cellular dimensions, biophysical properties of intracellular cytoskeletal elements, and cell-autonomous control of arbor topology and branching probability. Epigenetic influences on the pattern of branching morphogenesis instead arise from temporally or spatially constrained microenvironmental cues including homotypic and heterotypic cell-cell interactions, substrate-bound and diffusible chemoattractants and chemorepellents, hormones and growth factors, and patterns and levels of electrical activity. Ultimately, such signaling must converge at the level of the cytoskeleton, with the structural changes characteristic of neuronal branching arising through dynamic regulation of the actin cytomatrix, microtubules, and a variety of microtubule-associated proteins. This review provides a comprehensive summary of the current understanding of branching morphogenesis in developing vertebrate neurons, emphasizing recent findings describing key cellular mechanisms and molecular signaling pathways underlying branch formation and stabilization.

Introduction to Branching Morphogenesis in Vertebrate Neurons

Since the pioneering neuroanatomical studies of Santiago Ramón y Cajal beginning in the late 1800s, morphology has emerged as one of the main criteria used for identifying and characterizing distinct populations of neurons.[1-13] As the vertebrate nervous system develops, individual neurons undergo significant morphological changes through a sequence of neurite outgrowth, arborization, and synaptogenesis, leading to the maturation of an astoundingly diverse array of phenotypes (Fig. 1).[3,6-8,14-19] Due to the generation of particular structural attributes through this sequence of morphogenesis, critical functional properties begin to emerge, allowing the establishment of appropriate activity patterns within the developing neuronal network.[8,14,18,20-33] For example, since the majority of CNS synapses are localized to neuronal arbors, changes in arbor surface area influence the reception, integration, and transmission of electrical activity.[2,8,24,25,34-38] Consequently, dynamic regulation of neuronal branching morphogenesis is especially critical for both generating and maintaining the functional organization of the nervous system. While many of the mechanisms underlying branching morphogenesis are likely to be conserved among neuronal populations, the tremendous diversity in neuronal

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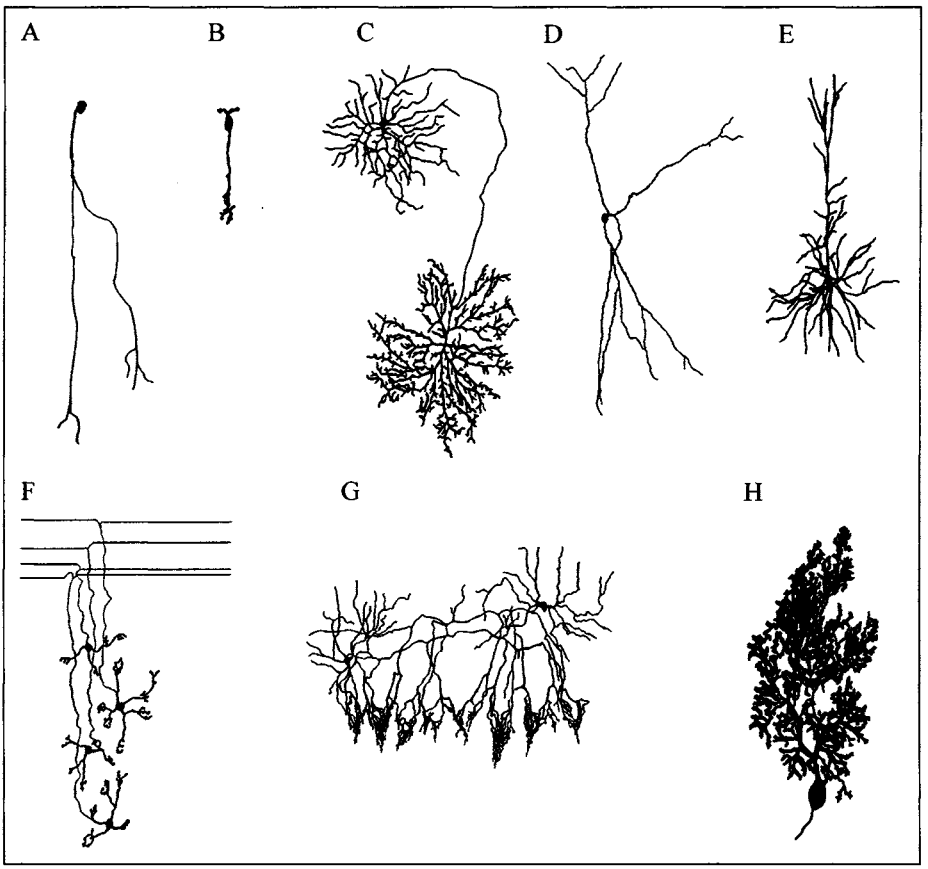

Figure 1. Variations in vertebrate neuronal morphology. A) Sensory neurons of the dorsal root ganglion, categorized as pseudo-unipolar neurons, produce a single elongated and fused axonal process that bifurcates into two functionally distinct branches, but no dendrites. In contrast, B) retinal and olfactory bipolar neurons develop both a single axonal process and a single arborizing dendrite. C) Visual system amacrine and horizontal cells lack typical axons, although specialized presynaptic and postsynaptic regions of dendritic processes exist. D) Neurons of the lateral geniculate nucleus, providing the link between retinal input and the primary visual cortex, are characterized by robust axonal arborization, but limited dendritic elaboration. Conversely, E) hippocampal pyramidal neurons possess distinct functional subpopulations of apical and basal dendrites, and an elongated axon which gives rise to multiple collateral branches. Within the cerebellum, F) granule neurons develop a signature "T-shaped" axon and several unbranched dendrites ending in claw-like termini. A significantly elaborated axonal structure is achieved instead by basket cells (G), which produce moderately arborized dendrites but numerous axon collaterals that form basket-like cages around Purkinje cell somata. In contrast, (H) Purkinje cells develop a planar highly-arborized dendritic tree studded with actin-enriched dendritic spines, but a relatively simple axon. Figure constructed with permission from data presented in references 1, 3, 14, 17, 40, 79, 440, 454 and 635.

cytoarchitecture suggests that some cell-type-specific differences in the regulation of arborization also must arise.[3,6-8,14-19,21-33] Through decades of intensive research, significant progress has been made toward identifying and characterizing the numerous extracellular molecules and cell-cell interactions that regulate aspects of branching morphogenesis. However, the subcellular molecular regulation of branching remains poorly understood. In fact, the degree to which variation in branching architecture among neuronal populations reflects fundamental

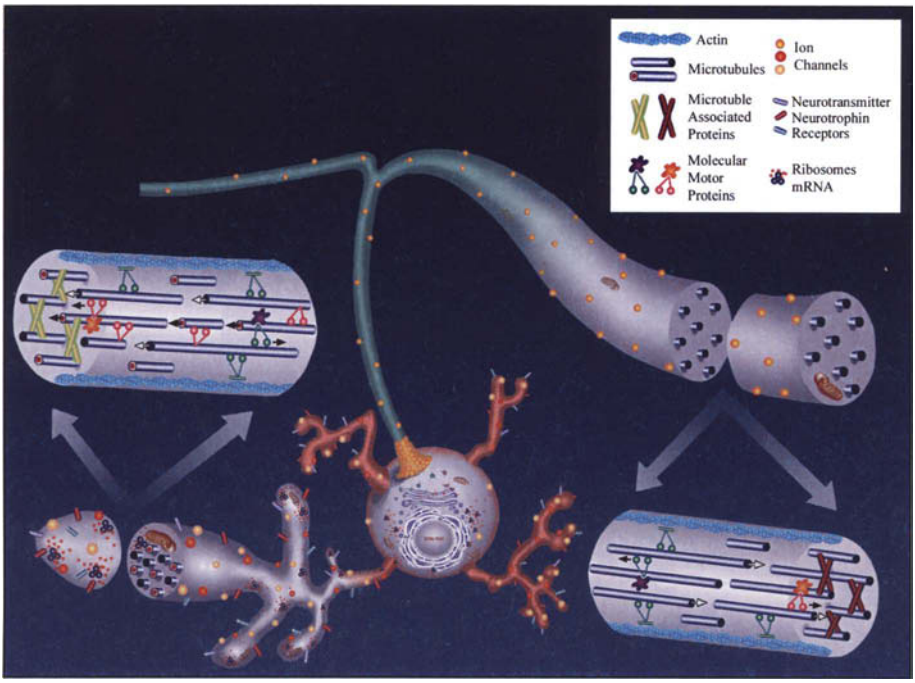

Figure 2. Schematic illustration of the distribution of cellular constituents in a well-polarized neuron. Neuronal morphogenesis typically culminates in the extension of an elongated primary axon and multiple short primary dendrites. Mechanisms that produce local subcellular differences in molecular and cytoskeletal constituents are necessary both for generating neuronal polarity and for triggering branching morphogenesis. At the ultrastructural level, the dendritic domain contains Golgi elements, rough endoplasmic reticulum, mRNA, tRNA, polyribosomes, transcription initiation factors, and a mixed population of plus-end and minus-end distal oriented microtubules. In contrast, the axonal domain excludes biosynthetic machinery but retains specific synapse-related proteins including Na^+ and K^+ channel isoforms, and a characteristic uniform population of plus-end distal oriented microtubules. Fully differentiated neurons thus display an asymmetrical distribution of cytoskeletal elements, cytoskeletal-associated stabilizing proteins, molecular motor proteins, organelles and vesicles, cytoplasmic and cell-surface proteins, and plasma-membrane components. Figure reprinted with permission from K.M. Kollins, constructed from data presented in references 8, 9, 36, 39, 40, 44, 47, 49 and 53.

differences in the control of arborization, or instead represents cell context-dependent modulation of common regulatory pathways, remains largely unclear. Therefore, one significant aim of current research is to identify regulatory pathways that underlie branching morphogenesis for all neuronal populations, and the degree to which branching may be modified through cell context-specific cues.[2,8,26-29,38,49,50,54,85-87,156-163]

The Importance of Neuronal Polarity during Branching Morphogenesis

Neurons are specialized secretory cells characterized by the heterogeneous compartmentalization of various cellular constituents into discrete and physiologically significant domains, the axon and dendrite (Fig. 2).[8,39-44] In turn, this asymmetric organization of cellular constituents allows the partitioning of cellular responses, such as electrical impulse reception, integration, propagation, and release of signaling molecules. Most significantly, the cellular specializations that support appropriate functional polarity also generate inherently different influences on the process of branching morphogenesis within the axonal and dendritic domains.[8,39-44]

Since all neuronal populations arise from neuroepithelial precursors, it has been postulated that developing neurons and epithelial cells may employ similar constraints on structural and functional polarity.[8,39,44] For epithelial cells, the luminal plasma membrane, or apical domain, is structurally separated from the parenchymal plasma membrane, or basolateral domain, by a circumferential band of tight junctions that produce a physiological fence. In addition, subjacent attachment regions of desmosomes and adherens junctions provide cytoskeletal-based structural support and some degree of chemical coupling between the plasma membrane surfaces of closely apposed epithelial cells.[8,9,16,39,41,44,45,77] For developing neurons, which do not possess tight junctions, the axonal domain instead appears to be functionally separated from the somatodendritic domain by a diffusion barrier intrinsic to the initial segment hillock, with the adherens junctions of epithelial cells thought to be an evolutionary antecedent of neuronal synapses.[8,39-43] Indeed, careful analysis of both the morphology and ontogeny of epithelial and neuronal cells has prompted the suggestion that the entire neuronal surface may in fact be equivalent to the epithelial basolateral domain, with distinct axonal and dendritic compartments arising through unique subpartitioning mechanisms evolved by neurons. If this interpretation is correct, axons may represent a highly specialized protein-sorting region, analogous to an elongated Golgi apparatus directly linked to the cell surface.[8,9,39-41,44,45]

Typically, neuronal morphogenesis culminates in the extension of a single elongated primary axon displaying periodic collateral branches, or distal branching within synaptic target regions, and multiple short primary dendrites that may be robustly arborized.[8,9-41,44] At the ultrastructural level, while the dendritic domain is continuous with the soma to a certain degree, containing Golgi elements, rough endoplasmic reticulum, mRNA, tRNA, polyribosomes, and transcription initiation factors, by contrast the axonal domain primarily excludes biosynthetic machinery but retains specific synapse-related proteins including Na^+ and K^+ channel isoforms.[8,39,40,44] Arguably, the most functionally important subcellular difference arising during neuronal development is the uniform plus-end distal microtubule orientation established within axons, and the mixed plus-end and minus-end distal microtubule orientation evident within dendrites.[2,8,39,40,44-49] As a consequence of this asymmetric cytoskeletal arrangement, distinctly different biomechanical forces are generated within the axon and dendrites, contributing to the directed transport of organelles and cytoskeletal polymers.[16,18,39,45,50-59]

As a rule, organelles and vesicles that selectively translocate toward the minus-ends of microtubules are expected to be mechanically excluded from the axons, while those that instead translocate toward microtubule plus-ends can be conveyed into both the axon and dendrites, due to the mixed microtubule polarity orientation characteristic of dendrites.[8,44,50,60-64] Additionally, it has been suggested that certain biosynthetic components are restricted from entering the mature axon due to the tight bundling of uniformly oriented microtubule polymers, achieved through axon-specific microtubule-associated proteins.[50,53,54,65,66] Consequently, localization of the majority of axonal proteins must be achieved through targeted delivery of proteins initially synthesized within the soma.[8,40,44,50,54,65,66] For dendrites, however, mRNAs and polyribosomes readily accumulate at postsynaptic sites underlying dendritic branches, suggesting a role for local protein synthesis in response to physiological cues.[39,40,44,66-75] Due to the microtubule orientation differences that arise between developing axonal and dendritic domains, fully differentiated neurons display an asymmetrical distribution of cytoskeletal elements, cytoskeletal-associated stabilizing proteins, molecular motor proteins, organelles and vesicles, mRNA, cytoplasmic and cell-surface proteins, and plasma-membrane components.[8,40,44] As a consequence, mature neurons are equipped to produce local responses to microenvironmental cues that are essential for generating appropriate neuronal branching morphology and for modulating synaptic plasticity.[8,39,40,44]

Mechanisms that produce local differences in molecular and cytoskeletal constituents are necessary both for generating neuronal polarity and for triggering branching morphogenesis, processes that are similarly initiated through symmetry breaking.[8,16,18,76,77] First applied to biological systems by Alan Turing[78] as a theoretical construct to explain embryonic

morphogenesis, spontaneous symmetry breaking describes the emergence of asymmetry from initially symmetric but unstable conditions, through internal dynamic processes. Accordingly, when a dynamic system, such as a neuron, reaches an internal state of biochemical or structural instability, the small irregularities that are produced through stochastic fluctuations, such as protein synthesis, turnover, or localization, become increasingly amplified. As a consequence, subcellular symmetry is typically abolished, leading to a new and stable state that, in the case of neuronal morphogenesis, typically produces neurite extension or branching.[8,9,18,39,76-78] Research conducted to determine what changes in cellular or molecular constituents are both necessary and sufficient to trigger neuronal symmetry breaking have uncovered critical roles for mitochondria and Ca^{2+} homeostasis, actin depolymerization, microtubule dynamics and motor protein activity, selective organelle localization, and directed membrane insertion, all of which can be affected by changes in the microenvironment of a developing neuron.[8,9,16,18,44]

Mechanisms of Axonal Branching Morphogenesis

Immediately after the commencement of neuronal morphogenesis triggered by symmetry breaking, significant cytoskeletal changes begin to sculpt the developing neuronal form. The earliest of these modifications involve rapid reorganization of the actin matrix that establishes dynamic membranous specializations termed growth cones.[2,79-94] Significant progress has been made toward describing axonal and dendritic growth cones at the ultrastructural level, and in characterizing physiological functions mediated by axonal growth cones during axonal elongation or retraction, pathfinding, and target recognition.[2,16,18,45,76,77-81,84,89-93,95,96] The mature axonal growth cone is distinguished by a thin fan-like morphology, consisting of membranous sheets largely filled with a filamentous actin meshwork, termed the lamellipodium, interspersed with microspikes of bundled actin fibrils, or filopodia, arrayed with their growing tips extending distally.[79,89,95,97-99] Well-differentiated growth cones can be further subdivided into two distinct domains on the basis of key structural and functional attributes. Accordingly, the most peripheral region, termed the P-domain, represents the dynamic leading edge, comprising both actin monomers and a filamentous actin (F-actin) matrix, but few associated organelles.[79,89,95,97-99] In contrast, the growth cone region closest to the neuronal soma, or central (C)-domain, constitutes a complex and dense network of actin, neurofilaments, polarized plus-end distal microtubules, mitochondria, endosomes and clear vesicles, membrane-bound vesicle stacks, and polyribosomes. Thus, the C-domain alone provides cellular machinery critical for energy production and the local synthesis or transport of proteins required for ongoing axonal growth and maturation.[79,89,95,97-99]

As neuronal differentiation proceeds, axonal growth cone morphology changes dynamically as attractive and repulsive interactions between local microenvironmental cues and the underlying cytomatrix guide axons toward appropriate synaptic targets.[79-84,93,94,100-107] Complex growth cone shapes emerge at decision points during encounters with a target-rich extracellular environment,[94,104-107] and the most simple shapes appear as growth cones fasciculate and extend rapidly along other axons of long-distance projections.[94,104-107] Throughout the developing axonal fascicles of long-distance projections and short-distance tracts alike, nascent branches begin to extend and retract. Early studies of neuronal branching morphogenesis suggested that axonal branches could arise either through the simple bifurcation of a growth cone tip, or through filopodial outgrowth from an axon shaft to form collateral branches well behind an extending growth cone (Figs. 3, 5). In fact, most vertebrate neurons establish connections with multiple targets through this process of collateral branching, in which a neuron initially extends a pioneer axon to a primary target and only after a prolonged delay then generates secondary branches along the axon shaft to innervate secondary targets.[2,90,104-109]

Once the focus of controversy, the interrelationship between axonal growth cone bifurcation and collateral branching has been gradually clarified through a number of ongoing investigations.[2,94,104-115] Initial studies by O'Leary and collaborators, beginning in the 1980s, generated important data that began to advanced the understanding of collateral branch

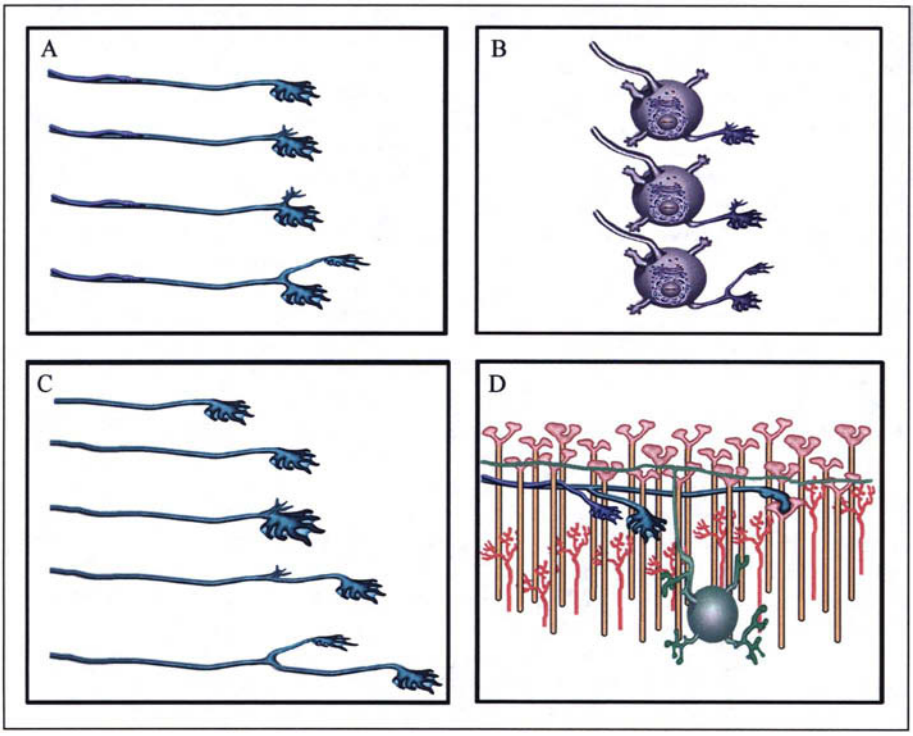

Figure 3. Schematic illustration of mechanisms proposed to underlie neuronal branching morphogenesis. A) Axonal branching produced through simple growth cone bifurcation, in which local microenvironmental cues stimulate cytoskeletal reorganization culminating in the formation of a second active growth cone. B) Dendritic branching produced through simple growth cone bifurcation. C) Axonal branching produced through growth cone pausing followed by collateral branch outgrowth, or "delayed interstitial branching," in which a side shoot extends from the axon shaft well after the primary growth cone has continued to elongate. D) Axonal branching produced as repellent molecule exposure (green neuron and vertical pink cells) triggers primary growth cone collapse (turquoise axon) and the subsequent sprouting of lamellipodia and filopodia from the axon shaft (turquoise axon branch). In addition, defasciculation of bundled axons (blue axon) often accompanies this form of branch induction. Figure reprinted with permission from K.M. Kollins, constructed from data presented in references 2, 15, 36, 38, 76, 79, 90, 98, 101, 106, 114, 115, 144, 279, 565, 636 and 637.

formation.[2,76,90,94,98,114,115] Examination of the axonal connectivity of cortical layer V neurons revealed that their stereotypical connections with the basilar pons in the hindbrain were not formed through simple growth cone bifurcation, but rather through "delayed interstitial branching," in which a side shoot is extended from the axon shaft well after the growth cone has continued to extend.[2,90,94,98,114,115] Similar delayed interstitial branching also underlies the establishment of a variety of developing neuronal circuits, including the collateral projection from the hippocampal formation to the mammillary bodies, the dorsal root ganglia projection to the spinal cord, and the retinal projection to the lateral geniculate nucleus and optic tectum.[2,106,110-115] More recent in vitro observations by Kalil and coworkers suggest that extension of branches from the middle of an axon shaft may result from bifurcation-related structural changes generated by an active growth cone that does not immediately bifurcate, but instead continues to elongate.[104-106] Another series of recent observations indicate that de novo branches can sprout from a developing axon in response to collapse of the primary growth

cone,[101] or at positions along the axon shaft demarcating points where growth cones paused in response to microenvironmental cues.[106,108,109] For example, collapse of retinal ganglion cell (RGC) growth cones, produced either through mechanical manipulation or contact with repellent molecules, can trigger lateral extensions of lamellipodia and filopodia from an axon shaft in addition to promoting defasciculation of bundled axons.[101] In vivo, local induction of this interstitial back-branching may be critical for establishing appropriate connectivity between RGC axons and their target optic tectal neurons during topographical mapping of the developing visual system.

Although several types of axonal branching have been identified, it remains unclear whether simple growth cone bifurcation, delayed interstitial branching, and collapse-induced branching arise through separate mechanisms or are instead achieved through a common pathway. Thus, the cellular and molecular mechanisms responsible for generating and stabilizing axonal branches are a current focus of intense study. To this end, the recent work of Kalil and collaborators has proved particularly significant in clarifying the sequence of de novo branching during development.[104-106,108,109-112] For example, direct observation of living cortical brain slices revealed that, after reaching their synaptic target regions, axonal growth cones paused, flattened, and enlarged as microtubules formed robust loops characteristic of slow-growth states.[105,116] During these periods, paused growth cones demonstrated repeating cycles of collapse, retraction, and extension without overall forward growth, shown to be necessary for demarcating the sites of future axonal branch points.[105-109] Once the primary growth cone resumed steady forward growth several hours to days after pausing, filopodial and lamellipodial remnants remained along the axon shaft as varicosities that began to elongate into interstitial branches tipped with active growth cones.[105,106,108]

Initiation of branching strictly at those points where complex growth cone behaviors occur suggests that specific microenvironmental cues trigger the pause in growth cone migration, local modification of the underlying cytomatrix, and the establishment of a nascent branch point through localized targeting of subcellular components.[105,106,108] According to this novel model of branching morphogenesis, Kalil and colleagues argue that delayed interstitial branching actually represents a form of target-induced growth cone bifurcation, since the original growth cone resumes forward advance while contributing to the formation of new growth cones along the trailing axon shaft (Fig. 3).[105,106] Microtubule reorganization is a critical component of this axonal branching process, involving the splaying apart of looped microtubules within the underlying axon shaft, accompanied by local microtubule fragmentation that allows short microtubules to begin invading the nascent branch.[2,85-87,93,104-106,117,118] Indeed, studies characterizing microtubule dynamics during cortical neuron axonogenesis demonstrated that when microtubules within an axon remain bundled, branches fail to form even when transient filopodia invested with microtubules arise along the axon shaft. Moreover, only those filopodia that capture sufficient numbers of invading short microtubules are able to develop into stable branches.[2,80,81,85-87,104-106,119,120]

Coincident with dynamic changes in microtubule arrangement, redistribution of F-actin is necessary for ongoing branching morphogenesis. For example, recent studies provided evidence that focal accumulation of F-actin is coordinated with microtubule splaying but precedes microtubule penetration into forming branches (Fig. 4).[104-106] In fact, time-lapse imaging of interactions between microtubules and F-actin within branching cortical axons revealed that co-localization of these cytoskeletal elements reflects their coordinated polymerization and depolymerization within an active growth cone, or at branch points.[105] Significantly, the inhibition of dynamic changes in either microtubule or F-actin polymerization abolishes branching, while allowing continued axonal elongation. Thus, bidirectional signaling between these cytoskeletal elements provides an essential pathway for regulating axonal growth and branching morphogenesis.[105,121-123] Following the initiation of stable axonal branches, ongoing morphogenesis is characterized by the transport of microtubules and organelles into growing branches, which may elongate differentially through a process termed sibling bias.[124] For example, hippocampal neurons

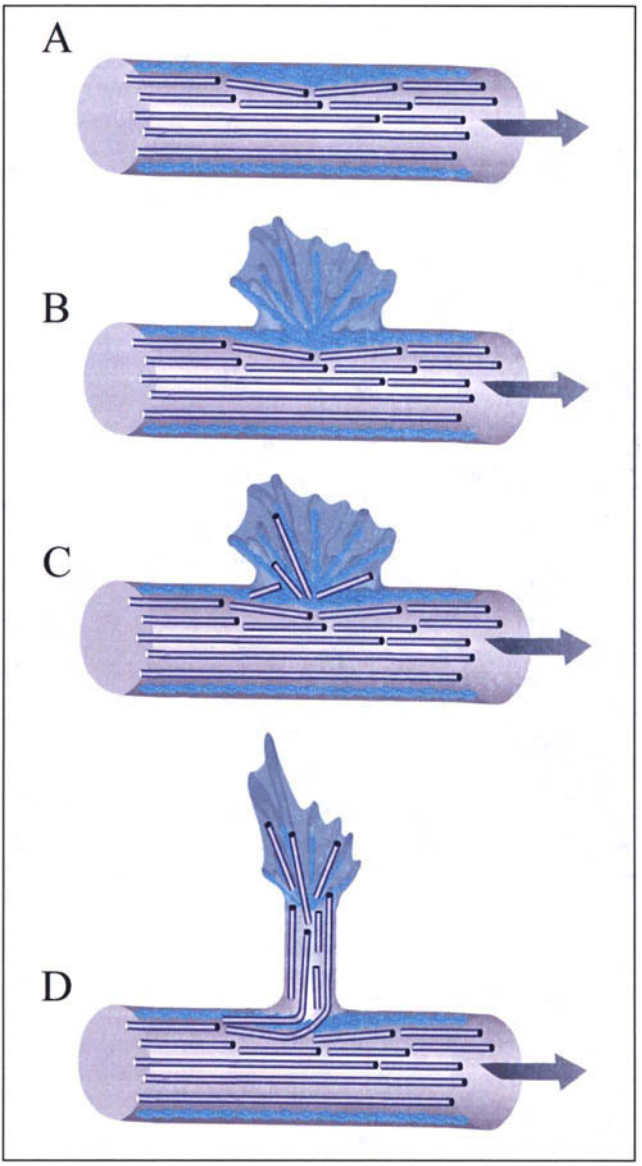

Figure 4. Schematic illustration of a model proposed for cytoskeletal reorganization occurring during axonal branching morphogenesis. A) The earliest cytoskeletal modifications during branching morphogenesis involve the splaying apart of microtubules (MTs) (blue tubules) within the underlying axon shaft, accompanied by local MT fragmentation and focal F-actin accumulation (turquoise filaments). B) Coincident with the emergence of an F-actin-enriched lamellipodium along the axon shaft, C) individual fragmented MTs begin to explore this nascent process through rapid cycles of extension and retraction. D) Short MTs continue to penetrate the nascent branch, while stabilized MTs already within the growing branch elongate through ongoing polymerization. As axonal branches mature, the colocalization of F-actin and MTs reflects their coordinated polymerization and depolymerization within active growth cones at branch points. Arrows indicate direction of axonal growth. Figure reprinted with permission from K.M. Kollins, constructed from data presented in references 2, 36, 52, 104-106, 108, 143, 156 and 157.

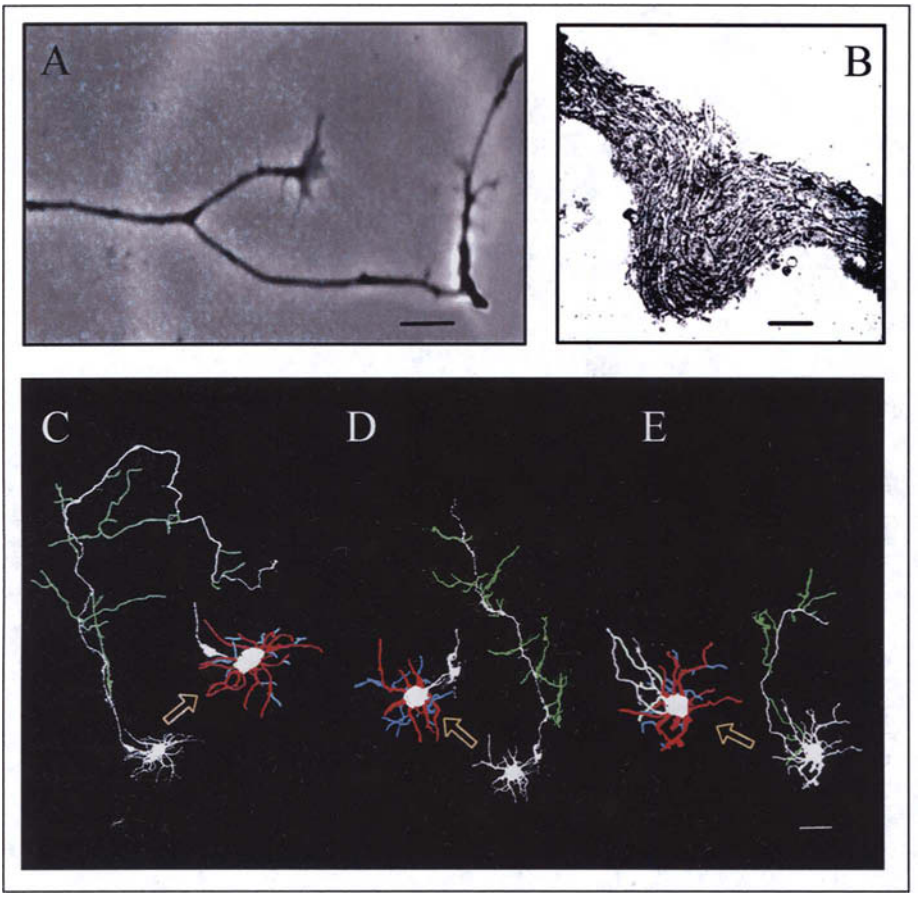

Figure 5. Examples of vertebrate neuronal branching. Branches can sprout from a developing axon in response to collapse of the primary growth cone, or at positions along the axon shaft demarcating points where growth cones paused, while dendritic branches arise through simple growth cone bifurcation. A) Temporal RGC axons encountering posterior optic tectal neurons in vitro exhibit growth cone collapse and sprouting of lateral extensions from the axon shaft. Scale bar = 10 μm. B) Temporal RGC axon sprouting lateral extensions in vitro was fixed and prepared for EM. The micrograph image reveals a kinked portion of the axon shaft filled with looped microtubules and associated organelles, characteristic of nascent branch points. Scale bar = 1 μm. C-E) Cerebellar granule neurons developing with chronic neurotrophin stimulation establish complex axonal and dendritic arbors in vitro. Granule neurons were maintained as high cell-density monolayer cultures seeded with lipophilic $DiIC18_{(3)}$ dye labeled neurons, fixed, and visualized with confocal microscopy. The digital montage comprises multiple low-magnification high-contrast confocal fields of mature granule neurons. Images are saturated to reveal thin neurites and branches, with axonal branches pseudo-colored green, dendrites pseudo-colored red, and dendritic branches pseudo-colored blue. Scale bar = 10 μm. Figure constructed with data obtained from K.M. Kollins and R.W. Davenport, unpublished observations, and references 36, 254, 446 and 565.

display characteristic patterns of alternating growth for separate branches extending from a single axon, presumably reflecting changes in the preferential transport of subcellular materials into one of several branches. As a consequence of the balance between various epigenetic influences and cell-autonomous constraints, axonal branch morphology retains some degree of plasticity throughout development and maturation, allowing ongoing sculpting of synaptic circuitry.

Mechanisms of Dendritic Branching Morphogenesis

For most vertebrate neuronal populations, axonal morphogenesis occurs under electrically silent conditions, or with low levels of spontaneous activity, whereas dendritic development instead proceeds in the context of various forms of neuronal activity. Consequently, a neuronal cell-type-dependent balance of specific forms and patterns of electrical activity is important for sculpting the architecture of dendritic branches.[2,15,38,125,126] Vaughn's synaptotropic dendritic branching hypothesis, formulated in response to static EM observations, proposes that branches form at regions of dendritic contact with afferent partners, and that these nascent branches are successively stabilized through synapse maturation.[19,126,127] More recently, a number of live-cell imaging experiments achieved through two-photon microscopy provided direct support for this hypothesized mechanism of dendritic branching.[642] For example, in zebrafish tectal neurons, new dendritic filopodia, the putative precursors to stable branches, are the favored sites for synapse formation, and dendritic filopodia that fail to make stabilizing synaptic contacts eventually retract.[642] Similarly, during hippocampal neuron development, branch formation is induced only in those dendrites receiving direct synaptic contact through afferent innervation,[128-133] and for ciliary ganglion cells the extent of dendritic arborization is directly proportional to the number of axonal contacts received.[12,128-133]

It follows then, that dendritic branches associated with immature, unstable, or weakly-active synaptic connections may retract passively through insufficient structural stabilization, or actively through neurotransmitter-based competition.[15,134-136] In fact, global activity blockade can influence the overall spread and branching pattern of developing dendritic arbors, while more local changes in neurotransmitter signaling can modulate the stabilization or retraction of individual dendritic branches.[134-139] For example, selective elimination of excitatory input to the ventral dendrites of chick nucleus laminaris results in retraction of these dendritic arbors, while innervated dorsal arbors are maintained.[137-139] Clearly, for numerous neuronal populations, the number of presynaptic contacts made with developing dendrites stimulates local dendritic branching and determines the resulting arbor complexity, while failure to establish mature and active synaptic contacts variously stunts neuronal differentiation or elicits dendritic arbor retraction.[15,38,125,133]

Dendritic arborization is a highly dynamic process for most differentiating neurons, characterized by filopodial-driven branch addition and retraction that is rapid during early developmental periods, but decreases with progressive neuronal maturation as arbors increasingly stabilize.[15,38,50,140-144] Neurotransmission plays a significant role in modulating these rapid changes in arbor remodeling. Consequently, the direction of dendritic filopodial extension is biased toward maximizing the number of contacts made with presynaptic axons from target neurons that display physiologically appropriate activity patterns or neurotransmitter release.[15,38,125,144,145,146] The sequence of subcellular reorganization within actively branching dendritic filopodia was recently characterized, facilitated by important technical advances in live-cell microscopy.[144-146] These time-lapse observations initially revealed that dendritic branching typically involves the bifurcation of an active growth cone, leading to the emergence of two similar, though smaller, growth cones that extend in divergent paths (Figs. 3, 5).[2,15,133,142,144] Additional developmental studies demonstrated that, during this process of dendritic branching, nascent branch points are first invaded by membrane-bound vesicles, forming membranous cisternae, and then successively by actin fibers and microtubules.[38,50] In fact, the molecular basis for cytoskeletal modifications underlying dendritic branching, similar to axonal branching, involves regulation of both the synthesis and stabilization of actin and microtubule networks.[15,38,50,125,133,144] Interestingly, ultrastructural observations have revealed that no microtubule nucleation sites are present within the bifurcation points of developing dendritic branches,[50] suggesting the contribution of other regulatory processes in directing branch elongation. Indeed, during the maturation of dendritic arbors, nascent actin-based branches are stabilized and lengthened through the proximo-distal invasion of microtubules, bent in relation to the orientation of microtubules within the primary dendrite shaft.[15,50,143] It remains

unclear whether the growth cone bifurcation mechanism initiating dendritic branching is followed by localized microtubule debundling and splaying to allow elongation, similar to that observed for developing axonal branches. Given the relative disparity between branch lengths achieved by dendrites as compared to axons, in combination with characteristic differences in underlying microtubule polarity, it is likely that significant differences in cytoskeletal reorganization are also produced for arborizing axons and dendrites.

Closely related to dendritic branching in the CNS is the formation of small, highly-motile protrusions termed dendritic spines. Receiving the majority of excitatory synaptic input in the mature cerebral cortex, dendritic spines display both structural and functional heterogeneity that ultimately influences neuronal signaling properties.[533,643-646] For this reason, the initial formation and ongoing morphological plasticity of dendritic spines has been a focus of intense study. Structurally, dendritic spines comprise a bulbous actin-rich head attached to the dendrite shaft through a narrow neck, and each of these elements exhibits tremendous variation among spines.[553,643-646] Morphologically, dendritic spines can be subdivided into two groups: small spines, characterized as filopodial or thin, and large spines, characterized as stubby, fenestrated, or mushroom-like.[553,643-646] Although the regulation of dendritic spine formation is yet unresolved, the sequence of spine outgrowth is well characterized. During cortical neuron development, dendrites initially generate long, thin, filopodial protrusions, but as differentiation proceeds, these labile dendritic filopodia are replaced first with polymorphic 'protospines' and then with knobby actin-rich spines containing postsynaptic density (PSD-95) clusters.[141,553,642-648] Thus, one significant area of investigation has centered on clarifying the relationship between morphological changes in dendritic filopodia and the onset of spine formation during synaptogenesis.

Tremendous progress in clarifying the mechanism of spine formation has been achieved through an elegant series of EM imaging and three-dimensional structural analysis studies, and recent live-cell observations performed with two-photon time-lapse imaging.[642,643,645] Together, these investigations revealed that exploratory dendritic filopodia grow into the neuropil, locate suitable axonal partners, and typically consolidate these initial contacts into stable synapses while transforming into mature spines, although shaft synapses also arise. Thus, spine formation appears to follow the initial stages of synapse formation.[642-646] Indeed, within a short interval after contacting appropriate axonal partners, but before spine formation, dendritic filopodia begin to accumulate active vesicles and subsequently PSD-95 clustering occurs.[642] A critical role for afferent activity in ongoing dendritic spine formation is evident from observations that, for an individual neuron, spine density is significantly greater in regions of the dendritic arbor receiving high levels of innervation as compared to uninnervated dendrites.[647] Taken together, these findings suggest that neurotransmission may be necessary to trigger the morphological and physiological transformation of dendritic filopodia into dendritic spines. Interestingly, in these recent studies a second population of dendritic filopodia was observed to persist as stable branches throughout tectal neuron development, suggesting that additional controls may be involved in determining which filopodia become branches or spines.[642] Ultimately, the ultrastructural changes within dendritic filopodia that produce branches or spines are critical for triggering physiological changes thought to underlie fast synaptic transmission and the consolidation of learning and memory.

The Regulation of Neuronal Branching Morphogenesis through Intrinsic Mechanisms and Epigenetic Cues

Defining Intrinsic and Epigenetic Regulation of Branching Morphogenesis

The variation in neuronal morphology evident throughout the nervous system is generated by patterns of differentiation unique to each population, reflecting those structural specializations that allow particular physiological properties to emerge. While many of the developmental mechanisms underlying morphogenesis are likely to be conserved among

neuronal populations, the tremendous diversity in neuronal cytoarchitecture suggests that cell-type-specific differences in the regulation of axonal and dendritic structure must also arise. Significant advances have been made toward characterizing the numerous genes, molecules, and cell-cell interactions that regulate early stages of axonal and dendritic outgrowth. However, much less is understood about the mechanisms involved in initiating and regulating the subsequent process of neurite arborization. In fact, the degree to which variation in branching architecture among neuronal populations reflects fundamental differences in the control of arborization, or instead represents cell context-dependent modulation of common regulatory pathways, remains largely unclear. Therefore, one essential aim of current research is to determine the relative contributions of cell-intrinsic and epigenetic regulation throughout branching morphogenesis.[2,8,26-29,38,49,50,54,85-87,156-163]

Generally, morphological characteristics that consistently appear during neuronal development, both in situ and in reduced culture conditions, are thought to represent invariant cell-type-specific attributes established through intrinsic regulation.[26-29] In one such pathway, a largely cell-autonomous program of gene expression can control intracellular signaling cascades and, in turn, the synthesis of molecular effectors and cytoskeletal components that generate neuronal form. In addition, intrinsic regulation of neuronal morphogenesis also reflects constraints imposed by cellular dimensions, the biophysical properties of microtubule polymers and the actin cytomatrix, and the corresponding exertion of various biomechanical forces upon changing neuronal structures.[8,18,26-29,38,44,50,52,76,77,106,125,144,164-170] In contrast, epigenetic influences on the pattern of neuronal morphogenesis arise from temporally or spatially constrained microenvironmental cues including homotypic and heterotypic cell-cell interactions, substrate-bound and diffusible chemoattractants and chemorepellents, hormones and growth factors, and patterns and levels of electrical activity.[8,29,85-87]

Although the distinction between intrinsic and epigenetic control of neuronal morphogenesis is a useful construct for examining certain stages of differentiation, in practice it is often difficult to separate cell-autonomous regulation from instructive or permissive effects induced by the environment. In fact, the weight of current evidence suggests that the structure attained by a mature neuron is largely determined by differential gene expression, produced by a combination of intrinsic developmental programs and epigenetic cues. Ultimately, set against a background of constitutively expressed genes and cell-autonomous transcription factor activity, cascades of gene induction are stimulated by an array of extrinsic cues. As such, the differentiation of each neuronal cell type reflects stereotyped transcriptional changes triggered by a sequence of epigenetic interactions, constituting developmental subroutines.[8,9,39,44,171,172] It follows that the complement of signals within the local microenvironment of a given neuron may influence the order in which these subroutines are induced during development. One important result of this type of regulation is that the onset of any given subroutine can limit the ability of a neuron to respond to other extrinsic cues, leading to progressive restriction of developmental potential.[8,171,172] As a consequence, the spatiotemporal control of exposure to individual epigenetic cues can orchestrate a unique program of branching morphogenesis for each developing neuronal population.

Control from the Inside Out: Intrinsic Regulation of Branching Morphogenesis

Intrinsic regulation of neuronal branching morphogenesis arises through a combination of structural constraints imposed by cellular dimensions, biophysical properties of intracellular cytoskeletal elements, and cell-autonomous control of arbor topology and branching probability (Fig. 6).

At the gross structural level, the size of the neuronal soma intrinsically delimits the number and area of primary axons and dendrites and associated branch projections, which can be described as the total amount of cross-sectional process area allowed.[29-33] Indeed, a direct correlation between the soma diameter and the combined cross-sectional dendrite area has been observed consistently within populations of motoneurons, hippocampal pyramidal cells, and both

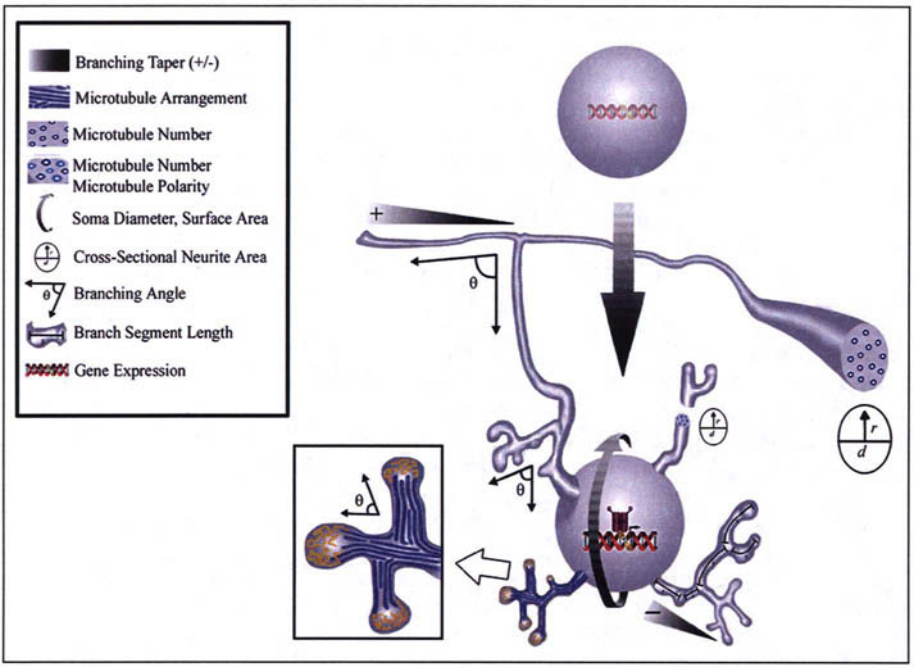

Figure 6. Intrinsic factors affecting the morphological differentiation of vertebrate neurons. The size of the neuronal soma dictates the total cross-sectional process area allowed to be partitioned into axons or dendrites (curving black arrow). The total cross-sectional area of the axonal domain may increase through increased branching proximally, or progressive proximo-distal enlargement of the axon (area symbol). In contrast, the cross-sectional area of dendrites may be conserved or instead decrease successively through partitioning into segments of decreasing diameter following the 3/2 power scaling law (area symbol). Neurite branching is constrained by the total cross-sectional process area, which may be partitioned into successive branch segments until a limiting size is met, representing the minimum number of microtubules required to maintain structural stability (blue circles). Developing neurites and their associated branches exhibit a characteristic projection orientation, termed the vector or branching angle, that results in the increased spread of the arbor through successive bifurcations along the neurite (angle symbol). Although the distance between branch points, or segment lengths, may vary for a given neuron, each neuronal cell-type exhibits a characteristic range of segment lengths for dendrites and the axon (segment length symbol). When the cross-sectional area decreases between branching segments, negative taper is produced, with positive taper instead resulting from increasing cross-sectional area between neurite branch points (gradient). The characteristic taper is established by the proportion of microtubules compartmentalized into successive branch segments, achieved in part through microtubule-associated protein binding and differential microtubule spacing or orientation (blue tubules). An additional form of intrinsic control over neuronal morphology during the development of polarity is produced through the background complement of genes expressed, independent of extracellular cues. Inset schematic represents an enlarged view of the typical cytoskeletal organization within a granule neuron dendrite. Figure reprinted with permission from K.M. Kollins, constructed from data presented in references 3, 8, 9, 26-29, 36, 49-54, 134, 164, 174-176, 189-191, 195, 196 and 343.

Purkinje cells and granule neurons of the cerebellum.[27-29] Further, the relative diameter, or caliber, of axons and dendrites differs significantly at their point of origin from the soma, and changes in cross-sectional area arising through subsequent branching follow distinctly different trends for these separate classes of neurites.[8] For example, the total cross-sectional area of the axonal domain may increase either through net increases in branching, progressive proximo-distal enlargement of the axon, or a combination of both parameters.[8,173-175] In contrast, the total

cross-sectional area of the dendritic domain is either conserved between branch points, or is successively partitioned into segments of decreasing diameter following the 3/2 power scaling law, described as: $P^{3/2} = D_1^{3/2} + D_2^{3/2}$, where P and D represent the diameters of the parent and daughter branches, respectively.[8,26,29,176] In fact, measurements across various neuronal populations reveal that the exponent of this descriptive branch power equation actually varies between 3/2 and 2, suggesting some degree of plasticity in the intrinsic regulation of branching.[8]

The arrangement of neurites arising from the soma may take the form of a single large process or multiple smaller-caliber processes, producing the characteristic arborization pattern observed for each neuronal population.[8,26-29,159,160] Thus, while cerebellar basket/stellate interneurons produce up to five dendrites and an average of two branches per dendrite, Purkinje cells, the sole output neuron of the cerebellum, instead extend one or two dendrites but may develop over 100 secondary and tertiary branches and more than 80,000 dendritic spines.[3,177-179] It is likely that the strict intrinsic control of neurite area reflects the limited plasma membrane surface area, and metabolic constraints on the rate and number of microtubules produced, together establishing the architecture of emerging processes.[26-29] For example, analysis of the cytoskeletal structure of rat Purkinje cell dendritic arbors has revealed that a consistent maximum number of approximately 800 microtubules are extended from the soma into the primary dendrite, which are then distributed into branches as this stem process arborizes.[26-29] Indeed, an essential property of neuronal branching is that the total amount of cross-sectional process area is partitioned into successive branch segments until a limiting size is met, which represents the minimum number of microtubules required to maintain structural stability.[8,29,159,160] For dendritic branches, sufficient stability is maintained to a minimal diameter of 0.5-1.0 μm, indicating a viable limit of three microtubules at distal dendritic segments.[8,29,159,160,180] Regulation of microtubule partitioning at axonal branch points appears to be accomplished, in part, through competition between regions of an extending filopodium within stimulatory or permissive regions of the microenvironment, leading to differential microtubule distribution. However, the lower limit of microtubules required to maintain axonal branch stability has not been adequately characterized [8,26,29,86,87,106,181]

While it is generally accepted that neurite branching is mediated through complex interactions involving epigenetic cues within the microenvironment, each neuronal population is predisposed to develop particular arbor characteristics through cell-type-specific constraints on branching.[2,38,85,86,106,125,182,183] Consequently, a surprising degree of similarity in mature arborization patterns has been observed within homogeneous populations of spinal cord neurons,[184] cortical neurons,[185] or hippocampal pyramidal neurons,[4] allowed to develop on patternless substrates in reduced culture conditions. Moreover, the characteristic arbor pattern developed by each neuronal cell type in vitro largely recapitulates the branching pattern observed for the corresponding population in situ.[4,182-185] This cell-autonomous control of neuronal arbor topology is evident in the angle of branch extension, the average distance between branches, and the trend toward increasing or decreasing branch diameter between branch segments.[26,29,161,162,182,183] Further, each of these structural parameters can be regulated differently for developing axons and dendrites as neurons gradually attain cell-type-specific arbor characteristics.

Developing neurites exhibit a characteristic projection orientation, often described as a vector or branching angle, resulting in increasing arbor spread through successive bifurcations along the neurite length.[29,161,162] Interestingly, axons and dendrites differ fundamentally with respect to their outgrowth patterns and branching angles, possibly reflecting intrinsic differences in cytoskeletal composition.[29,161,162] Thus, in an essentially patternless microenvironment, axons tend to grow in straight paths and form minor bends of less than 17°, as measured through fractal analysis, attributed to the inherent "stiff elastic" properties of microtubule polymer bundles.[182,183,186-188] Significantly, the presence of local epigenetic cues during axonogenesis in situ allows regulated axon pathfinding through regions of complex topology, and consequently

axons have been observed to form angles of 90° or more.[182,183,189] Similarly, axonal branch extension is generally characterized by obtuse angles.[14,26-29,40] In contrast, dendritic outgrowth generally does not entail the long-distance pathfinding characteristic of axonogenesis, and while the range of dendritic branch angles varies across neuronal cell types, branching typically produces acute angles.[14,40]

A second morphological parameter useful for characterizing developing neurons is the distance between successive branches, or segment length. Typically, segment lengths are greater in axons than dendrites, and greater between secondary branches than tertiary or higher order branches, although tremendous variation is evident within the developing nervous system.[8,9,29,180] In fact, segment lengths between successive axonal or dendritic branches also can vary significantly within the arbor of a given neuron.[29,180] Remarkably, despite such plasticity in branch distribution, each neuronal population exhibits a characteristic range of segment lengths, with the greatest dendritic segment lengths observed in hippocampal pyramidal neurons.[29,180]

An additional morphometric parameter that describes changes in neurite structure through successive branching is the taper, which is characterized as positive when the cross-sectional area increases between segments, and negative when the cross-sectional area decreases between branch points.[26,29-32] In fact, both positive and negative taper may develop along the extent of a given axon or dendrite, such that cross-sectional area can be differentially distributed between each of the branch segments generated.[26,29-32] The specific direction of neurite taper is established by the relative proportion of the microtubule population compartmentalized into successive branch segments, in combination with microtubule-associated protein (MAP) molecules that space these microtubule bundles.[29,49,50,53,190-193] Furthermore, by virtue of the differing subcellular complement of plus- and minus-end distal microtubules, and the segregation of various MAP isoforms, axons and dendrites demonstrate intrinsic constraints on the degree of taper which may result.[46,49,50,59,65,156,157,190,191,193-198] Indeed, the reorganization of various cytoskeletal elements throughout branching morphogenesis is critical for generating those structural and functional characteristics that define well-polarized neurons.

During neuronal development, dendritic trees expand through a cell-type-specific pattern of branching and branch elongation or retraction.[124,133,199,200] Accordingly, the overall rate of dendritic arborization depends on both the total number of dendrites and the branching probability for each dendrite as a function of time.[133] In fact, the rate of individual dendritic growth cone branching events may not remain constant during development, as limited intracellular constituents are increasingly partitioned among a growing number of branch segments.[124,133] For example, recent examination of dendritic branching in rat cortical neurons revealed that the branching probability for an individual dendritic segment decreases with increasing numbers of dendritic branches, likely reflecting increased competition for cytoskeletal elements.[133] Indeed, a variety of earlier studies demonstrated that cortical neurons display a pattern of robust dendritic branching during the earliest stages of development, followed by a protracted period of branch elongation without increases in branching.[133] This rapidly decreasing baseline branching rate suggests that the largest drive for dendritic branching occurs during the first phase of differentiation for at least one neuronal population, possibly reflecting significant developmental events.[133,144,199,200] Two non-mutually exclusive scenarios may account for these observations: first, cell-autonomous regulation, or exposure to certain epigenetic factors, may initiate a program of biochemical changes that gradually restricts neuronal sensitivity to branching cues; second, the progressive stabilization of individual branches may bias ongoing microtubule transport into these more mature processes. Similar analysis of axonal branching probability will be necessary to determine whether changes in the rate of branching morphogenesis follows stereotyped developmental trends for both neurite classes. In addition, since neurons employ a variety of cell-autonomous constraints on morphogenesis, it will be interesting to determine whether the rate and probability of branching are regulated differently in separate neuronal populations.

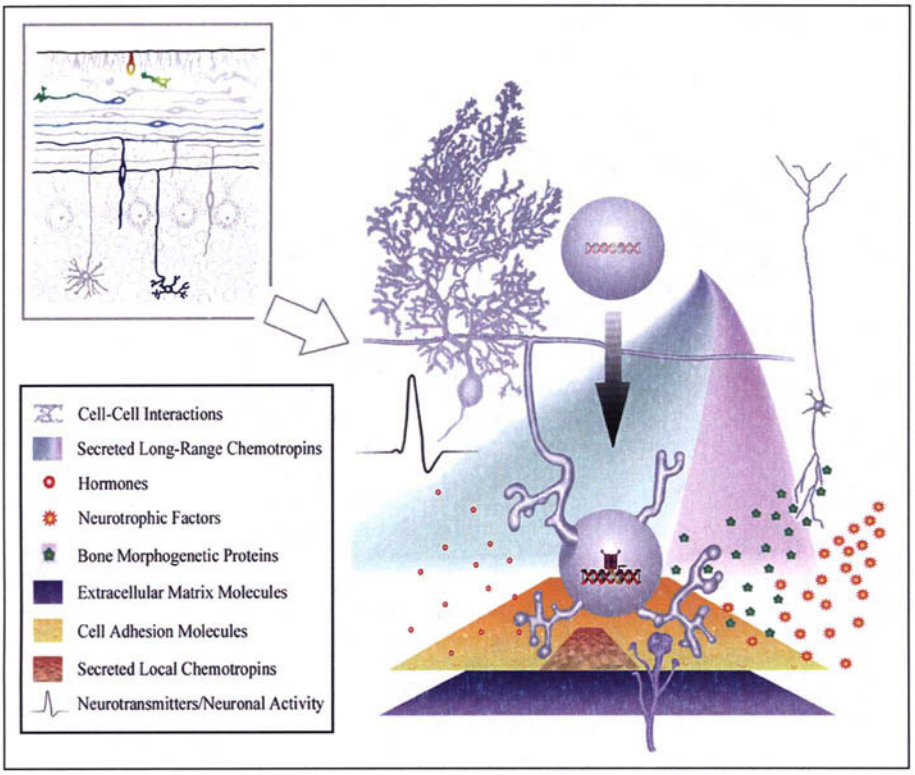

Figure 7. Epigenetic factors affecting the morphological differentiation of vertebrate neurons. While the more general morphological characteristics of developing neurons are regulated in large part though intrinsic mechanisms, attainment of mature neuronal morphology and appropriate physiology requires complex epigenetic interactions. Such epigenetic factors include: extracellular matrix components (blue plane) and cell adhesion molecules (yellow plane), secreted long-range chemoattractant and chemorepellent molecules (multi-color gradient), secreted local chemotropins (textured plane), cell-cell interactions (neurite matrix), hormones and hormone-like factors (red spheres), secreted bone morphogenetic proteins (green stars), various secreted neurotrophic factors (orange spheres), and neurotransmitters and distinct forms of neuronal activity (action potential symbol). Inset schematic illustration of the spatiotemporal sequence of cerebellar granule neuron differentiation depicts one representative neuron for each successive stage of morphogenesis. Figure reprinted with permission from K.M. Kollins, constructed from data presented in references 3, 8, 9, 18, 36, 38, 39, 44, 85, 86, 106, 125, 164, 201-203, 279, 324, 333, 360, 370, 484 and 638-641.

Control from the Outside In: Epigenetic Regulation of Branching Morphogenesis

Since the phenotype attained by a neuron is partly determined through signaling cascades triggered by extracellular cues, recent studies have sought to characterize the epigenetic factors involved in regulating branching morphogenesis. Experimental evidence suggests that many of the extracellular cues known to serve early developmental functions during neurite outgrowth and pathfinding may also modulate the more advanced stages of neuronal arborization. Such epigenetic factors include: extracellular matrix factors and cell-surface adhesion molecules, secreted long-range chemoattractant and chemorepellent molecules, hormones and hormone-like factors, bone morphogenetic proteins, neurotrophic factors, and neuronal activity (Fig. 7).[2,8,18,38,39,44,76,85-87,106,125,144,164,201]

Extracellular Matrix and Cell-Surface Adhesion Molecules

Morphological changes that accompany the development of branches involve dynamic cytoskeletal reorganization, in part regulated through interactions between neuronal cell-surface receptors and the local extracellular matrix.[44,201-210] Indeed, recent structural comparisons of neuronal populations maintained in the presence of soluble or substratum-localized extracellular matrix (ECM) molecules have implicated differential adhesion as an early mechanism underlying neurite outgrowth and arborization.[84,201,211-219]

Within an active growth cone, actin filaments respond to a variety of secreted ECM substrate components through direct interactions with cell-surface adhesion molecules.[84,202,219-223] As such, axonal outgrowth, guidance, and the establishment of appropriate neuronal connectivity, are critically dependent on the spatial distribution of ECM cues within the extracellular milieu. In fact, activation of cell-surface receptors through local or global exposure to ECM components can produce distinctly different regulatory effects on neurite extension and arborization.[8,44,224-229] For example, a local source of collagen IV promotes the outgrowth of rat superior cervical ganglion cell axonal arbors, while a substrate of the complex combination of ECM molecules in the basement membrane protein extract, matrigel, stimulates axonal elaboration and also increases the production of dendrites.[8,225,229] Most recently, the Kallmann syndrome gene product, KAL-1, was shown to mediate axonal branching for *C. elegans* sensory neurons through a novel regulatory pathway involving binding with heparin sulfate proteoglycans thought to localize to the ECM.[230]

Classic cell and substrate adhesion molecules (CAMs and SAMs) were originally characterized as cell-surface molecules that mediate both cell-cell and cell-ECM interactions.[203,206-209,215,216,223,231-239] In fact, accumulating evidence has implicated CAM/SAM activity in regulating diverse aspects of neuronal morphogenesis including stimulation of axonal and dendritic arborization.[38,200,215,216,220,221,231] Cell-surface adhesion receptors fall into four separate families: the integrins, the immunoglobulin gene superfamily, and the cadherins, all of which influence branching morphogenesis, and the selectins, which do not.[232,238,240-243] Although these CAM/SAM families are united by similar functions in regulating cell adhesion during the establishment of neuronal morphology, the specific developmental actions mediated by each adhesion molecule are quite distinct and cell context-dependent.

Integrins

Integrins constitute membrane-spanning noncovalently-bound heterodimers that facilitate local transmembrane linkages between the ECM and underlying cytoskeletal structures, such as are generated in focal adhesion complexes.[220,221,232,233,238,239,244-246] Expression of individual integrin receptor subunits can be selectively compartmentalized to a particular subcellular domain, such as the concentration of $\alpha 5$ integrin within the primary apical dendrites of hippocampal pyramidal neurons, and exclusion from basal dendritic arbors.[237,238,247-253] In this way, morphogenetic changes also can be selectively compartmentalized to particular axonal or dendritic domains. For example, the apical and basal dendritic arbors of hippocampal neurons generate strikingly different morphologies in response to local adhesive cues, due to the differential distribution of integrin receptors.[237-239]

Immunoglobulin Gene Superfamily

Members of the immunoglobulin gene superfamily (IgSF) of cell adhesion molecule/ECM receptors are widely expressed throughout the nervous system, and mediate their diverse functions, in part, through their specific membrane-linkages and cell-surface distributions.[44,206-209,254-259] Typically, IgSF members are plasma membrane-spanning molecules differentially localized to the axonal domain, such as L1, or the somatodendritic domain, as evidenced by the neural cell adhesion molecule 180 isoform ($NCAM_{180}$).[206-210,255,256] However, several IgSF members instead are tethered to the noncytoplasmic surface of the neuronal plasma membrane through a glycosyl-phosphatidylinositol (GPI) anchor, suggesting the potential for unique cell-surface localization and downstream signaling properties.[255,256,259,260]

In the case of transmembrane NCAM family members, recent studies have demonstrated that corticospinal axons elaborate interstitial branches in response to polysialic acid (PSA) modification of NCAMs that normally promote fasciculation.[261] Interestingly, PSA follows a characteristic spatiotemporal distribution pattern during development, initially restricted to distal axon segments in parallel with the onset of collateral branching, and expanding along the axon shaft in conjunction with increased branching.[261] Analysis of the physical properties of PSA during branching morphogenesis suggests that PSA modification attenuates cell-cell and cell-substrate interactions directly mediated by NCAMs, thereby reducing axonal fasciculation and enhancing axonal exposure to local branching cues.[261]

Cadherins

Cadherins comprise a superfamily of Ca^{2+}-sensitive adhesion proteins, widely distributed within the adult CNS, but characterized by distinct region-specific expression patterns for certain isoforms during nervous system development.[44,262] At least 80 members of the cadherin superfamily have been identified to date, including classic cadherins, desmogleins, desmocollins, protocadherins, cadherin-related neuronal receptors, Fats, seven-pass transmembrane cadherins, and Ret tyrosine kinases.[262,264,265] Indeed, the combinatorial expression and localization of cadherin superfamily members allows tremendous variation in the adhesive affinities of developing neurons during branching morphogenesis and the establishment of functional connectivity.[44,262-266] Within the developing cerebellum, for example, N-cadherin indiscriminately stimulates Ca^{2+}-dependent cell adhesion and neurite outgrowth among various neuronal populations. However, M-cadherin instead produces changes in neuronal adhesive affinity that selectively mediates the formation of synaptic glomeruli between granule neuron dendrites and mossy fiber axonal termini.[262,264,265]

Secreted Long-Range and Local Chemoattractants and Chemorepellents

Members of the ephrin, semaphorin, and Slit chemotropic families mediate neuronal morphogenesis through direct chemoattraction or chemorepulsion of axonal or dendritic processes in a cell-type-specific manner. Originally characterized for their function as guidance cues during axonal outgrowth, additional roles for these regulatory molecules have been described recently, including stimulation of axonal and dendritic branching morphogenesis.[2,87,106,217,267-279] Indeed, Kalil and colleagues suggest that axon guidance and interstitial branch formation might be similarly regulated by chemotropic molecules that modulate growth cone dynamics,[104-106] implicating these molecules in a variety of morphological pathways necessary for establishing functional neuronal circuits.

Ephrins

Ephrins comprise a family of multifunctional chemotropic signaling molecules, some of which serve critical roles in establishing appropriate topographic patterning of retinotectal connections during visual system development.[217,218,273-282] In addition to their well-characterized functions in the visual system, particular ephrins also have been implicated in axon repulsion within the developing hippocampus, thalamus, midbrain dopaminergic system, striatum, and olfactory cortex,[267,283,284] enhanced neurite outgrowth for sympathetic ganglion neurons,[217,267] and stimulation of axonal and dendritic branching for a variety of neuronal populations.[2,38,44,279,281] Taken together, such findings demonstrate that chemotropic ephrin molecules can function bi-directionally as either attractive or repulsive signals in a cell-type-specific manner during nervous system development.[273,276,278,279,285] Ephrin proteins are ligands for the Eph family of receptor tyrosine kinases,[273,279,286,287] currently known to comprise 14 receptor isoforms.[217,218,273,279] Ephrin ligands can be subdivided into two distinct classes based on their particular membrane linkages and Eph receptor binding affinities, which are thought to confer specific functional properties during neuronal development.[283,288-290] While ephrin-A ligands are GPI-anchored, binding preferentially to the EphA class of receptors, ephrin-B ligands

instead are transmembrane proteins, and bind preferentially to cognate EphB receptors.[288] Interestingly, only GPI-anchored ephrin-A signaling stimulates morphological changes that do not directly contribute to initial axon guidance.[273,276-279,288] For example, ephrin-A5 signaling has been found to produce local changes in cortical neuron adhesion by activating β1 integrin expression, in turn stimulating changes in morphology consistent with the initial stages of neurite branching.[290-292] In contrast, EphA3 receptor activity stimulated by GPI-linked ephrin ligands decreases both apical and basal dendrite branching for developing cortical pyramidal neurons.[273,283,291] In combination, these recent studies demonstrate that ephrins serve numerous roles during neuronal morphogenesis, collectively regulating axonal or dendritic outgrowth, fasciculation, and arborization.

Semaphorins

Semaphorins constitute a large family of secreted and transmembrane proteins variously involved in growth cone collapse (Collapsin-1/Semaphorin IIIA[107]), axon guidance through chemorepulsion (Collapsin-1/Semaphorin IIIA, IIID[293-295]), stimulation or inhibition of axonal arborization (Semaphorin IIIA[85-87,296]), and neuronal apoptosis (Semaphorin IIIA[297]). Semaphorin-mediated signaling occurs in a cell-type-specific manner through the differential activation of neuropilin (NP) family receptors. Consequently, the multifunctionality of semaphorin activity may be determined chiefly through the complement of available NP receptors and downstream effector molecules as a function of neuronal development.[107,268,272,294,295,298-300] Within the mammalian cortex, Semaphorin (Sema) IIIA activity serves as a chemorepellent cue for cortical axons and inhibits branching morphogenesis, mediated by localized NP-1 receptor signaling.[295] In contrast, RGC axons in the developing *Xenopus* visual system respond to SemaIIIA/NP-1 activity with transient growth cone collapse followed by robust axonal branching upon recovery.[296,301,302] In fact, specific RGC growth cone collapse, turning, or branching responses are age-dependent and produced through varying levels of cGMP second messenger signaling, indicating changing neuronal sensitivity to SemaIIIA activity.[291,296] When immature *Xenopus* RGCs are aged in culture, they develop SemaIIIA responsiveness in parallel with age-matched RGCs developing in vivo, corresponding with the onset of NP-1 expression.[296] Expression of Plexin family receptor molecules, also critical for NP-1 signaling, follows a similar developmental time course both in vitro and in vivo.[296,303] Therefore, an intrinsic "molecular clock" mechanism has been postulated to regulate RGC growth cone sensitivity to SemaIIIA, which may be critical for confining the growth cone collapse-associated branching effects mediated by this molecule to the correct terminal position within the optic tectum.[296] Ongoing constitutive expression of SemaIIIA observed in mature populations of olfactory neurons, cerebellar Purkinje cells, and both cranial and spinal motoneurons, may indicate an additional function for this molecule in regulating branching plasticity within the adult CNS.[268,293,304]

Slit Proteins

Slit proteins are secreted factors with multifunctional roles during neuronal development, including growth cone chemorepulsion at the CNS midline during axon pathfinding, stimulation of axonal elongation in some cell contexts, and the recently characterized promotion of branching.[270,274,305-311] Slit2 is a mammalian homolog of *Drosophila* Slit, encoding a large (190-200 kDa) secreted protein that is proteolytically cleaved into two bioactive fragments, the 140 kDa amino terminus and the smaller carboxyl terminus.[270,292,305,307,308] Mammalian Slit protein signaling is mediated in turn by homologs of *Drosophila* Robo receptor proteins, Robo1-3, which demonstrate an expression pattern complementary to that of Slit isoforms during CNS development.[270] Similar to ephrin and semaphorin signaling, the morphoregulatory effects produced through Slit/Robo signaling are also cell-type-specific and depend on the developmental context of each neuronal population. For example, the purified amino-terminal fragment, Slit2-N, but not the full-length molecule, Slit2, stimulates axonal arborization for dorsal root ganglion (DRG) sensory neurons by increasing both the number of branchpoints

and individual branch lengths.[270,292] Recent studies indicate that full-length Slit2 may actually function as an antagonist of Slit2-N in many contexts,[292] suggesting that the competing processes of axon guidance and axonal arborization may be developmentally regulated through post-translational enzymatic cleavage of Slit proteins.[314] However, in certain cell contexts full-length Slit proteins also stimulate branching morphogenesis. For example, early exposure to Slit2 induces premature arborization for central trigeminal axons entering the brainstem, and generates robust axonal arborization for maturing neocortical interneurons.[312-314] In addition to Slit activity during axonal morphogenesis, recent studies have demonstrated a role for Slit1 in stimulating robust dendritic growth and branching for cortical neurons developing in vitro.[311] Together, these findings indicate not only that Slit proteins serve multifunctional roles, but also that the nature of the morphoregulatory response appears to be dependent on the neuronal cell type and developmental stage, potentially allowing individual populations within the same cortical environment to pursue separate developmental programs.

Hormones and Hormone-Like Factors

Hormonal influences on neuronal morphogenesis have been examined extensively, revealing dendrite-specific regulatory effects for both gonadal hormones and glucocorticoids, and pleiotropic actions for thyroid hormones. Collectively, hormones and hormone-like factors produce numerous cell-type-specific modifications to neuronal structure and function, often exhibiting a developmental critical period or characteristic periodic time course for these effects to emerge.[38,39,203,315-319]

Gonadal Hormones

Gonadal steroid hormones serve various morphoregulatory roles during neuronal development, and mediate synaptic connectivity within the adult central nervous system.[318,321] Through these pathways, gonadal hormones have been found to influence the circuitry of vertebrate neuronal populations within the arcuate nuclei, the lateral septum, the medial amygdala, the hypothalamic ventromedial nuclei, the preoptic area, and the hippocampus.[318,320-322] Examination of dendritic structure in CA1 hippocampal pyramidal neurons has revealed that significant morphological changes are produced through cyclic fluctuations in estradiol, estrogen, and progesterone.[318,320,321] For example, in adult hippocampal slice cultures estradiol promotes dendritic elaboration and spine outgrowth,[320,322] estrogen increases dendritic spine density, but progesterone reduces both dendritic arborization and synaptic contacts.[318,321] The functional significance of such striking gonadal hormone-mediated control of dendritic morphology in CA1 hippocampal neurons remains largely unclear, however. Given the role of the CA1 neuronal population in memory storage, it is possible that these structural changes may critically link reproductive processes with learning and memory.[318] Similar effects on dendritic elaboration induced through estradiol stimulation also have been reported for slice cultures of mature hypothalamus or preoptic area cortex, indicating that a variety of CNS neuronal arbors retain a great degree of plasticity not only throughout development, but also into adulthood.[321,323,324]

Glucocorticoids

In contrast to the largely stimulatory effects of gonadal hormones on dendritic morphology, glucocorticoids instead appear to chiefly inhibit morphogenesis, producing a range of structural and physiological deficits including diminished dendritic plasticity.[325-330] For example, chronic or acute cortisol administration during a critical developmental period reduces dendrite numbers and limits dendritic arborization for stellate neurons in the embryonic chick telencephalon.[327] Similarly, late embryonic adrenalectomy results in dendritic arborization failure for slow developing hippocampal granule neurons within the rat dentate gyrus, although rapidly developing pyramidal neurons within the CA1 and CA3 regions remain unaffected.[329] As such, it is likely that glucocorticoids affect dendritic branching morphogenesis most significantly during developmental stages characterized by the greatest degree of neuronal plasticity, representing a transient period of enhanced sensitivity to epigenetic perturbations.

Thyroid Hormones

Appropriate levels of the thyroid hormones T3 and T4 are essential for regulating a wide range of developmental processes within the CNS.[3,38,315-317,331-337] Consequently, regions of the brain characterized by postnatal differentiation, including the hippocampus, olfactory bulbs, and cerebellum, demonstrate significant defects in both neuronal proliferation and morphogenesis with restricted thyroid hormone exposure.[316,317,332-337] For example, neuronal populations developing in hypothyroid animals generally exhibit reduced axonal and dendritic arbors, contrasting with greatly enhanced dendritic arborization produced for neurons developing within hyperthyroid animals.[38,335,336] Interestingly, treatment of normal neonatal rats with thyroid hormone rapidly stimulates dendritic arborization for hippocampal pyramidal neurons; however, adult hippocampal neurons exposed to thyroid hormone display only moderate dendritic spine extension.[38,335,336] Thus, it is likely that a critical period exists during which developing neurons are maximally responsive to the influence of thyroid hormone activity on branching morphogenesis.

Bone Morphogenetic Proteins

Members of the bone morphogenetic protein (BMP) subfamily of the transforming growth factor-β (TGF-β) superfamily are secreted morphogens originally characterized for their role in osteogenesis.[339,341,343] More recently, BMPs have been implicated in regulating various aspects of dendritic morphogenesis for PNS and CNS neuronal populations.[338-344] Similar regulation of axonal morphogenesis has not been reported, however, suggesting that BMP-mediated morphogenetic effects may be dendrite-specific. The particular effects these proteins exert upon dendritic differentiation appear to be independent of the extent to which the target neurons rely upon intrinsic or epigenetic cues during development. Thus, for PNS populations, in which dendritic arborization critically depends on extrinsic factors, and for CNS populations, which elaborate dendrites in reduced conditions, BMPs similarly mediate robust increases in dendritic length or branching.[339,341,342] For example, BMP-7, also called osteogenic protein-1 (OP-1), has been reported to stimulate both dendritic elongation and branching for populations of hippocampal pyramidal neurons developing in vitro.[340,345-347] Within the cerebellum, BMP-5 expression is sustained at high levels throughout development, suggesting a possible role for this factor during dendritic branching morphogenesis in early-differentiating Purkinje cells and basket/stellate neurons, as well as for later-differentiating granule neurons.[341,348]

The regulatory effects of BMP activity during branching morphogenesis are mediated through long-range signaling as gradient morphogens, and through short-range cell-cell communication. Both forms of BMP-mediated signaling are initiated through ligand-dependent association of hetero-oligomeric complexes of type I/II serine/threonine kinase receptors.[341,343] These heteromeric receptor complexes act in a combinatorial manner to induce distinctly different signaling responses, depending on the identity of the associated type I and II receptors.[341,343] To date, however, those molecular mechanisms downstream of BMP activity that mediate aspects of dendritic differentiation remain largely uncharacterized. Interestingly, OP-1 has been found to regulate expression of the cell adhesion molecules L-1 and N-CAM in a neural cell line, suggesting that one important pathway affected by BMPs during dendritic morphogenesis may involve modulation of neuronal adhesion.[201,349] Members of the TGF-β family regulate synthesis of homeodomain-containing transcription factors; therefore, it is possible that the morphoregulatory signaling mediated by diverse BMPs also converges at the level of differential gene expression.[339,341,350,351]

Neurotrophic Factors

Neurotrophic factors, a family of structurally related homodimeric proteins originally identified through their ability to sustain neuronal survival, also regulate diverse aspects of neuronal differentiation and morphogenesis. These epigenetic proteins, widely expressed throughout both the developing and mature PNS and CNS, include the prototypic neurotrophic factor, nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3),

neurotrophin-4/5 (NT-4/5), and novel neurotrophins recently cloned from fish (NT-6 and NT-7).[86,125,168,169,352-369] In many regions of the mammalian CNS, neurotrophin expression is developmentally regulated, producing a characteristic pattern of maximum NT-3 synthesis and release during embryonic periods, with BDNF availability instead largely restricted to periods of postnatal differentiation.[370-372] In turn, both the synthesis and release of neurotrophins can be upregulated dynamically through positive feedback signaling triggered either by additional neurotrophin stimulation, or by various forms of neuronal activity.[367,368,370,373-388] Thus, precise spatiotemporal control of neurotrophin signaling through regulated expression and release may underlie distinct stages of neuronal morphogenesis.

Signal transducing receptors for the neurotrophins constitute two distinct classes: the solitary low-affinity p75 receptor ($p75^{LNTR}$), a member of the tumor necrosis factor receptor/fas/CD40 superfamily, and a structurally related group of high-affinity proto-oncogene receptor tyrosine kinases, collectively referred to as Trk receptors. These include TrkA, the cognate receptor for NGF, TrkB, which binds both BDNF and NT-4/5 with high affinity and NT-3 with low affinity, and TrkC, the high-affinity receptor for NT-3.[367,368,389-406] Trk receptor signaling influences neuronal differentiation by eliciting both short-term changes in protein phosphorylation, and long-term changes in gene expression through the activation of transcription factors such as cyclic AMP-response-element-binding protein (CREB).[163,168,353,366,384,399,400,405,407-412] The modulation of particular aspects of differentiation by neurotrophin activity appears to depend on the cell-surface distribution of Trk receptor isoforms, the activation of individual transduction pathways, the availability of downstream signaling substrates, and the developmental context of exposed neurons. In this way, neurotrophins can regulate neuronal precursor proliferation and initiate neurite outgrowth, as well as stimulating processes associated with terminal differentiation, including branching morphogenesis and synapse formation.[19,125,166-169,397,402-404,413,414]

The numerous structural changes underlying axonal and dendritic branching morphogenesis ultimately arise through the combined effects of differential gene induction and reorganization of specific cytoskeletal proteins, processes known to be downstream targets of neurotrophins.[86,125,163,168] For example, actin, microtubules, and numerous microtubule-associated proteins have been reported to be regulated by NT-3 and BDNF at the level of both transcription and post-translational modification.[415-421] Despite their ability to exert similar influences on the cytomatrix of axons and dendrites, neurotrophic factors also can produce separate and distinct structural changes for each of these neurite classes during branching morphogenesis.

Neurotrophin Modulation of Axonal Branching

Throughout the nervous system, target-derived neurotrophins regulate axonal outgrowth and branching morphogenesis during neuronal development, and mediate aspects of cytoskeletal reorganization that underlie presynaptic plasticity changes in mature neurons.[19,86,125,168,312,358,359,422-424] These effects are particularly well characterized in the vertebrate visual system.[144,382,407,425-442] For example, BDNF promotes rapid and prolonged changes in both the complexity and dynamic state of *Xenopus* RGC axonal arbors in vitro, with similar effects induced through neurotrophin microinjection or delivery through microspheres localized to the optic tectum in vivo.[144,431-434,443] Interestingly, this role for BDNF in preferentially stimulating RGC axonal arborization is achieved, in part, due to the localization of TrkB receptors to the axonal cell-surface domain of these neurons.[144,433,442,443] Within the primary visual cortex, infusion of BDNF or NT-4/5 into layer IV blocks the appropriate formation of ocular dominance columns during mammalian visual system development, presumably through exuberant branching of axonal terminals arising from the lateral geniculate nucleus, the functional counterpart of the non-mammalian optic tectum.[444,445] Similarly, chronic BDNF exposure during cerebellar granule neuron development in vitro stimulates atypical early increases in axonal branching and branch elongation.[446] Thus, the strict spatiotemporal regulation of Trk receptor expression, and neurotrophin release, is likely to impose direct local control on axonal branching morphogenesis necessary for the formation of appropriate circuitry during CNS development.

Neurotrophin Modulation of Dendritic Branching

Neurotrophic factors act on dendrites in a cell-type-specific manner to modulate the initial extent of arborization, regulate branch stabilization or retraction, and mediate ongoing dynamic changes in branch structure that underlie synaptogenesis.[38,125,435-453] While neurotrophic factors influence dendritic branching morphogenesis throughout the developing nervous system, these effects are often manifested differently for PNS and CNS populations, partially reflecting differences in the complement of neurotrophins and Trk receptors expressed.[38,125,435-453] For autonomic ganglion cells of the PNS, there is a clear correlation between the number of afferent inputs received through the process of preganglionic convergence, and the maximum dendritic arborization achieved, suggesting a critical role for limiting levels of target-derived neurotrophin.[19,454,455] Consistent with this model, increased NGF signaling in sympathetic ganglion cells acts instructively to induce rapid increases in both the number and length of primary dendrites, and enhance dendritic arborization.[19,352,454-457]

Within the CNS, each morphological attribute of dendritic arbors, including the number and length of primary and higher-order branches, can be differentially regulated by separate neurotrophic factors.[38,125,418,458,459] The range of dendritic branching responses elicited by individual neurotrophins has been particularly well described for pyramidal neurons developing within the visual cortex.[125,144,407,408,425-427,443] In this system, each neurotrophin produces distinct structural changes in either the apical or basal dendritic arbors of pyramidal neurons as a function of their laminar position within the cortex.[125] Thus, for pyramidal neurons developing within cortical layer IV, basal dendritic branching is stimulated with exogenous BDNF and NT-4, but not NT-3, while in layer VI, NT-4 increases dendritic arborization, NT-3 elicits no changes, and BDNF instead decreases dendritic branching.[125] Significantly, these lamina-specific responses demonstrate exquisite local control of instructive morphological changes within functional groups of neurons. It is likely that this degree of autonomy is necessary for pyramidal neurons to develop phenotypically appropriate dendritic arbors, allowing the establishment of particular synaptic input patterns.[125] In contrast to the segregated activity of particular neurotrophins within the developing visual cortex, other CNS populations instead require combinatorial neurotrophin signaling during branching morphogenesis. For example, establishment of appropriate dendritic arbors within the cerebellum necessitates cooperative BDNF and NT-3 signaling for Purkinje cells,[370,460-462] although BDNF alone mediates dendritic elongation and branching for their synaptic partners, the stellate/basket cells and granule neurons.[179,370,414,424,446,463-471]

Endogenous neurotrophins also produce antagonistic effects on dendritic branching in a cell context-dependent manner.[86,87,125,144] In fact, neurotrophins are thought to serve as potent triggers for dendritic branch retraction under certain conditions, possibly by inducing a requirement for stabilization of nascent branches, mediating destabilization of actin or tubulin polymers, or upregulating expression of repellent molecules.[86,125,459] For example, BDNF stimulation of developing *Xenopus* RGCs significantly increases axonal arborization, but paradoxically reduces dendritic branching through local inhibition of both branch formation and stabilization.[430-434,443] These antagonistic branching effects are especially interesting given the cell-surface concentration of TrkB receptors along the axon,[144,433,442,443] suggesting that changes in dendritic structure might arise indirectly through downstream signaling cascades triggered at the axonal domain. Alternatively, low-level BDNF signaling achieved through sparsely distributed TrkB receptors within immature dendrites might generate a distinctly different complement of downstream events. It is also possible that, in certain neuronal populations, neurotrophin signaling alternately stimulates or inhibits branching depending on the changing developmental context in which axons and then dendrites are elaborated. Such differential effects could arise through changes in the association of particular neurotrophins with ECM microdomains,[472] through localized neurotrophin delivery by target axons, through changes in Trk receptor expression or cell-surface distribution,[358,359,377,442,473-476] or through changes in downstream signaling substrates or background gene expression.[477-479]

Consistent with this developmental model, recent data suggests that distinct morphological effects elicited by neurotrophin activity are partly contingent upon the unique ontogenetic history of each neuron.[125,477-479] For example, BDNF-mediated TrkB signaling is required during early stages of cerebellar Purkinje cell development to allow complete dendritic differentiation during much later stages of maturation.[460,461,463,464] In fact, phenotypically mature dendritic arbors fail to develop in postnatal Purkinje cells cultured in the absence of BDNF-secreting granule neurons, and appropriate dendritic differentiation is not rescued with supplemental BDNF.[406,460,461] Instead, exogenous BDNF selectively increases dendritic spine density for these Purkinje cells, demonstrating that individual aspects of dendrite arbor structure may be independently regulated by neurotrophins during development.[460,461] When considered together, recent findings indicate that a variety of pathways contribute to the spatiotemporal regulation of neurotrophin signaling, enabling the local control of dendritic branching that is necessary for establishing appropriate circuitry during nervous system development.

Neurotransmitters and Neuronal Activity

Within the developing nervous system, a variety of neurotransmitter classes directly regulate morphological differentiation, and organize local circuit connections, by generating specific patterns and levels of electrical activity.[38,39,125,144,480-484] In tandem, neuronal activity can variously enhance or restrict the expression of numerous epigenetic molecules implicated in branching morphogenesis, modulating the physiological effects produced by these cues.[70,231,378,379,471,473,485] As such, a limited number of active signaling pathways can generate a complex array of effects during neuronal differentiation, contingent upon the complement of molecular effectors recruited.[70,231,378,379,471,473,485] Collectively, the processes regulated or modulated by neuronal activity that influence branching morphogenesis involve: selective induction of downstream second messenger signaling cascades, regulated changes in intracellular Ca^{2+} levels, posttranslational protein modifications, and differential gene expression.[2,18,38,39,44,76,106,125,144,164,195,196,480-482,484,486,487]

For most CNS populations, axonal differentiation occurs under electrically silent conditions, or with low-levels of spontaneous activity, whereas dendritic development proceeds in the context of specific forms and patterns of electrical activity.[2,15,38,106,125,144,488,489] Not surprisingly, electrical activity serves important roles in sculpting dendritic architecture at the earliest stages of neuronal development, and both establishing and refining synaptic connections at maturity.[15,38,106,125,144,346] In fact, individual neuronal populations can respond to various sources of electrical activity in a cell context-dependent manner, illustrating some degree of cell-autonomous control during dendritic branching morphogeneisis.[2,15,38,125,144,346] For example, tetanic electrical stimulation increases both the rate and number of dendritic filopodia extended from hippocampal pyramidal neurons developing in slice cultures, while excitatory *N*-methyl-D-aspartate (NMDA) glutamate receptor signaling instead abolishes filopodial dynamics.[2,38,125] In contrast, NMDA-mediated activity is necessary for appropriate extension of RGC dendritic filopodia.[15,38,125,144,490] Significantly, inhibitory γ-aminobutyric acid (GABA) receptor activation reverses the effects of glutamatergic signaling during dendritic morphogenesis for a number of neuronal populations, suggesting that physiological sculpting of neuronal architecture may occur through variable patterns of excitatory and inhibitory activity.[2,15,38,125,144,164,203,484,491,492]

During later stages of neuronal development, the processes of dendritic arborization and synaptogenesis are closely linked, such that appropriate patterns and levels of activity serve to stimulate or restrict branching and synapse formation in parallel.[2,15,19,38,106,125-127,135,144,346,493-495] Accordingly, Vaughn's synaptotropic hypothesis proposes that dendritic outgrowth and branching may be modulated directly by synaptic contacts, with arborization occurring preferentially in target regions retaining the greatest availability of presynaptic elements.[126,127,135,493,494] Indeed, developmental studies have shown that increasing the number of axonal contacts made with

dendritic filopodia increasingly stimulates dendritic branching and arbor complexity, while activity blockade variously stunts branching or elicits dendrite retraction.[15,38,125,134,136,144,496] Moreover, activity-mediated enhancement or maintenance of dendritic arbors is often localized to the discrete regions of contact between presynaptic axonal termini and postsynaptic dendritic branches or spines.[15,38,125,144] Another important observation is that the direction of dendritic arborization is governed by a tendency toward maximizing the number of contacts made with presynaptic axons from specific target regions that display physiologically relevant activity patterns.[15,38,125,133,144] For example, in the developing visual system, ocular dominance columns are established and maintained through the segregation of eye-specific afferent inputs that are characterized by distinct patterns of electrical activity. In this way, the dendritic growth properties for neurons positioned within individual columns can be differentially regulated as a function of location, generating eye-specific circuits.[38,125,145,146,437,438] Consequently, dendrites near an ocular dominance column border region elongate and branch only within the confines of that discrete functional unit, and do not extend inappropriate arbors into the adjacent column.[38,125,145,146,437,438] It has been postulated that nascent branches may "test" the local microenvironment for appropriate target axons displaying particular patterns or levels of activity, with initial contacts developing into synapses only when physiological activity is maintained, in some contexts triggering stop-growing pathways.[15,144] Because specific activity patterns also have been found to direct selective pruning of dendritic arbors, neuronal activity is thought to regulate the overall degree and rate of dendritic branch additions and retractions as neurons mature and form synaptic contacts.[15,38,125,144]

Throughout the developing nervous system, dendritic branches unable to compete successfully for limiting amounts of neurotransmitter, or axonal surface area, are often stunted or eliminated through pruning. For example, during cerebellar development, Purkinje cell dendrites that fail to establish functional synapses with granule neurons differentiate incompletely, suggesting a critical role for glutamatergic activity in the morphogenesis of these arbors.[463,464,482,486,487,497-501] Although eliminating endogenous electrical activity prevents dendritic branching for immature Purkinje cells, their dendrites continue to elongate, suggesting that functional synapses may be required to switch from a default pathway of linear growth to a developmental pattern of branching.[463,464,482] Interestingly, such alterations in dendritic growth patterns occur in parallel with changing intracellular Ca^{2+} regulation, indicating that the onset of electrical activity may produce shifts in Ca^{2+} homeostasis, thereby stimulating various forms of Ca^{2+}-dependent cytoskeletal remodeling important for dendritic arborization.[15,38,125,144,482] Since embryonic exposure to BDNF is also necessary for subsequent elaboration of Purkinje cell dendrites,[460-464] the chief role of neuronal activity in modulating branching morphogenesis may be to integrate or amplify downstream signaling cascades stimulated by a range of epigenetic cues. Alternatively, early neurotrophin signaling may be required to prime developing neurons to respond appropriately to subsequent electrical activity by inducing selective gene expression or stimulating post-translational protein modifications.[460-464] Context-specific morphological responses also are produced through activity-dependent targeting and translation of TrkB mRNA within stimulated dendrites for a variety of neuronal populations, providing a complementary mechanism for dynamic local control of arbor plasticity.[383,442,475,476] Taken together, these findings indicate that the onset of neuronal activity during later stages of dendrite maturation may enable a greater degree of control over arbor development, and the orchestration of synaptogenesis, through the activation of diverse signaling pathways.

As neuronal development continues, specific forms and patterns of activity are thought to mediate the stabilization of dendritic arbors by inhibiting dynamic cycles of branch elongation and retraction, and strengthening nascent synaptic contacts.[15,38,125,144,171,172,502] One mechanism thought to underlie this activity-dependent control of arbor maturation is the differential expression of particular combinations of glutamate receptors as a function of development.[503-507] For example, in the visual system, nascent contacts between RGCs and optic tectal neurons are characterized by a large proportion of silent synapses that are exclusively mediated by NMDA

receptors, potentiating dendritic arbor expansion. However, as these initial contacts are strengthened and mature as synapses, α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA)-type receptors are additionally recruited, resulting in more robust activity and the corresponding stabilization of dendritic arbors.[15,144,508,509] Similarly, during hippocampal pyramidal neuron development, synaptically-released glutamate stabilizes dendritic spines through AMPA receptor activation, and failure to recruit sufficient AMPA receptors results in dendritic branch retraction.[15,144] In conjunction with changing glutamate receptor populations, certain cytoskeletal elements, channel proteins, and vesicular proteins, appear to be initially targeted to dendritic arbors by activity-independent mechanisms, with subsequent retention in functionally significant microdomains regulated by the onset of synaptic activity.[39,54,66-75,510] Thus, a number of important subcellular modifications are triggered by emerging neuronal activity as development proceeds, collectively promoting dendritic branching morphogenesis. When considered together, the various roles served by neuronal activity demonstrate exquisite spatiotemporal control over the arborization of individual dendrites, allowing the establishment of physiologically appropriate circuitry.

Molecular Regulation of Branching Morphogenesis

Since neurons differentiate as part of a developing circuit, instructive cues provided within the local microenvironment, and through cell-cell signaling, are critical for synchronizing the progression of branching morphogenesis among neuronal partners.[8,9,15,16,18,39,45,76,77,144,164,195,196] Ultimately, these complex signaling pathways converge at the level of the cytoskeleton, with the structural changes characteristic of neuronal branching arising through dynamic regulation of the actin cytomatrix, microtubules, and a variety of microtubule-associated proteins. Within the last decade, tremendous progress has been made toward identifying molecular mechanisms that orchestrate the cytoskeletal reorganization underlying both axonal and dendritic branching.[2,15,38,49-51,104-106,125,144] These recent studies have revealed that persistent morphological remodeling may arise in one of two ways: as the consequence of a short-duration signaling event that stimulates local post-translational modifications to certain cytoskeletal proteins, or one that activates an epigenetic sequence of long-term changes in gene expression.[15,38,125,144,163,172,399,400,511-516] Both forms of morphological regulation involve rapid changes in local intracellular free Ca^{2+} levels that subsequently produce downstream changes in protein phosphorylation. In this way, multiple epigenetic cues may be integrated through Ca^{2+}-mediated signaling pathways acting on different time scales to influence branching morphogenesis.

Calcium Signaling

During neuronal development, rapid changes in intracellular Ca^{2+} levels can be achieved through several non-mutually exclusive pathways. First, signaling through molecular asymmetries within the microenvironment can stimulate local Ca^{2+} influx or release from intracellular stores. Second, with a relatively homogeneous distribution of ECM molecules, or secreted and substrate-bound factors, local Ca^{2+} signaling can result from a cell-surface gradient of receptors and ion channels, or subcellular asymmetries in signal transduction molecules. Third, in a related mechanism, preferential membrane insertion at the growth cone leading edge through exocytosis can serve an active role in morphogenesis through the local insertion of voltage-gated or ligand-gated Ca^{2+} ion channels. Finally, the onset of depolarizing electrical activity can stimulate Ca^{2+} influx through NMDA-type glutamate receptors and other voltage-gated Ca^{2+} channels.[2,8,16,45,76,77,164,196,220,221,517,518]

Endoplasmic reticulum and mitochondria have been reported to localize at nascent branch points in developing neurons, suggesting that these organelles are spatially oriented to mediate dynamic Ca^{2+} release or uptake necessary for branching morphogenesis, in addition to regulating metabolic processes.[18,164,196,519,520] For branching achieved through simple growth cone bifurcation, induction of a local intracellular Ca^{2+} gradient can trigger F-actin depolymerization

and also increase microtubule protrusion into the growth cone, in tandem with the activation of Ca^{2+}-binding proteins that modulate microtubule stability.[76,77,85-87,165,196,244,245,521-527] Thereafter, the rate of branch elongation is inversely proportional to the intracellular accumulation of free Ca^{2+}, requiring the establishment of a cytosolic Ca^{2+} gradient with the lowest levels underlying developing neurites.[8,16,18,39,45,76,77,164,196] Similar local Ca^{2+} influx and sequestration mechanisms are likely to underlie the formation of interstitial collateral branches, which also arise through coordinated dynamic changes in actin and microtubule polymerization.[2,85,87,106]

Downstream of rapid intracellular Ca^{2+} elevation, the activation of specific Ca^{2+}-dependent proteins can produce a wide range of cytoskeletal modifications that drive branching morphogenesis.[15,18,38,39,125,144,164,195,196,227,228,528] For example, studies examining developing hippocampal neurons indicate that activation of cyclic AMP (cAMP)-dependent protein kinases or Ca^{2+}/calmodulin-dependent serine/threonine kinases (CaMKs) is required for both axonal and dendritic branching, while increased protein kinase C (PKC) and protein kinase A (PKA) activation enhance dendritic arborization alone.[529,530] This redundancy in molecular control of branching morphogenesis suggests that cell context may critically determine downstream cytoskeletal changes, owing to developmental shifts in the complement of specific protein kinases expressed, the availability of second messengers, and background gene expression.

In addition to regulating branching morphogenesis through direct control of cytoskeletal plasticity, the activation of Ca^{2+} signaling cascades also provides an important pathway for modulating neuronal structure through selective changes in gene transcription.[386,388,409,410,531-533] For example, elevation of intracellular Ca^{2+} is essential for activating cAMP-response-element-binding protein (CREB), a transcription factor involved in regulating long-term changes in gene expression through activation of the cAMP-response-element (CRE) DNA target.[2,409,410,412,531,532,534] As such, a variety of extracellular molecules can induce specific immediate-early genes, such as *c-fos* and *c-jun*, and subsequently upregulate late-response genes, together orchestrating the differential protein expression required for structural and functional changes underlying branching morphogenesis.

Rho-Family GTPases

The earliest epigenetic control of neuronal branching appears to trigger rapid local modulation of the actin cytomatrix through one pathway, while inducing differential gene expression through a more protracted downstream signaling cascade. Recent findings suggest that at least one class of molecular effectors, the Rho-family GTPases, commonly mediates dynamic actin remodeling during these early stages of branching, induced by a variety of extracellular cues including: ECM interactions, secreted and substrate-bound chemoattractants and chemorepellents, neurotrophins, and electrical activity.[88,535-546] Through Rho GTPase signaling, significant changes in the local microenvironment may be rapidly translated into specific patterns of cytoskeletal remodeling which drive the competing processes of branch extension and retraction during development.[140,538-546]

Rho-family GTPases are members of the Ras superfamily of small GTP-binding proteins, and include: RhoA, RhoG, Rac1, Rac2, Cdc42, and the recently identified Rnd proteins Rnd1, Rnd2, and Rnd3/RhoE.[538-547] Acting as molecular checkpoints during neuronal development, each of these Rho-family GTPases serves a distinct function in regulating branching morphogenesis by transducing a complex array of extracellular signals into specific changes in actin polymerization.[538-547] Typically, while Rho activity increases neurite retraction or abolishes branch outgrowth, Rac and Cdc42 instead stimulate robust neurite extension and arborization.[6,45,77,88,312,313,536,545-549] For example, during *Xenopus* RGC development, Rac1 and Cdc42 promote robust dendritic branching whereas RhoA functions as a strong negative regulator for branch induction.[550] Axonal arborization also is regulated in a cell non-autonomous manner by Rho-family GTPase signaling, with high levels of Rac activity required to stimulate appropriate branching geometry for a variety of neuronal populations.[551] Characteristically,

the majority of Rho-family GTPases involved in early axonal morphogenesis demonstrate overlapping roles in regulating similar aspects of dendritic differentiation during successive stages of neuronal development.

Rho-family GTPase signaling efficacy is regulated in turn by GTPase-activating proteins (GAPs) and guanine nucleotide exchange factors (GEFs), which accelerate the process of GDP/GTP exchange.[535-537,547-549] For example, Trio is a newly characterized GEF that selectively activates the Rac pathway via RhoG through one binding domain, GEFD1, and instead activates the RhoA pathway through the separate GEFD2 binding domain.[549] Recent studies also have identified a novel effector protein specifically involved in modulating the activity of Rnd GTPases, called Rapostlin.[552] Binding to activated brain-specific Rnd2 in a GTP-dependent manner, Rapostlin next binds directly to neuronal microtubules from the amino-terminal region, which has been observed to induce rapid neurite branching for PC12 cells.[552] Characterization of the developmental role of Rapostlin will be necessary in order to understand the functional consequences of this unique pathway for affecting multiple cytoskeletal elements in tandem.

Numerous effector molecules that function downstream of Rho-family GTPases have been identified, including molecules of the p21-activated kinase (PAK) family of serine/threonine kinases, Rac1- and Cdc42- specific LIM domain-containing protein kinases, and IQGAP, Cdc42-specific neuronal Wiskott-Aldrich syndrome protein (N-WASP), and Rho kinases (ROCKs).[140,536,553-559] Downstream signaling through activated Rho-family GTPases begins with stimulation of Rho-dependent kinases (such as p65 ^{PAK} or p160ROCK) that phosphorylate one of the two isoforms of LIM kinase (LIMk1 and LIMk2), which subsequently phosphorylate cofilin and actin-depolymerizing factor to regulate the state of actin polymerization.[140,536,553,560] In addition, recent reports suggest that RhoA-dependent inactivation of myosin phosphatase may enhance the early myosin-actin interactions that ultimately drive retrograde actin flow during filopodial extension, while RhoA-induced growth-associated protein 43 (GAP-43) activity instead promotes later stages of neurite stabilization.[556-558,561-564] Given the antagonistic effects produced by Rho GTPase signaling cascades, recent investigations have focused on context-dependent recruitment of separate Rho effectors and the interplay between individual Rho GTPases. Significantly, these studies have suggested that the actin-reorganizing effects of Rac and Cdc42 GTPases are either dominant over the stabilizing actions of RhoA in actively growing neurites, or instead downregulate RhoA activity, thus potentiating outgrowth.[16,45,77,88,565] Considered together, the ability of each Rho-family GTPase to effect distinct changes in the actin cytomatrix suggests that sequential expression, or activation, of these molecules may orchestrate specific stages of neuronal branching morphogenesis.

In the early stages of neuronal branch formation, nascent F-actin enriched filopodia extend from developing neurites, and these protrusions enlarge as they are subsequently invested with microtubules.[2,38,104-106,125,537] It is likely that epigenetic cues which trigger local changes in actin polymerization during branching may do so by activating or inactivating particular Rho GTPases, allowing subsequent redistribution of microtubules and providing multiple pathways for reinforcing cytoskeletal changes.[140,551,552,566-568] Several alternative scenarios may account for these regulatory interactions throughout neuronal development. First, branch-inducing cues localized to the ECM could directly activate Rac and Cdc42 GTPases accumulated within the underlying cytosol, thereby overriding Rho and allowing microfilament depolymerization and the commencement of neurite outgrowth. Second, cues present within an extracellular microdomain could instead indirectly modulate the efficacy of Rho-family GTPase signaling by directly regulating the expression, localization, or activation state of GAPs or GEFs. Third, simultaneous activation of Rho-family GTPases and other actin-regulating effectors could destabilize the cortical actin cytoskeleton through independent but parallel pathways.[76,140,282,547,569-572] Through these mechanisms, it is possible for the combined effects of multiple actin-regulatory molecules to reinforce key signaling cascades that underlie branch formation, while also allowing precise spatiotemporal control of the dynamic actin changes produced.

In order to clarify the regulation of Rho-family GTPase activity during branching morphogenesis, recent studies have examined interactions producing actin reorganization during axonal and dendritic arborization in a variety of neuronal populations.[537,539-542,546,550-560] During development of the visual system, physiological branching of RGC axons has been shown to be a critical event in retinotectal map formation,[90,98,114,115,279,282,285,569,573] and may be induced through repellent optic tectal cell signaling.[286,296,542,574-577] In vitro, chick temporal RGC axonal growth cones rapidly collapse and retract after encountering repellent cues presented by posterior optic tectal cells.[101,296,297,565,578] Subsequently, lateral extensions appear along the RGC axon tract, reflecting a combination of nascent interstitial branches and defasciculating trailing axons separating from the pioneer axon.[101,102,279,296,297,565] This stereotyped collapse-induced branching is associated with depolymerization and redistribution of actin filaments both within the growth cone and along the axon shaft, mediated through Rho-family GTPase activity.[579] For example, inhibiting RhoA or the RhoA effector, p160ROCK, inhibits the generation of lateral extensions from cultured chick RGC axons,[565] while overexpression of Rac1B stimulates robust axonal branching.[565,568] Rho-family GTPases also have been shown to play a role in SemaIIIA-induced growth cone collapse for chick DRG neurons, and in ephrin-A5-induced collapse of chick RGC growth cones, although it is unclear whether these triggered actin redistributions are necessarily linked to the formation of interstitial branches.[579-581] Further support for a model of axonal branching in which inhibitory stimuli initiate actin rearrangement has been provided by recent experiments revealing functional interactions between Rho-family GTPases and the Plexin class of chemorepellent semaphorin receptors. In these studies, active GTP-bound Rac was found to interact directly with the cytoplasmic domain of mammalian Plexin-B1, allowing localized signal transduction to the underlying cytoskeleton.[303,535,582] Despite advances in characterizing Rho-family activity during branching morphogenesis, it remains unclear whether axonal growth cone collapse, retraction, and the formation of interstitial branches are inherently regulated independently of each other, or may be linked via the same molecular mechanisms.

In contrast to the wealth of data describing Rho GTPase activity during axonal morphogenesis, the regulatory roles of Rho-family GTPases during dendritic branching have only recently begun to be characterized.[140,142,150,550,583-585] An elegant series of studies in the developing *Xenopus* visual system initially revealed that early dendritic morphogenesis for both tectal neurons and RGCs involves downstream activation of Rac1 or Cdc42 to stimulate dendritic branching, and activation of RhoA to restrict subsequent dendritic growth.[140,150,550] Similarly, direct time-lapse imaging of developing chick RGCs demonstrated that constitutively active Rac1 or Cdc42 GTPases promote exuberant dendritic branching, while RhoA signaling instead suppresses branch formation.[142] Constitutively active RhoA has additionally been shown to reduce both dendritic growth and arborization for developing hippocampal neurons in slice cultures.[566,585] Considered together, these recent findings suggest that selective activation of particular Rho-family GTPases may constitute a conserved molecular mechanism important for dendritic remodeling and synaptic pruning as dendrites mature. Moreover, the correlated activation of specific combinations of Rho GTPases in presynaptic axons and postsynaptic dendrites is likely to be necessary for orchestrating plasticity changes that underlie synapse formation.

Since branching morphogenesis involves the dynamic redistribution of a variety of cytoskeletal elements, as axonal and dendritic branches elongate, the protruding sites of concentrated actin become engorged with microtubules.[2,15,39,85,87,144] Recent studies describing a regulatory interaction between microtubule dynamics, Rho-family GTPase activity, and actin reorganization, revealed that the various cytoskeletal changes underlying neurite branching may, in fact, be interdependent.[140,547,566,585] For example, continuous growth of microtubule polymers provides a positive feedback mechanism for Rac GTPase activation, and dynamic changes within the actin matrix of developing fibroblasts.[547] For these cells, tubulin monomers preferentially associate with Rac1-GDP, and tubulin polymerization activates Rac1, in turn allowing Rac1-GTP

to dissociate from a growing microtubule and interact with the local actin matrix.[547] If this regulatory mechanism is recapitulated in differentiating neurons, the presence of growing microtubule polymers within the region of destabilized actin might be expected to amplify or potentiate filopodial dynamics produced through Rac GTPase activity. In turn, cycling between periods of microtubule growth and depolymerization would be expected to regulate the activity of Rac and Rho GTPases, respectively, modulating local actin polymerization and providing a vector for orienting the protrusion or retraction of growth cones.[547]

Several recently discovered functions for RhoA, Rac1, and Cdc42 are novel activity-based roles, likely involved in regulating ongoing axonal and dendritic maturation during synaptogenesis. For example, Cdc42 expression is induced within the CNS following the onset of several forms of neuronal activity,[586] and in turn modulates voltage-dependent Ca^{2+}-currents in vitro, as does active Rac1.[587] In yet another study, excitatory NMDA receptor-mediated signaling was shown to reduce RhoA activity in developing optic tectal neurons, thereby increasing dendritic branching and branch elongation.[150] In fact, establishment of appropriate neuronal arborization is likely to involve the dynamic regulation of RhoA-GTPase activity, allowing early robust branch outgrowth followed by cytoskeletal stabilization as synaptic contacts are initiated. According to this model, local modulation of dendritic branching could be achieved through spontaneous glutamatergic activity at the onset of synaptogenesis, leading to exuberant branching through increased Rac1 and Cdc42 activity and downregulated RhoA signaling. However, as initial synaptic contacts mature, and AMPA-type glutamate receptors are recruited,[508,509] RhoA-GTPase expression or signaling may be upregulated relative to Rac1 and Cdc42, and contribute to the stabilization of both axonal and dendritic arbors. In parallel, individual branches that fail to receive appropriate stabilizing synaptic contacts may be stunted and subsequently retract through persistent RhoA stimulation.[584,585] Alternatively, the physiological activity of RhoA may predominate during the earliest stages of neurite morphogenesis, serving as a developmental 'block' to branch outgrowth, with the onset of Rac1 and Cdc42 activity then sculpting arborization that is ultimately stabilized through synapse formation. Clearly, strict spatiotemporal control of Rho-family GTPase expression and activation is necessary, both for neuronal morphogenesis and for the establishment of appropriate circuitry within the developing nervous system.

Microtubule-Associated Proteins and Microtubule Affinity-Regulating Kinases

The development of neuronal branches involves a number of processes acting at the level of the cytoskeleton, including regulation of actin assembly, microtubule polymerization, and microtubule transport.[2,15,38,45,50-52,77,85-87,104-106,125,140,144] Following initial actin-based stages of branching morphogenesis, modulated in large part through Rho-family GTPase activity, later stages involve the combined effects of structural and motor microtubule-associated proteins (MAPs), microtubule affinity-regulating kinases (MARKs), and Ca^{2+}/calmodulin-dependent kinases (CaMKs) and phosphatases (calcineurin/PP2B).[2,8,9,15,16,39,44,45,53,54,190,191,418,506,514,515,588,589]

As nascent branches begin to fill with microtubules, ongoing morphogenesis involves a combination of branch segment lengthening and further partitioning of these segments into smaller diameter branches until a limiting size is met.[8,29,159,160] Structural MAPs bind to microtubules in a reversible but static manner to perform a number of important roles during these later stages of arborization, which include: promoting microtubule assembly through enhanced tubulin polymerization, stabilizing new microtubules through the formation of polymer bundles, regulating the spacing between individual bundled microtubules, and regulating the overall plasticity or stability of developing branches.[53,590] In turn, structural MAP activity is regulated chiefly through the actions of specific MARKs, which trigger phosphorylation changes in response to localized epigenetic cues.[53,590] Enhanced phosphorylation at most sites along a structural MAP protein serves to weaken binding interactions with microtubules, which become more widely spaced, while dephosphorylation instead limits dynamic instability by

promoting ongoing tubulin polymerization and bundling.[8,16,45,53,164,190,191,195,196,590,591] Recent studies indicate that the phosphorylation state of structural MAPs may play a critical role in regulating neuronal arborization through significant changes in microtubule spacing, with MAP phosphorylation increasing the probability of branching, while dephosphorylation instead favors neurite elongation.[322,529,530,588,592] Using this experimental data to generate a computational model of branching, Hely and colleagues showed that the rate of dendritic elongation or branching can be determined theoretically from the ratio of phosphorylated to dephosphorylated MAP isoforms alone.[588] These findings suggest that the wide variation in arborization geometries displayed by neuronal populations is likely to develop, in part, due to significant differences in the subcellular localization or activation of specific MAPs and MAP kinases or phosphatases. Ultimately, such asymmetries may arise through purely stochastic fluctuations in molecular components, or through targeted signaling produced by cues within the local microenvironment.

Individual structural MAP isoforms have been categorized primarily according to their molecular weight, with high molecular mass MAPs including MAP1A, MAP1B, MAP1C, and neuron-specific MAP2A and MAP2B, and lower molecular mass proteins comprising MAP2C, MAP2D, and tau.[8,9,40,44,54] In addition, structural MAPs can be classified into functional groups with respect to characteristic differences in their subcellular distribution between phenotypically mature axonal and dendritic domains. For example, mature axons are enriched with the dephosphorylated form of microtubule-associated tau protein, while mature dendrites instead localize MAP2 isoforms and exclude tau.[8,9,44,54,590,593-595] One important consequence arising from this asymmetrical MAP distribution is the emergence of directional organelle and vesicle transport due to differences in microtubule spacing, and thus steric hindrance, between the axonal and dendritic domains.[8,9,44,53,54,190,191,590,593,596] As a result, axonal and dendritic branches attain significantly different subcellular compositions, allowing functional specializations to develop in parallel with branching morphogenesis.[2,8,9,38,40,44,85-87,125] Despite retaining separate classes of MAP isoforms and organelles, presynaptic axons and postsynaptic dendrites regulate the relative degree of microtubule plasticity through similar means as development proceeds.

For developing axons, specific microenvironmental cues are thought to trigger a pause in growth cone migration, local modification of the cytoskeletal matrix, and the establishment of a nascent branch point through localized targeting of subcellular components.[104-109] Microtubule reorganization is a critical component of this branching process, requiring localized microtubule fragmentation, or debundling, concomitant with actin accumulation.[104-109] Consequently, when microtubules within an axon remain bundled, stable branches fail to form even when transient filopodia invested with microtubules arise along the axon shaft.[104,106] Recent observations of cerebellar granule neurons developing in vitro suggest that the modifications in microtubule bundling required for axonal branch formation may be selectively mediated through changes in tau MAP phosphorylation.[594,595] As such, the dephosphorylated form of tau is enriched for portions of the axon shaft with tightly bundled microtubules, but in discrete regions of splayed microtubules, presumably representing areas of nascent branch formation, the phosphorylated form of tau predominates.[594,595] It remains unclear whether the growth cone splitting mechanism underlying branching in dendrites similarly requires microtubule splaying, although the reported increase in dendritic branching with MAP2 phosphorylation suggests that this may be the case.[53,322,530,588,597-599]

Providing an additional level of complexity to the regulatory interactions underlying microtubule dynamics is the recent finding that MAP phosphorylation varies significantly as a function of development for some neuronal populations.[503-505,597-599] Moreover, separate MAP phosphorylation sites can be regulated independently as neuronal maturation proceeds.[503-505,597-599] Such characteristic developmental changes in MAP phosphorylation reflect, in part, the regulatory activity provided by the onset of neurotrophin signaling cascades and neuronal activity. For example, administration of exogenous BDNF and NT-3 rapidly

increases both the expression level and phosphorylation state of several MAP2 isoforms for early embryonic cortical neurons developing in vivo.[421] Glutamate receptor activation also efficiently regulates the phosphorylation state of various MAP isoforms.[504,505,600,601] Interestingly, the ability of certain neuronal populations to couple glutamatergic activity to changes in MAP2 phosphorylation differs with maturation, largely established by the specific glutamate receptor subtypes expressed at particular developmental stages.[503-505] For example, neonatal hippocampal pyramidal neurons respond to glutamate receptor stimulation with MAP2 phosphorylation, whereas dephosphorylation of MAP2 is only inducible in mature neurons.[504,505] Thus, for at least some neuronal subtypes, aspects of branching morphogenesis may be regulated indirectly as immature neurons gradually attain a mature complement of biochemical machinery and the competence to dephosphorylate MAPs, prolonging arbor plasticity.[504,505] Since phosphorylation of tau and MAP2 is also regulated by exposure to certain epigenetic factors, the unique developmental functions performed by these MAPs reflects a dynamic combination of cell-autonomous regulation and direct control exerted through the changing microenvironment.

In vivo, the degree of neuronal MAP phosphorylation is tightly controlled by a number of protein phosphatases and kinases, including MARKs.[53] MARKs comprise a spatiotemporally regulated gene family including MARKs1-4, each of which may occur in several splice variant forms. Structurally, these proteins possess a highly conserved N-terminal catalytic domain containing two activating phosphorylation sites, a region near the C-terminus thought to represent a membrane-targeting motif, and an extended spacer domain which is also thought to contribute to membrane localization.[53] Functionally, all MARKs are activated through phosphorylation at their catalytic domain by upstream kinases, in turn promoting MAP activation and the modulation of microtubule organization and stability that underlies the establishment of neuronal branches.[53] The physiological importance of regulated MARK activity is evident from striking observations of increasing cytoskeletal disorganization and cellular dysfunction with MARK overexpression, presumably resulting from diminished microtubule stability following the dissociation of MAPs.[53,190,191] These results have prompted the hypothesis that differential MARK activity may serve as a 'molecular switch' for developmentally relevant changes in the microtubule-based transport of microtubule polymers, vesicles, or membranous organelles.[53] According to this theory, MARK-induced depletion of MAPs within a localized region could decrease steric hindrance and in turn promote microtubule-based transport, potentially driving branch elongation. Ultimately, dynamic regulation of branch stability or plasticity during neuronal development may be mediated through the complement of particular MAP isoforms expressed, the subcellular localization of these MAPs, or dynamic changes in the MAP phosphorylation state.[53,602,603]

Several additional regulatory molecules that link microenvironmental cues with rapid cytoskeletal reorganization through changes in MAP phosphorylation include cAMP - dependent kinases, CaMKs, and the Ca^{2+}/calmodulin-dependent protein phosphatase, calcineurin.[15,38,39,125,144,195,196,227,228,409,410,531,532,588] Indeed, many of the morphological changes that occur during neuronal development are mediated through changing Ca^{2+} levels, and thus CaMK or calcineurin activity.[15,144,514,515,588,604] For example, recent studies revealed the fundamental role for Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII) in dendritic branching by demonstrating a 30% reduction in branching with CaMKII inhibitors and greater than a 200% increase in branching when CaMKII activity was enhanced.[322] CaMKII mRNA is targeted to dendrites, and both translation and activation of CaMKII are enhanced by various forms of activity,[39,66,70,605] providing a mechanism for the local dynamic regulation of dendritic arbor plasticity during synapse formation.[144,506,507,529,530,588,606-611] In the basal state CaMKII is inactive, but increased Ca^{2+} influx through voltage-gated or ligand-gated Ca^{2+} channels, or triggered Ca^{2+} release from intracellular stores, results in rapid kinase phosphorylation and activation.[514,515,604] Consequently, multiple neuronal inputs, ranging from diffusible neurotrophins and local membrane-bound molecules to patterns and levels of activity, can be

integrated through these Ca^{2+}-dependent pathways.[220,221,409,410,514,515,531,532,612-616] Following branch outgrowth and the development of phenotypically appropriate arborization geometry, neuronal branches are typically stabilized during synaptogenesis to allow the maturation of functional neuronal circuits.[15,38,125,144,495,506,507,608] In the developing retinotectal system, the transition from dynamic tectal cell dendritic arbor growth to structural stabilization is mediated through local increases in αCaMKII,[608] which similarly restricts the outgrowth of presynaptic RGC axonal arbors.[15,144,506,608] In order to enhance the formation and stabilization of appropriate synaptic connections in this maturing circuit, patterns of activity both restrict and maintain dendritic arborization by modulating MAP-binding interactions through changing CaMKII activity. Ultimately, as functional connectivity develops within the nervous system, dynamic regulation of branching morphogenesis requires a cell-type-specific balance of microtubule stability and plasticity modulated through rapid changes in MAP phosphorylation.

Gene Expression Changes during Branching Morphogenesis

Many of the molecular signaling cascades that underlie neuronal branching morphogenesis ultimately produce long-term changes in gene expression. Converging at the level of the cytoskeleton, various forms of epigenetic regulation allow both short- and long-term modifications in the transcriptional or translational level of immediate-early genes (IEGs) and late-response genes (LRGs). While LRGs constitute a wide array of gene types, IEGs instead comprise two classes, the transcription factor genes and the effector genes, both of which are involved in neuronal morphogenesis and the modulation of synaptic plasticity.[15,18,38,125,144,163,164,196,409,410,491,492,515,531,532,534,617-620] In addition to well-characterized changes in the expression of various cytoskeletal element genes that occur in parallel with neuronal branching, significant changes in effector genes also have been recently identified. Of the novel effector genes known to be directly involved in neuronal branching morphogenesis, the best characterized include: the activity-regulated cytoskeletal-associated (*Arc*) gene, the closely related neuronal activity-regulated pentraxin (*Narp*) gene, and a variety of candidate plasticity genes.[73,151-155,502,508,509,621-624]

Developmental regulation of gene expression within the CNS often begins with excitatory glutamatergic signaling, providing one important pathway for modulating structural and functional plasticity changes through the activation of particular second messenger cascades.[490,515,533,534,612,618-620,625-627] For example, activity-mediated elevation of intracellular Ca^{2+} through voltage-gated ion channels is essential for inducing CREB, a transcription factor involved in generating long-term changes in gene expression through a Ca^{2+}/calmodulin-dependent kinase (CaMKIV) regulated pathway.[409,410,532-534] In fact, recent findings indicate that the activity-dependent regulation of protein synthesis and protein targeting necessary for neuronal morphogenesis can occur through several independent pathways. First, certain physiologically relevant patterns or levels of activity can induce transcription factor genes, such as *CREB*, in turn stimulating mRNA transcription and translation within the soma for transport to diverse neuronal sites.[39,54,66-68,70-75,510,622] Second, appropriate patterns or levels of activity can target newly transcribed mRNAs toward remote domains for local translation at their site of function, as occurs with dendritic *Arc* and *Narp* genes.[73-75,502,621,622] Third, the onset of physiologically relevant activity can selectively enhance the translation of mRNA previously localized to a particular subcellular region, as recently described for *Arc* and also certain neurotrophic factors.[39,54,66-75,621,622] In combination, these activity-mediated pathways allow rapid and selective induction of IEGs, and subsequent regulation of downstream LRGs, collectively producing the differential protein expression required for branching morphogenesis.[409,410,531,532,534,618-620]

The molecular control of activity-dependent dendritic remodeling critically involves *Arc* and *Narp* genes, both of which are present at low levels basally and induced by strong electrical activity.[502,621] Following robust excitatory stimulation, newly synthesized *Arc* mRNA is targeted specifically to those regions of the dendritic arbor receiving strong activity, aggregating at

postsynaptic sites. In tandem, *Arc* mRNA is depleted from neighboring unstimulated dendrite segments, suggesting that electrical activity may trigger the redistribution of a preexisting pool of mRNA, in addition to stimulating gene transcription.[621,622,628,629] In fact, recent findings suggest that strong electrical stimulation effectively 'tags' a synaptic site for preferential accumulation of newly synthesized *Arc* mRNA.[628,629] Thereafter, translated Arc protein remains localized to the actin-rich matrix beneath the plasma membrane of activated dendrite segments, which may establish a spatially-regulated pathway linking robust NMDA-mediated activity with local cytoskeletal modifications.[73-75,502,621,622,628,629] Although the precise function of Arc protein during dendritic branching morphogenesis and synapse formation remains unclear, recent findings support a role for rapid *Arc* gene induction in memory consolidation. Accordingly, dendritic targeting and translation of *Arc* mRNA is associated with the stabilization of long-term potentiation (LTP) in the hippocampus, a specific inducible form of synaptic plasticity.[73-75,622,628,629]

Similar to *Arc*, the *Narp* immediate-early gene is induced by excitatory glutamatergic activity during synaptogenesis, and also modulates ongoing changes in dendritic arbor plasticity.[15,144,508,509,630-633,650] Widely expressed within the developing nervous system, Narp protein is one member of the pentraxin family of secreted Ca^{2+}-dependent lectins, and forms N-terminal covalently-linked complexes with NP1 pentraxin.[630-633,650] In fact, recent studies indicate that the ratio of these aggregated pentraxins depends on both the developmental and electrical history of a neuron, with *Narp* rapidly induced by robust activity and subsequently integrated into NP1 assemblies at excitatory synapses.[630-633,650] Once these mixed pentraxin assemblies form, their homologous C-terminal domains promote AMPA-type glutamate receptor clustering, effectively increasing synaptogenic activity within the stimulated dendrite segment.[650] Further, as a direct consequence of localized Narp-mediated changes in glutamate receptor distribution and activity, the potentiation of excitatory signaling drives dendritic branching morphogenesis and synapse strengthening in tandem.[15,144,154,508,617,630-633,650] For example, nascent contacts between RGCs and optic tectal neurons are initially characterized by a large proportion of silent synapses, mediated by NMDA receptors, which subsequently recruit AMPA-type receptors as activity increases and synapses are stabilized.[15,144] Since active Narp/NP1 assemblies co-cluster AMPA-type receptors with pre-existing NMDA receptors at these developing excitatory synapses, reinforcing intracellular signaling cascades can efficiently promote ongoing structural and functional maturation of neuronal circuits.

A third key group of immediate-early genes activated through glutamatergic signaling comprises the candidate plasticity genes (CPGs), which encode transcription factors important for establishing functional CNS circuits and modulating structural plasticity during synaptogenesis.[151-155,634] Of the CPGs identified to date, the most completely characterized is CPG15, or *neuritin*,[155] encoding a small activity-regulated protein anchored to the extracellular cell surface by a glycosyl-phosphatidylinositol (GPI) linkage. Because of this structural motif, CPG15 is highly mobile within the plasma membrane, allowing it to act as a local cell-surface growth-promoting molecule for closely apposed neurons.[151-154,634] CPG15 is widely expressed by neuronal populations within the visual, auditory, and olfactory systems during the sequential stages of dendritic branching, afferent innervation, and synaptogenesis.[151-155,634] For example, during visual system development, CPG15 is expressed by presynaptic RGCs and also by postsynaptic optical tectal neurons, suggesting a regulatory pathway which may coordinate the differentiation of multiple neuronal structures that comprise functional synapses.[151-154,634] Indeed, the current understanding of *Xenopus* visual system maturation proposes that visual activity induces local expression of CPG15 within the developing RGC axonal domain, in turn stimulating dendritic differentiation for target optic tectal neurons.[152,153] In parallel, CPG15 expressed by optic tectal neurons is transported to their axonal domains, and is thought to influence dendritic arborization for postsynaptic target neurons in a cell non-autonomous manner.[152,153] Moreover, postsynaptic tectal neuron expression of CPG15 has been observed to

reciprocally enhance the elaboration of presynaptic RGC axons, promoting the formation and maturation of functional retinotectal synapses through the recruitment of non-NMDA glutamate receptors.[154]

Considered together, the various developmental roles served by activity-induced IEG expression demonstrate a similar high degree of spatiotemporal control. It is likely that such regulation is critical for orchestrating the local progression of branching morphogenesis and synaptogenesis through the integration of complex intracellular signaling cascades.

Future Directions

Within the developing vertebrate nervous system, strict control of morphogenesis is essential since the geometry of neuronal arbors critically influences the establishment of physiologically appropriate circuitry. As such, one aim of intense study within recent decades has been to identify and characterize the specific molecules and cellular mechanisms underlying spatiotemporal control of neuronal branching. Tremendous progress has been made toward identifying extracellular cues that stimulate or inhibit branching, and intracellular pathways leading to cytoskeletal reorganization as branching proceeds. However, many aspects of neuronal branching morphogenesis remain poorly understood. In the future it will be important to determine: (1) the relative importance of developmental critical periods versus spatiotemporal restriction of neuron exposure to epigenetic cues in producing appropriate arborization patterns, (2) the different subcellular effects stimulated by local versus global neuron exposure to epigenetic cues known to affect branching, (3) the role of cell-autonomous programs of background gene expression in conjunction with gene induction triggered by changing epigenetic cues, (4) the combinatorial branching effects generated by multiple cues within the extracellular milieu, and the mechanisms involved in integrating these complex signaling cascades, and (5) the pathways involved in synchronizing axonal and dendritic arbor plasticity changes throughout synaptogenesis, first as the CNS develops and later during learning and memory consolidation.

Facilitating these studies, recent advances in high-resolution real-time imaging of living neurons will allow direct observation of the formation and maturation of neuronal arbors. In this way, delayed interstitial branching and collapse-induced branching can be examined under a variety of conditions that enhance, perturb, or direct branch outgrowth. In addition, recent developments in microcontact printing and magnetic patterning techniques, designed to control the positioning of individual neurons forming cellular circuits in vitro,[649] may prove to be a powerful tool for studying cell-cell interactions involved in triggering or abolishing branching. The ability to employ green fluorescent protein (GFP)-tagged protein constructs, or inject fluorescent dyes and molecular probes, will greatly enhance visualization of the interplay between microtubules, MAPs, molecular motor proteins, and actin filaments throughout branching morphogenesis. Moreover, real-time imaging of these cytoskeletal elements will be imperative for unraveling the precise sequence of subcellular reorganization underlying discrete stages of branching morphogenesis. In combination with this technique, neurons undergoing behaviors of interest will need to be fixed and prepared for EM imaging and 3-D reconstruction in order to characterize the full complement of ultrastructural changes occurring during successive stages of branch formation. Elucidating the complex combination of molecular pathways regulating branching morphogenesis will be greatly aided by advances in proteomics and recombinant gene technology, together with the availability of a wide array of genetic mutants.

One of the greatest challenges in the field of developmental neuroscience is first to identify the molecules and mechanisms both necessary and sufficient for regulating branching in all neuronal cell-types, and then to determine the relative importance of cell context and ontogenetic history in sculpting cell-type-specific arbors. Future studies in these underrepresented areas of investigation will be critical for a more complete understanding of neuronal branching morphogenesis.

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