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Review article

Branching mechanisms shaping dendrite architecture

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ABSTRACT

A neuron's contribution to the information flow within a neural circuit is governed by the structure of its dendritic arbor. The geometry of the dendritic arbor directly determines synaptic density and the size of the receptive field, both of which influence the firing pattern of the neuron. Importantly, the position of individual dendritic branches determines the identity of the neuron's presynaptic partner and thus the nature of the incoming sensory information. To generate the unique stereotypic architecture of a given neuronal subtype, nascent branches must emerge from the dendritic shaft at preprogramed branch points. Subsequently, a complex array of extrinsic factors regulates the degree and orientation of branch expansion to ensure maximum coverage of the receptive field whilst constraining growth within predetermined territories. In this review we focus on studies that best illustrate how environmental cues such as the Wnts and Netrins and their receptors sculpt the dendritic arbor. We emphasize the pivotal role played by the actin cytoskeleton and its upstream regulators in branch initiation, outgrowth and navigation. Finally, we discuss how protocadherin and DSCAM contact-mediated repulsion prevents inappropriate synapse formation between sister dendrites or dendrites and the axon from the same neuron. Together these studies highlight the clever ways evolution has solved the problem of constructing complex branch geometries.

1. Introduction

Higher order functions of the human cortex such as consciousness, creativity, language, sensory perception, learning and memory are dependent on the ability of many different neuronal populations to relay information to and from other cortical areas and subcortical regions in a highly synchronized manner. The unique stereotypic architecture of individual neuronal subtypes is fundamental to their ability to integrate into functional neuronal circuitry and dictates the extent and quality of information flow across the neural network. In both vertebrates and invertebrates, functional integration of neuronal activity is achieved through the projection of elaborately branched dendritic trees into multiple target areas. For each neuronal subtype throughout the nervous system the geometry of the dendritic tree directly determines synaptic density, size of the receptive field and type of synaptic input, all of which influence the firing pattern of the neuron (Dong et al., 2015). In the context of the neocortex abnormal dendritic branching can generate diminished or excessive synaptic connectivity, leading to impaired cognitive function, memory acquisition and motor coordination, and is associated with neurodevelopmental conditions, including autism and schizophrenia, and neurodegenerative disorders, such as Alzheimer's disease (Cochran et al., 2014; Forrest et al., 2018; Martínez-Cerdeño, 2016).

The geometry of the dendritic tree is unique to each neuronal subtype (see Fig. 1 for examples) and is regulated by the complex interplay between extrinsic and intrinsic factors. Environmental factors impinge on pivotal intracellular signalling pathways to determine the position of the branch point along the shaft, branch length and the degree and orientation of branching. Short- and long-range guidance cues, including the Wnts and Netrins, control the choice of branch point and navigation to the target, and also limit expansion into nonpermissive territories. Repulsive receptors such as DSCAM and the clustered protocadherins ensure that dendrites fill all available space within their predetermined territories by preventing overlap between dendrites from the same neuron. Here we review the molecular and cellular mechanisms that promote dendritic branching and constrain growth within the developing brain. We specifically focus on the role of the actin cytoskeleton and the cell surface receptors and downstream effectors that regulate actin remodelling. In many instances axonal growth and branching employ equivalent mechanisms (reviewed in detail: Kalil and Dent, 2014; Schelski and Bradke, 2017; Stoeckli, 2018). Hence we will draw on our knowledge of this field to provide further insights into dendrite morphogenesis.

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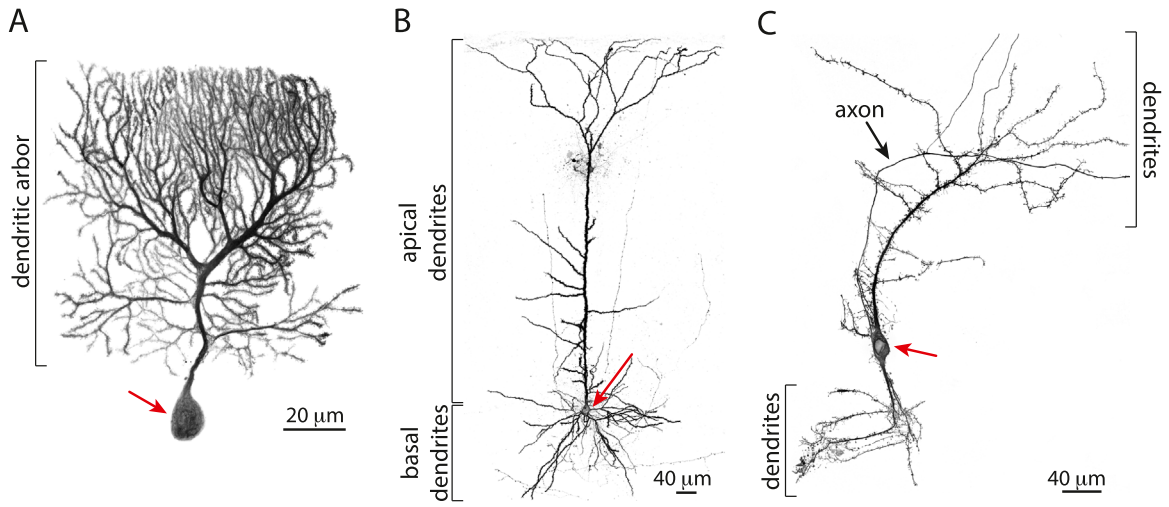

Fig. 1. The unique stereotypic architecture of individual neuronal subtypes is fundamental to their ability to integrate into functional neuronal circuitry. High-resolution confocal images of (A) a Purkinje cell from the adult mouse cerebellum. Purkinje cells extend their dendrites into the molecular layer of the cerebellum where they receive excitatory inputs from parallel and climbing fibers, and inhibitory inputs from basket and stellate cells. (B) a thick-tufted layer 5 pyramidal neuron from the rodent primary visual cortex. These neurons receive excitatory inputs on their basal and proximal apical dendrites and inhibitory inputs predominantly on their basal dendrites and distal apical dendrites. (C) a cultured mouse hippocampal neuron which has adopted a pyramidal dendritic morphology similar to that seen in vivo. Hippocampal pyramidal cells receive most inhibitory inputs on their proximal dendrites, whereas excitatory inputs preferentially target distal dendrites. Red arrow indicates neuronal soma.

2. The birth of dendrites and axons

Neurons are highly polarized and morphologically complex cells comprising a single axon and an elaborate dendritic tree (dendritic arbor) (Fig. 1). Dendrites and axons are spatially and morphologically discrete neurite compartments (Fig. 2) defined by distinct protein and lipid compositions. Although not the focus of this review, we present a brief overview of the developmental events driving dendrite formation that precede branching (for detailed reviews see Bentley and Banker, 2016; Schelski and Bradke, 2017; Yogev and Shen, 2017). Induction of neuronal polarity in a newborn neuron to generate a single long axon and multiple shorter dendrites is a highly regulated process involving both intrinsic and extrinsic signals. This process is best exemplified in hippocampal neuronal cultures in which the axon and dendrites emerge in a specific temporal sequence (Dotti et al., 1988; Goslin and Banker, 1989; Yogev and Shen, 2017). Initially, neurons extend and retract multiple short neurites in random directions. Symmetry is broken when one neurite undergoes prolonged extension and adopts axonal characteristics. The remaining neurites subsequently transform into dendrites. Axonal or dendritic identity is dependent on their distinct cytoskeletal configurations. The emerging axon contains periodic actin rings underlying the plasma membrane which advance distally as the axon grows (He et al., 2016), whereas actin rings are less prominent in dendrites. Although yet to be confirmed, it is thought that these rings are integral to neurite stability. Axonal processes also comprise stable microtubule arrays with plus-ends exclusively oriented away from the cell body, whereas microtubule filaments in mammalian dendrites are less stable, thinner and exhibit mixed orientation (Baas et al., 1988; Yogev and Shen, 2017). Maturation into distinct dendritic and axonal compartments is accomplished through differential sorting of dendritic and axonal proteins into discrete vesicular populations which are then selectively transported along microtubules into the growing dendrites or axon (Al-Bassam et al., 2012; Bentley and Banker, 2016; Burack et al., 2000).

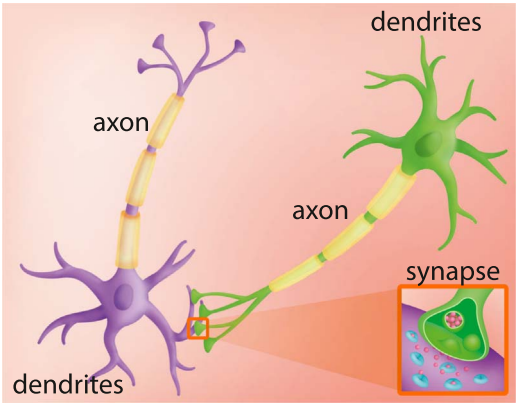

Fig. 2. Neurons are highly polarized and morphologically complex cells comprising a single axon and an elaborate dendritic tree (dendritic arbor). Electrical signals (axon potentials) travel down the axon to the terminals where they trigger the release of neurotransmitters from the presynaptic membrane. The neurotransmitters then stimulate specialized ion channels and other signalling pathways in the postsynaptic membrane to initiate or inhibit neuronal activity. The outcome of synaptic transmission is determined by the excitatory or inhibitory nature of the presynaptic neuron.

3. Initiation of dendrite branching

As maturation progresses, dendrites elaborate highly stereotypic and often highly complex branched architectures. Expansion of the dendritic arbor is under strict spatiotemporal control. New dendritic branches arise from dynamic filopodial protrusions, actin-rich microstructures that rapidly extend and contract along the entire dendritic shaft. Blocking the polymerization of F-actin with cytochalasin D in early neurite development prevents filopodia formation and neurite outgrowth (Dent et al., 2007). Moreover, filopodia extension is also governed by local environmental cues.

Establishment of the stereotypic geometry of a dendritic arbor requires that the branch emerges at a preprogramed position along the dendrite shaft. The molecular mechanisms that select this critical point are not well understood. However, an elegant mechanism promoting the spatially-restricted initiation of axonal branching has recently been uncovered in *C.elegans* where opposing Wnt (CWN in *C. elegans*) gradients confine actin polymerization precisely to the prospective branch point (C.H. Chen et al., 2017) (Fig. 3). An anterior-high CWN-1 gradient induces actin depolymerization along the anterior shaft, whereas a posterior-high CWN-2 gradient prevents actin assembly in the posterior shaft. Hence, actin polymerization, and thus filopodium extension, occurs only at the point where the concentration of both Wnts is minimal. Inappropriate actin deposition along the shaft occurs in the absence of both Wnts, leading to ectopic branching. In this

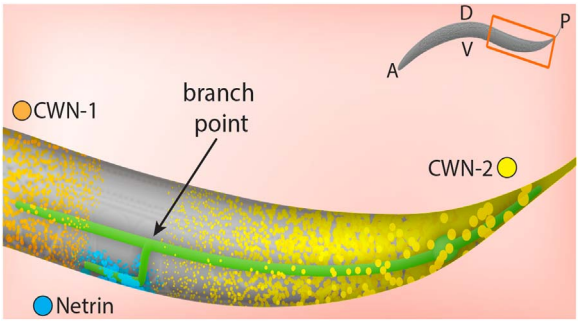

Fig. 3. In the *C.elegans* PLM axon the choice of branch point along the shaft is defined by opposing Wnt (CWN) gradients in the underlying tissue. Actin polymerization and filopodial extension are precisely confined to the prospective branch point where the concentration of both Wnts is minimal. Orientation of branch extension is then determined by a ventral-high, dorsal-low Netrin gradient in the tissue underlying the branch point.

system orientation of branch extension is also reliant on the Netrin guidance cue and its attractive receptor DCC (UNC-6 and UNC-40 in the worm) (C.H. Chen et al., 2017). A ventral-high Netrin gradient is established in the tissue underlying the future branch point and activation of UNC-40/DCC within the Netrin gradient promotes nascent branch outgrowth towards the ventral side (Fig. 3). Given that the Wnt and Netrin signalling pathways are highly conserved across species and between axons and dendrites, it is likely that these extrinsic cues fulfil a similar instructive role in the specification of dendrite branch points.

Microtubule nucleation and extension at branch points are essential for dendrite branching, growth and stabilization. Microtubule polymerization maintains the structural integrity of the expanding dendritic tree by facilitating the distribution of key organelles, protein complexes and lipids along the growing branch. Central to efficient microtubule-based vesicular trafficking along the shaft are the microtubule motors. Both kinesin- and dynein-motor complexes are evolutionarily conserved and mutations in components of these complexes result in repositioning of branch points close to the cell body (Satoh et al., 2008; Zheng et al., 2008). In addition, prevention of cargo engagement with kinesin through the mutation of adaptor proteins such as GRIP also reduces branch formation (Geiger et al., 2014).

Components of the protein synthesis and secretory machinery can be recruited to the branch point to facilitate dendrite branching and extension. Dendrite branching and growth are dependent on microtubule minus end-directed transport of the endoplasmic reticulum (ER; Aridor et al., 2004; Cui-Wang et al., 2012). A continuous network of ER pervades the dendritic shaft and newly synthesized membrane proteins, including synaptic ion channels, are concentrated within regions of the ER membrane adjacent to nascent branches. Fragments of the Golgi complex, known as Golgi outposts, are also found at prospective branch points and are correlated with initiation sites for microtubule nucleation in highly branched arbors (Horton et al., 2005; Ori-McKenney et al., 2012; Ye et al., 2007). However, a mandatory role

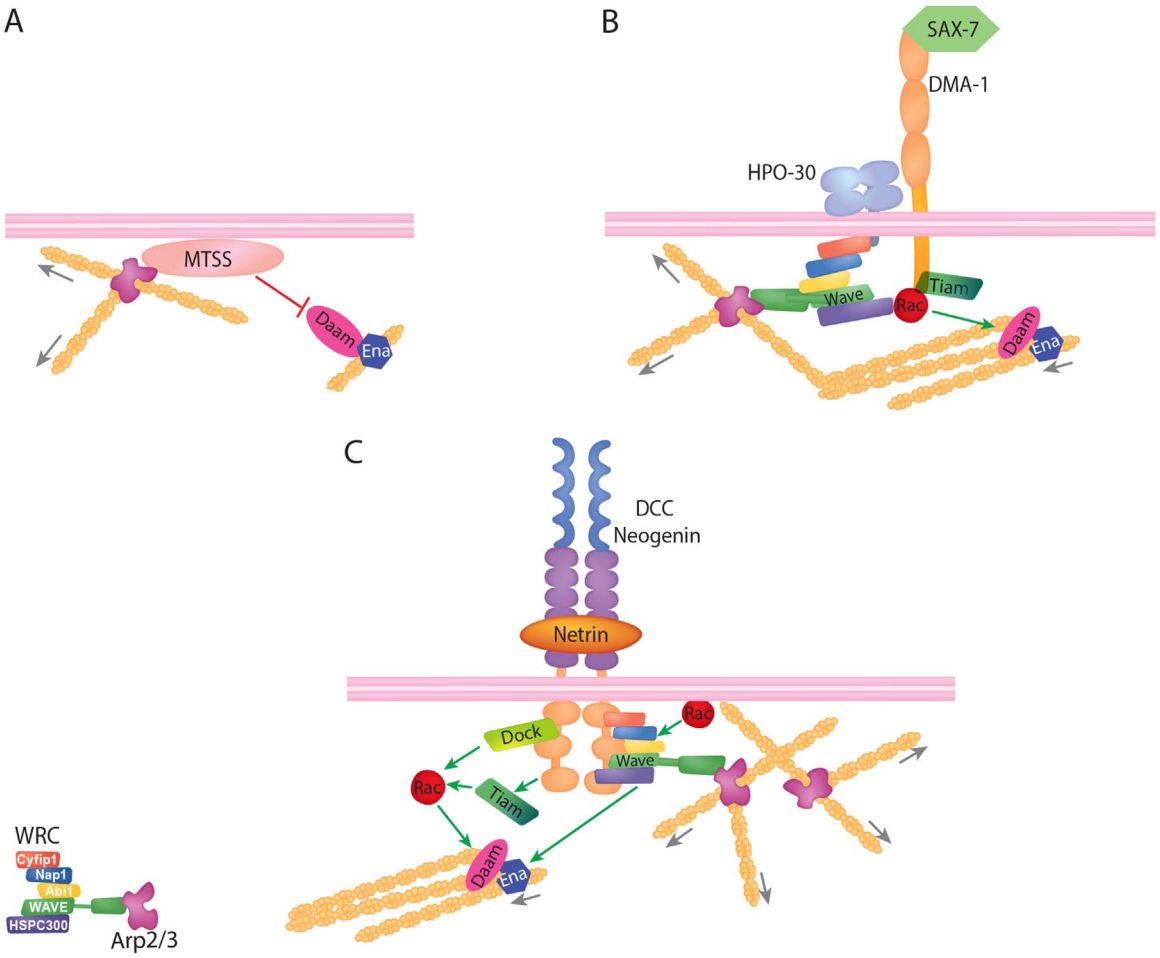

Fig. 4. Signalling pathways controlling dendrite branching. (A) MTSS1 acts to fine-tune the actin cytoskeleton by regulating the balance between linear and branched actin filaments. (B) The WRC and Tiam1 are anchored to specific points along the dendritic shaft through their interaction with the coreceptors HPO-30 and DMA-1 and ensure coordinated actin nucleation of the linear and branched actin networks at the preprogramed branch point. The DMA-1 ligand, SAX-7, is expressed in the underlying tissue. (C) Netrin, its cell surface receptors DCC and Neogenin, and their downstream effectors ensure synergistic linear and branched actin nucleation through a signalling hub centred on the WRC. Actin nucleation and elongation factors then work in unison to ensure that the information encoded in the local environment is effectively transmitted to the actin cytoskeleton.

for Golgi outposts in branch extension remains controversial as there is evidence that localization of Golgi outposts at branch points is not always a prerequisite for microtubule nucleation (Nguyen et al., 2014; Ye et al., 2007).

4. Actin remodelling drives growth and branching

In axonal and dendritic filopodia the actin cytoskeleton is a dynamic structure in which actin filaments undergo continual turnover (Kalil and Dent, 2014; Siton-Mendelson and Bernheim-Groswasser, 2017). Actin nucleation is energetically unfavourable and is thus the rate-limiting step for assembly of unbranched actin. Nucleation promoting factors such as Daam1 and Cordon-bleu (Cobl) promote *de novo* nucleation and extension of linear actin within axonal and dendritic filopodia, and are directly regulated by the Rho GTPases (Fig. 4) (Siton-Mendelson and Bernheim-Groswasser, 2017). Cobl overexpression accelerates actin filament formation, leading to excessive dendrite branching, whereas the dendritic tree is markedly simplified after Cobl depletion (Ahuja et al., 2007). Similarly, loss of Daam1 results in failed dendrite arborization (Colombo et al., 2013). After nucleation, elongation factors such as Ena/VASP continuously promote the addition of G-actin to the barbed end of the growing filament (Fig. 4) (Siton-Mendelson and Bernheim-Groswasser, 2017). Ena/VASP promotes profilin-catalysed actin polymerization, thereby increasing filopodia activity and enhancing neurite growth and branching (Kalil and Dent, 2014; Lebrand et al., 2004), and its loss disrupts dendrite branching (Gao et al., 1999). Ena/VASP, activated by Rho GTPases, lies downstream of many receptors known to control filopodial activity, including adhesion and guidance receptors (Fig. 4). Therefore actin nucleation and elongation factors work in unison to ensure that the information encoded in the local environment is effectively transmitted to the actin cytoskeleton.

In contrast to the axon, dendritic filopodia also contain a branched actin network (Korobova and Svitkina, 2010). Arp2/3, a 220 kDa heptameric enzyme complex, initiates branching from the pre-existing actin filament at a 70 degree angle (Kawabata Galbraith et al., 2018; Pizarro-Cerdá et al., 2016). The Arp2/3 complex is an inefficient actin nucleator and requires activation by nucleation promoting factors, including the WASP (Wiskott-Aldrich Syndrome Protein) family members, WAVE and N-WASP (Fig. 4) (Pizarro-Cerdá et al., 2016). Overexpression of N-WASP in cultured hippocampal neurons results in an increased number of dendritic branches, whereas blocking the N-WASP-Arp2/3 interaction leads to a reduction in distal branching and a concomitant increase in proximal branching (Nakamura et al., 2011). Within dendritic filopodia, linear and branched actin remodelling must be tightly coordinated. This is highlighted during the morphogenesis of the highly branched Purkinje arbor (Fig. 1). MTSS1, an I-BAR protein, couples bending of the plasma membrane with the recruitment and upregulation of Arp2/3 actin nucleation (Fig. 4A) (Kawabata Galbraith et al., 2018). Moreover, MTSS1 directly binds G-actin through its WASP homology domain and inhibits actin assembly by directly interacting with Daam1. Therefore, MTSS1 acts to fine-tune the actin cytoskeleton by regulating the balance between linear and branched actin filaments. Loss of MTSS1 decreases the complexity of the Purkinje dendritic tree and mutant mice display cerebellum-associated neurological and behavioural deficits (Kawabata Galbraith et al., 2018).

Tight spatiotemporal control of Arp2/3 activity is also achieved through its association with the WAVE Regulatory Complex (WRC), comprising 5 subunits organised into the WAVE/Abi/HSPC300 and Cyfip1/Nap1 subcomplexes (Chen et al., 2014, 2010) (Fig. 4). The WRC has also been implicated in the regulation of linear actin filament extension via the Ena/VASP pathway (Hayashi et al., 2014). I-BAR proteins recruit the WRC and Arp2/3 to the plasma membrane (Kawabata Galbraith et al., 2018). However, the mechanism by which the branched actin nucleation machinery is spatially-restricted to a specific point along the membrane is poorly understood. In the highly branched PVD *C.elegans* neuron, the WRC and the Rac guanine nucleotide exchange factor (GEF), Tiam1, are anchored to specific points along the dendritic shaft through their interaction with the coreceptors HPO-30 and DMA-1, respectively (Fig. 4B) (Zou et al., 2018). Precise localization of this receptor complex is achieved through the interaction between DMA-1 and its ligand, SAX-7, which is expressed in a striped pattern in the underlying tissue that correlates with the positions of the tertiary and quaternary branches. This elegant mechanism ensures synergistic actin nucleation of both linear and branched actin networks at the exact branch point.

5. Rho GTPases coordinate actin dynamics

Spatiotemporal regulation of actin polymerization is coordinated through the Rho GTPases, including RhoA, Rac1 and Cdc42, which govern the directionality of cell motility by directly linking a diverse array of actin modulators to upstream signalling molecules and cell surface receptors (reviewed in Hodge and Ridley, 2016). In the context of dendrite morphogenesis, loss of dendritic complexity is observed for mammalian hippocampal and *Drosophila* neurons when Rac1 activity is inhibited or RhoA is hyperactivated (Lee et al., 2003; Nakayama et al., 2000). GTPase downstream effectors that impinge on actin polymerization, including Daam1 and Cobl, are important mediators of dendrite growth and branching (Ahuja et al., 2007; Colombo et al., 2013; Hodge and Ridley, 2016). Cdc42 and Rac1 also prevent actin disassembly by directly activating the serine/threonine kinase Pak1, which in turn inhibits the actin depolymerizing enzyme cofilin via LIM kinase (Edwards et al., 1999). Pak1 is a central player in dendrite branching as dominant-negative Pak1 suppresses dendrite complexity, whereas constitutively active Pak1 increases branching in hippocampal neurons (Hayashi et al., 2007). Conversely, constitutively active RhoA prevents expansion of the dendritic tree in mammalian retinal ganglion and hippocampal neurons (Nakayama et al., 2000; Wong et al., 2000). RhoA inhibition of dendritic branching is known to be dependent on the downstream effector ROCK (Nakayama et al., 2000) and ROCK activation of LIM kinase prevents cofilin-mediated severing of F-actin, thereby suppressing dynamic actin remodelling and neurite outgrowth (Sarmiere and Bamburg, 2004).

The small GTPases cycle between an inactive GDP-bound and an active GTP-bound state, a process tightly regulated by guanine nucleotide exchange factors (Hodge and Ridley, 2016). The Rac GEFs Tiam1 and Dock1 (also known as Dock180) play key roles in dendrite morphogenesis as silencing their GEF activity reduces dendritic complexity (Fig. 4) (Lanoue et al., 2013; Tolias et al., 2005). Although GEFs and Rho GTPases directly affect the filopodial cytoskeleton, they also modulate other actin-dependent processes affecting dendritic branching. The exquisitely complex branch structure of Purkinje neurons (Fig. 1) is critically dependent on Dock1, its coreceptor ELMO1 and the upstream receptor BAI3 (Lanoue et al., 2013). BAI3 (Brain Angiogenesis Inhibitor 3) is a member of the adhesion G protein-coupled receptor family and has been linked to schizophrenia (DeRosse et al., 2008). Transgenic mice expressing a dominant-negative BAI3 mutant exhibit excessive Purkinje branching, indicating that the BAI3/ELMO/Dock1 pathway plays a central role in limiting branching (Lanoue et al., 2013). At first sight, inhibition of branching through the activation of Rac1 appears contradictory. However, BAI receptors are known to promote engulfment via ELMO/Dock (Park et al., 2007), suggesting that BAI3 may control branching through membrane recycling, a process also dependent on the actin cytoskeleton.

6. Charting dendritic territories

During the developmental period, exuberant extension and retraction of nascent dendritic branches allow the neuron to explore potential territories. Exploration of the local environment is mediated by highly dynamic filopodial protrusions at the tips of growing dendritic

branches which are able to detect and decipher a complex milieu of competing guidance cues. Long-range guidance cues form chemotactic gradients along the predetermined pathway. Membrane-bound or secreted short-range cues direct growth to intermediate and final targets. Attraction is achieved by asymmetrical actin filament extension towards the source of the cue, leading to filopodial protrusion and growth cone turning. Conversely, repulsion promotes asymmetrical actin depolymerization, leading to filopodial retraction, growth cone collapse and, ultimately, migration away from the cue. Rac1 and Cdc42 direct attractive growth cone turning, whereas RhoA induces repulsion (Dent et al., 2011; Hodge and Ridley, 2016; Shekarabi et al., 2005). Although all guidance families, including Ephrins, Slits and Semaphorins participate in dendritic growth and branching (Dong et al., 2015), we restrict our discussion to the Wnt and Netrin pathways which are arguably the best characterized. We will focus on the instructive roles played by these guidance cues in sculpting the dendritic tree. In particular, we have chosen examples that best illustrate the elegant ways evolution has solved the problem of specifying complex branch geometries.

6.1. Wnts: master regulators of dendritic morphogenesis

The Wnt family of extracellular ligands, through their cell surface receptors (Fzds, Ryk, Ror; Fig. 5), activate several distinct, but integrated, signal transduction pathways pivotal to embryonic development (Clark et al., 2012; Niehrs, 2012). The canonical (Wnt/β-catenin) pathway regulates stem cell proliferation and self-renewal, cell fate determination and axis formation by modulating gene expression. On the other hand, the noncanonical PCP and Wnt/Ca^{2+} pathways regulate polarity, migration and guidance through remodelling of the actin cytoskeleton via a β-catenin-independent mechanism. Signalling through each of the Wnt pathways, as well as crosstalk between them, plays a critical role in the establishment of the complex architecture of the vertebrate central nervous system.

The noncanonical Wnt pathways promote polarized filopodial activity by modulating actin dynamics, and as such, are positive regulators of dendrite growth and branching. The PCP pathway increases hippocampal dendrite growth and branching by promoting actin remodelling. Wnt7b increases dendrite complexity in hippocampal neurons via the Dvl/Rac1/JNK pathway, and the introduction of dominant-negative forms of Rac1 or JNK, or the loss of Dvl1, reduces complexity (Rosso et al., 2005). The loss of the core PCP pathway component, Vangl2, also significantly reduces dendrite complexity (Hagiwara et al., 2014), thereby confirming a central role for Wnt/PCP signalling in promoting dendrite arborization.

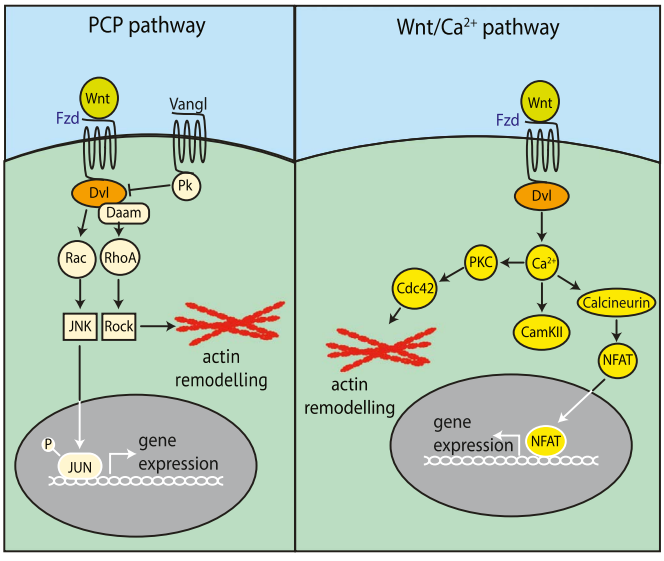

Fig. 5. Signalling through the noncanonical PCP and Wnt/Ca^{2+} pathways plays a critical role in the establishment of complex dendritic architecture. The noncanonical Wnt pathways modulate actin dynamics, and as such, can act as either positive or negative regulators of dendrite growth and branching. Detailed pathway descriptions can be found in Clark et al. (2012) and Niehrs (2012).

A recent study has linked mutations in *FZD9* to the increased dendrite growth and spine density observed in atypical Williams syndrome (Chailangkarn et al., 2016), demonstrating that Wnt signalling can also limit dendritic complexity. Individuals with Williams syndrome, a neurodevelopmental disorder, exhibit hypersociability and compromised cognitive and linguistic abilities. In postmortem cortical tissue layer 5/6 cortical dendrites were found to have an increased number of segments and branch points. A similar phenotype was seen in cortical neurons derived from patient induced pluripotent stem cells. This phenotype could be rescued by the GSK3 inhibitor, CHIR98014, implicating the involvement of the β-catenin pathway.

6.2. Ryk limits dendritic branching

Ryk, a noncanonical Wnt receptor, utilises the Wnt/Ca^{2+} pathway to concomitantly promote axon outgrowth and chemorepulsion (Keeble et al., 2006; Li et al., 2009; Liu et al., 2005). Recent studies suggest that Ryk is also a central player in limiting the extent of dendritic branching in the developing cortex and hippocampus (Clark et al., 2014; Lanoue et al., 2017). Loss of Ryk in mouse hippocampal and cortical neurons promotes excessive dendrite growth and branching in vitro, whereas overexpression of wildtype Ryk restricts branching. *Ryk* haploinsufficient postnatal mice exhibit excessive dendrite growth and branching in layer 2/3 pyramidal neurons of the somatosensory cortex, thereby confirming that it acts to restrain dendrite arborization in vivo (Lanoue et al., 2017). Notably, manipulation of Ryk activity impacts on secondary and higher order branching only, indicating that it plays a precise role in shaping the dendritic tree. Loss of Ryk in the primary motor cortex of the mouse has recently been shown to enhance the expansion of motor maps into adjacent cortical areas after spinal cord injury (Hollis et al., 2016). This raises the intriguing possibility that Ryk may influence the plasticity of cortical circuits by modifying dendritic structure to promote functional recovery.

In *Drosophila*, Wnt5a-Ryk (Derailed in *Drosophila*) interactions limit dendrite branching in order to confine dendritic territories on the adult epidermis (Yasunaga et al., 2015). Epidermal sensory dendrites cover the whole epidermis in stereotypic patterns restricted to predetermined territories. The boundary of the dendritic field in the ventral abdomen is defined by a tight band of Wnt5a produced by the underlying tissue. Wnt5a promotes Ryk-dependent dendritic termination through activation of RhoA via the Rho GEF Trio, and disruption of Ryk signalling results in dendrite overgrowth into inappropriate territories. In this instance, Ryk determines the outer limits of the dendritic territory rather than affecting growth or branching directly.

6.3. Wnts regulate dendrite branching in response to synaptic activity

Synaptic activity strongly influences dendritic arborization and activity-dependent induction of Wnt activity has been shown to be an important regulator of arborization. In hippocampal cultures the addition of KCl to mimic synaptic activity increases Wnt production and the number of branches through stabilization of β-catenin, whereas the Wnt antagonist Dickkopf, suppresses activity-dependent branching (Yu and Malenka, 2003). In a subsequent study, synaptic activity was shown to induce Wnt expression through activation of the CREB transcriptional complex (Wayman et al., 2006). Thus, the Wnt/β-catenin pathway regulates dendrite branching in response to synaptic activity.

Synaptic activity is also essential for the maintenance of dendritic arbors, and degeneration of dendritic structure is correlated with

cognitive decline, depression, schizophrenia and Alzheimer's disease (Cochran et al., 2014; Forrest et al., 2018; Martínez-Cerdeño, 2016). A recent study has identified Wnt5a as a critical cell-autonomous factor in the sustained maintenance of dendritic arbors in the adult mouse hippocampus (C.M. Chen et al., 2017). Selective knockdown of Wnt5a in CA1 pyramidal neurons induces severe degradation of dendritic structure, leading to impaired synaptic function and defects in spatial learning and memory. Remarkably, and in opposition to the commonly held belief that dendritic growth in the adult brain is extremely limited, substantial recovery of dendritic arborization was observed after replacement of endogenous Wnt5a. Wnt5a was shown to act through the noncanonical Wnt pathway by increasing CREB-mediated transcription of the NMDA receptor subunit GluA1, leading to enhanced synaptic activity.

6.4. Netrins sculpt the dendritic tree

It is now well established that Netrin and its receptors comprise a major molecular guidance system driving axon and dendrite morphogenesis in both vertebrates and invertebrates. Netrin promotes outgrowth and attraction or repulsion, depending on the developmental context. Attraction is mediated by DCC or Neogenin homodimers, whereas UNC-5 alone, or DCC-UNC-5 heterodimers promote repulsion (Bell et al., 2013; De Vries and Cooper, 2008; Hedgecock et al., 1990; Hong et al., 1999). The signal transduction cascades initiated by Netrin-DCC interactions have been dissected in some detail, revealing an intricate network of interactions involving intracellular tyrosine kinases, second messengers, calcium signalling, and Rho GTPases (Boyer and Gupton, 2018; Shekarabi et al., 2005; Sun et al., 2011). Attractive Netrin-DCC interactions activate both Rac1- and Cdc42-mediated actin polymerization resulting in filopodia extension towards the Netrin source. Conversely, Netrin-UNC-5 interactions induce RhoA-mediated actin disassembly and filopodia collapse.

Protrusive filopodial activity driving the attractive response to Netrin is dependent on linear actin polymerization regulated by the Rac GEF, Tiam1 (Fig. 4C) (Demarco et al., 2012). Ena/VASP lies downstream of the DCC-Tiam1 pathway, and is necessary but not sufficient for actin remodelling (Adler et al., 2006; Boyer and Gupton, 2018; Lebrand et al., 2004). In addition, DCC promotes actin assembly via Rac1 activation of the WRC which also binds and regulates Ena/VASP (Fig. 4C) (Bernadskaya et al., 2012; Havrylenko et al., 2015). Furthermore, the Rac GEF, Dock1 directly binds Netrin receptors and the Wave subunit of the WRC (Li et al., 2008; Namekata et al., 2010). This suggests that Netrin-DCC interactions may coordinate linear and branched actin polymerization within dendritic filopodia through the activation of a signalling hub centred on the WRC. The DCC paralogue, Neogenin, localizes the WRC and Arp2/3, and thus actin nucleation, to restricted regions of the plasma membrane through its C-terminal WRC interacting receptor sequence (WIRS) (Lee et al., 2016; O'Leary et al., 2017) (Fig. 4C). As DCC also contains a WIRS motif, this provides a plausible molecular mechanism through which to convey the spatial information contained in Netrin gradients to the actin cytoskeleton. As the WIRS motif is also present in other receptors known to regulate neurite growth and guidance, including UNC-5D, the Slit receptor Roundabout (Robo) and the protocadherins (Chen et al., 2014), this is likely to be an important general mechanism regulating the choice of the dendritic branch point and the elaboration of complex dendritic trees.

As in axon guidance, Netrin acts as a long-range guidance cue for dendrites and collaborates with other guidance systems to precisely define dendritic territories. *Drosophila* leg motor neuron dendrites map onto their muscle targets in discrete stereotypic patterns. The position of the dendritic field is determined by the balanced response to attractive Netrin and repulsive Slit gradients (Brierley et al., 2009; Mauss et al., 2009). DA3 motor neuron branches are confined to lateral territories, whereas those from the LL1 neuron expand into the intermediate region. Coordinated spatial control of targeting is dependent on the relative activity of the Netrin and Slit receptors, DCC and Robo, on each dendrite type. Lateral targeting of DA3 dendrites requires high Robo and low DCC expression. Conversely, increased DCC activity relative to Robo permits dendrite invasion into the intermediate field. A reversal in the relative activities of these receptors results in expansion of dendrites into forbidden fields. Therefore, tight control of guidance receptor activity on the dendrite is key to defining the geometry of the dendritic field.

Restriction of Netrin-DCC activity exclusively to the dendrite has also been observed in the *C.elegans* DA9 neuron (Teichmann and Shen, 2011). In this neuron Netrin acts in a short-range mode to promote dendritic growth, but not guidance, through dendrite-restricted DCC activity. DCC signalling is confined to the dendrite by the downstream serine-threonine kinase, PAR4, which is also restricted to the dendritic compartment. Confinement of DCC activity to the dendrite is important as Netrin-UNC-5 interactions induce repulsive axon guidance in the same neuron. Inappropriate axonal localization of DCC and its effectors, or expansion of UNC-5 into dendrites, leads to aberrant axonal and dendritic projections (Poon et al., 2008; Teichmann and Shen, 2011). Therefore, the asymmetric distribution of receptors and downstream signalling components in axons and dendrites enables independent responses within the same Netrin expression domain.

7. Avoiding the relatives

Dendrites do not intersect with sister dendrites or the axon from the same neuron, thereby ensuring maximum coverage of the neuron's receptive field. On the other hand, dendrites from neighbouring neurons of the same subtype often make contact and also form functional synapses on target axons. This raises the intriguing question of how individual dendrites discriminate between self and non-self. Complex molecular self-avoidance strategies have evolved to prevent sister dendrite and axon overlap. These include the homophilic protocadherin and DSCAM adhesion receptors which rely on contact-mediated repulsion. Moreover, these adhesion receptors work in concert with other guidance mechanisms to fine-tune dendritic architecture. Failure in these mechanisms results in disruption to the neural network's receptive field and connectivity.

In mammals, an elegant solution to the self-recognition problem is provided by the protocadherin superfamily of homophilic adhesion receptors which has the capacity to generate a vast repertoire of isoform combinations. Protocadherins are encoded by 58 tandemly arrayed genes subdivided into the α, β and γ subfamilies. Trans homophilic binding between identical isoforms on opposing sister dendrites results in branch repulsion and maximum expansion of the dendritic tree (Lefebvre et al., 2012). Specificity is further enhanced by the ability of protocadherins to form cis tetrameric complexes between and within subfamilies. For each α, β or γ protocadherin gene, alternative splicing generates 14, 22, or 22 distinct isoforms, respectively (Kohmura et al., 1998; Wu and Maniatis, 1999). Stochastic promoter activity within each locus further boosts combinatorial diversity (Kaneko et al., 2006). Together these mechanisms have the capacity to generate millions of potential isoform combinations. Thus, each individual neuron will express a unique set of α, β and γ protocadherins, creating a private isoform code. Importantly, this elegant strategy avoids repulsive interactions between dendrites from neighbouring neurons as it is unlikely that two neurons of the same subtype will share the identical isotype combination.

A striking example of dendrite discrimination is the highly branched starburst amacrine cells (SACs) of the retina that respond to directional movement and then refine and transmit this information to the visual centres of the brain by forming synapses with other SAC subtypes. SAC dendrites interact with dendrites from 30 to 40 other SACs while avoiding contact with sister dendrites (Lefebvre et al., 2012). After SAC-specific inactivation of all γ protocadherin genes in

the mouse retina, SAC dendrites fail to repel sister dendrites resulting in the aberrant formation of autosynapses (Kostadinov and Sanes, 2015). In contrast, the forced expression of a single γ protocadherin isotype in all SACs prevents interaction between dendrites of adjacent SACs while maintaining self-avoidance between sister dendrites. Monitoring of circuit activity in the mutants revealed that these genetic manipulations profoundly affect information flow across the retina.

DSCAM adhesion receptors also promote self-avoidance through homophilic contact-mediated repulsion. In *Drosophila*, neuron-specific DSCAM1 codes are generated from extensive alternative splicing of ectodomain exons (Schmucker et al., 2000; Zipursky and Grueber, 2013). Combinatorial diversity generates over 38,000 unique isoforms which undergo selective isoform-specific binding (Miura et al., 2013; Neves et al., 2004; Wojtowicz et al., 2004, 2007). In vertebrates DSCAMs lack this immense molecular diversity, but still function as repulsive self-avoidance receptors (Fuerst et al., 2008). Evidence is now accumulating that self-avoidance mechanisms cooperate closely with other guidance cues to ensure the fidelity of dendritic geometry. In order to innervate neighbouring neurons, growing sister branches must also navigate together along the same pathway while experiencing DSCAM-mediated self-repulsion. DSCAM1 collaborates with Netrin to ensure sensory dendrites reach their targets while uniformly filling the available space within the target field (Matthews and Grueber, 2011). As dendrites expressing both DCC and DSCAM1 approach their Netrin-expressing target they undergo DSCAM1 repulsion. In the absence of DSCAM1, excessive dendrite accumulation occurs specifically at the target, indicating a failure in self-avoidance but not guidance. Conversely, loss of DCC alone results in the misprojection of dendrites into inappropriate regions, whereas dendrite spacing is unaffected. Thus, dendrite guidance and self-avoidance mechanisms work collaboratively to ensure correct targeting and prevent overcrowding.

Secreted guidance cues can also be redeployed to directly impose dendritic self-avoidance. In the absence of the *C.elegans* netrin, UNC-6, repulsion between sister dendrites is prevented (Smith et al., 2012). In this instance, netrin activity requires both the attractive receptor, UNC-40/DCC and the repulsive receptor UNC-5. These observations lead to a novel two-step model in which UNC-40/DCC first captures netrin at the growing dendrite tip and then presents it to UNC-5 on the opposing dendrite, thereby initiating a repulsive response.

8. Conclusion

Santiago Ramón y Cajal won the 1906 Noble Prize in Physiology or Medicine for his pioneering work in neuroanatomy where he revealed for the first time "*cells with delicate and elegant shapes*" (Ramón y Cajal, 1889). This review highlights the tremendous advances that have been made over the past 120 years in our understanding of the fundamental principles governing the construction of dendritic arbors. As underscored here, the genetic manipulation of both vertebrate and invertebrate models, coupled with sophisticated, high-resolution imaging techniques, has provided invaluable insights into the clever ways evolution has solved the problem of constructing complex branch geometries. We now have a robust understanding of how information contained in the local environment of the expanding dendritic tree is interpreted by cell surface receptors and transmitted by their downstream effectors to coordinate linear and branched actin remodelling, the driving force underpinning dendrite growth and branching. In particular, these studies have revealed the elegant molecular strategies employed to ensure maximal coverage of the dendritic field while constraining growth and branching within predetermined territories.

Nonetheless, our understanding of some critical processes regulating dendritic morphogenesis remains rudimentary. As individual neuronal subtypes have unique stereotypic branch structures, they each must employ a neuron-specific repertoire of surface receptors and downstream effectors in order to correctly initiate and extend nascent branches within a highly complex milieu of extrinsic cues. Moreover, the activity of these mediators must be spatiotemporally regulated as the growing branches explore new territories. Several major questions remain to be comprehensively investigated: what is the composition of the neuron-specific repertoire of surface receptors and effectors and how are their expression profiles and cellular localization coordinated in space and time? What are the general principles that govern the hierarchy of signalling pathways, and thus, the output of the integrated signalling network? Finally, the transcriptional programs that endow each neuronal subtype with their individual identities are yet to be deciphered. With the advent of single cell genomics, transcriptomics and proteomics, a more comprehensive picture of the molecular networks that oversee the elaboration of unique dendritic architectures will soon emerge.

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