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Signaling Pathways Regulating Axogenesis and Dendritogenesis in Sympathetic Neurons

Vidya Chandrasekaran

Abstract

The post-ganglionic sympathetic neurons play an important role in modulating visceral functions and maintaining homeostasis through complex and reproducible axonal and dendritic connections between individual neurons and with their target tissues. Disruptions in these connections and in sympathetic nervous system function are observed in several neurological, cardiac and immune-related disorders, which underscores the need for understanding the mechanisms underlying neuronal polarity, axonal growth and dendritic growth in these neurons. The goals of this chapter are to explore our current understanding of the various growth factors, their signaling pathways, downstream effectors and interplay between these pathways to regulate different stages of axonal and dendritic growth in sympathetic neurons.

Keywords: sympathetic neurons, growth factors, neurotrophins, cytokines, BMPs, axons, dendrites

1. Introduction

The sympathetic nervous system is an important component of the peripheral autonomic nervous system responsible for controlling the visceral functions of the body to maintain homeostasis and the “flight or fight response” [1]. The sympathetic pathway is composed of two neurons – a preganglionic neurons located in the intermediolateral horn of the spinal cord, originating from the thoracolumbar region of the spinal cord and the postganglionic neuron that is, in most cases, located in the paravertebral sympathetic ganglia chain on either side of the spinal cord. Some of the preganglionic axons synapse with pre-vertebral sympathetic ganglia such as the celiac, mesenteric and pelvic ganglia, which innervate the gastrointestinal and urinary tracts and are not part of the sympathetic chain [2]. The superior cervical ganglia (SCG) is the first and the largest ganglia in the sympathetic chain and innervates most of the tissues in the head and neck region including the pineal gland, cerebral blood vessels, carotid body, vestibular system, muscles in the iris, lacrimal glands and piloerector muscles. Of the sympathetic neurons, SCG neurons are one of the most studied to understand various aspects of neuronal development in the peripheral nervous system. In recent years, the observation of autonomic dysfunction in many diseases such

as Parkinson's disease, cardiac disorders, multiple system atrophy, multiple sclerosis, diabetes and immune-related disorders, has renewed an interest in understanding neuronal development and maintenance of sympathetic neurons [3–11].

During early development, the precursors of the post-ganglionic sympathetic neurons are derived from the trunk neural crest cells, which then migrate ventrally along the neural tube, through the anterior portion of the sclerotome and coalesce near the dorsal aorta to form the sympathetic ganglia [12]. In rodents, the neural crest migration occurs between E8 and E11, with cells forming coalesced sympathetic ganglia around E12–E14 with the more rostral ganglia forming before the caudal ones. Studies on the early sympathetic neuron specification and neural crest migration show that growth factors such as neurotrophins, semaphorins and ephrins are important for migration of these neural crest cells, with bone morphogenetic proteins (BMPs) being important for their differentiation into sympathetic neuronal lineage. The exposure to BMPs leads to the induction of transcription factors such as *Phox2b*, *Mash1*, *Hand2*, *Gata3*, *Insm1*, *Sox4* and *Sox 11*, which lead to the survival of these neurons and their differentiation into noradrenergic neurons [12]. Following the specification of these neurons, the next crucial step to create a functional sympathetic network is the extension and maturation of axons and dendrites. In this chapter, we will explore the pathways that are important for establishing and refining axonal and dendritic arbors in sympathetic neurons.

2. Growth factors and signaling pathways involved in axonal growth

Following the specification of sympathetic neurons, the first sign of neuronal polarity is the extension of a single axon from the cell body [13]. In rodents, although the initiation of axonal growth from sympathetic ganglia starts as early as E12, most of the axonal growth occurs around E14–E15, with target innervation continuing into first few weeks of postnatal life [13–15]. Axonal growth has three stages – initiation of axons from the post-ganglionic neurons, elongation of the axons towards the final targets and finally target innervation which involves branching as well as restriction of axonal growth. Research using cultured sympathetic neurons *in vitro* and *in vivo* studies have identified multiple growth factors, extracellular matrix molecules and downstream signaling targets, involved in different stages of axonal growth and axonal guidance, functioning either as activators or inhibitors of axonal growth. In this section, we will examine the various molecules and their roles in these three stages of axonal growth.

2.1 Hepatocyte growth factor

Hepatocyte growth factor (HGF) or scatter factor is one of the few growth factors that appears to be involved in initiation of axonal growth in sympathetic neurons. Both HGF and its receptor Met tyrosine kinase are co-expressed in the sympathetic neurons throughout embryonic, starting as early as E12.5, with HGF being secreted by the sympathetic neurons and functioning as an autocrine regulator of axonal growth [16–18]. Treatment of cultured sympathetic neurons with HGF induces axonal growth and enhances the axonal growth promoted by nerve growth factor [16]. Also, inhibition of HGF activity through treatment with anti-HGF antibodies and *Met* signaling mutants show decreased axonal growth and branching compared to wildtype embryos [17–19]. Although HGF promotes survival of sympathetic neuroblasts, it is not necessary for the survival of post-mitotic sympathetic neurons [17].

Furthermore, *in vitro* studies and studies on docking site mutants for Met receptors suggest that HGF exerts its effects on axonal growth in mice through activation of the mitogen-activated protein kinase (MAPK) pathway and PI-3 K pathway [20]. Although lack of HGF signaling *in vivo* results in decreased axonal growth, it does not lead complete lack of axons in sympathetic neurons, suggesting the involvement of other factors in the first step of axonal growth.

2.2 Artemin

Artemin, a member of the glial derived neurotrophic factor (GDNF) family ligands (GFLs) plays an important role in the axonal elongation and guidance of the postganglionic axons to their targets [21–24]. In addition to Artemin, other members of the GDNF family, including GDNF and Nerturin have been shown to enhance neurite growth in subpopulations of sympathetic neurons [21, 22, 24]. Artemin mRNA is expressed at high levels near the dorsal aorta around E12.5 and then in the smooth muscles of many of the blood vessels along which the sympathetic axons migrate to their targets [25, 26]. The receptors for Artemin – Ret and GFRa3 are both expressed in the sympathetic ganglia as early as E11.5 and then expression gets restricted to subsets of cells later in embryonic development [26–29]. Treatment of nascent sympathetic ganglia (E13.5) with artemin induces axonal growth with axons showing branching and radial outgrowth. Also, axonal growth from explant cultures of the ganglia are directed towards beads coated with artemin, suggesting artemin has the ability to guide axons to their targets [30]. In addition, Artemin knockout mice show decreased axonal growth postnatally, [31] and mice lacking either GFRa3 or Ret show reduced, depleted or abnormal neuronal projections and abnormal branching indicating that Artemin signaling mediated by Ret:GFRa3 receptor complex is necessary for proper migration of sympathetic neurons during development [26, 28]. Although early studies suggest a role for Artemin in sympathetic neuron survival with the superior cervical ganglia being smaller in Artemin, Ret and GFR α 3 knockout animals compared to wild type animals [29, 32], more recent studies suggest that the decreased neuronal cell numbers in the absence of Artemin signaling are an indirect effect of aberrant axonal migration and target innervation [28]. Taken together, the data suggest that the members of the GDNF family act as early guidance molecules to promote axon elongation and target innervation.

2.3 Neurotrophins

Neurotrophin family of growth factors – nerve growth factor (NGF), neurotrophin-3 (NT-3), neurotrophin-4 (NT-4) and brain derived neurotrophic factor (BDNF) have been implicated in many aspects of neuronal function, including differentiation, survival, axonal growth and dendritic growth [33–37]. These neurotrophins are synthesized and secreted as proneurotrophins, which are the proteolytically cleaved to generate mature neurotrophins that activate different isoforms of Trk tyrosine kinase receptors (Trk) and p75 neurotrophin receptors (p75^{NTR}) and activate a variety of downstream signaling pathways [33–36, 38].

2.3.1 Nerve growth factor

NGF synthesis begins in targets of sympathetic neurons in concert with the arrival of the sympathetic axons and is correlated with increased expression of

TrkA [39–43]. Although NGF is necessary for survival for sympathetic neurons in the early stages, the neurons lose their dependence on NGF for survival in the later stages *in vivo* and *in vitro* [42, 44, 45]. Exposure of sympathetic neurons to exogenous NGF, overexpression of NGF in the target tissues or adding NGF to compartments containing the distal axons leads to increased axonal growth and hyperinnervation of the target tissues [46–51]. Conversely, mice lacking NGF or TrkA (NGF receptor) show decreased survival of sympathetic neurons and decreased target innervation [52–54]. In addition to NGF, proNGF promotes axonal elongation and branching in postnatal sympathetic neurons through activation of the p75^{NTR} receptor rather than the TrkA receptor [55].

NGF's axonal growth effects are independent of its effects on neuronal survival. Mice lacking both NGF and Bax, a pro-apoptotic gene necessary for apoptosis in sympathetic neurons [56, 57], show normal early axonal growth and guidance along the vasculature but show differential loss of innervations in the different target tissues with sympathetic innervation being completely absent in salivary glands and cardiac ventricles, reduced in the liver and unaffected in the trachea [58]. These evidence supports the argument that NGF is important for axon growth of the distal axons and target innervation. It is interesting to note that this requirement for target-derived NGF in the terminal axonal growth varies between the different targets, suggesting that other growth factors are important for target innervation in some of these tissue [58].

NGF's effects on axonal growth are primarily mediated through activation of the TrkA receptors. NGF and phosphorylated TrkA are retrogradely transported in endosomes from the axon terminals [59–62] and regulate axonal growth through changes to cytoskeletal proteins and transcription factors such as cyclic AMP response element binding protein (CREB) and early growth regulator 3 (Egr3) [49, 63–67]. Also, local reintroduction of NGF to NGF-deprived neurons in culture results in profuse axonal growth, suggesting that NGF promotes axonal growth both locally and through retrograde signaling [68]. NGF also upregulates the expression of its receptor TrkA in sympathetic neurons [41] and activates downstream effectors such as PI-3Kinase-Akt pathways and MAPK pathways leading to cytoskeletal changes resulting in axonal growth [69]. In addition, NGF, through its binding to TrkA receptors, activates glycogen synthase kinase-3 (GSK-3), which results in the phosphorylation of microtubule-associated protein 1B (MAP1B) and decrease in MAP1B phosphorylation is correlated with decreased axonal growth [70]. NGF signaling during axonal elongation and termination is dependent on activation SHP-2, a protein tyrosine phosphatase. Inhibition of SHP-2 *in vitro* leads to decreased axonal growth by inhibiting extracellular signal-regulated kinase (ERK) signaling, however interfering with SHP-2 signaling results in increased axonal density within the targets [71]. Also, studies suggest that Wnt 5a is upregulated in sympathetic targets in response to NGF, and blocking Wnt5a activation using an antibody suppresses NGF-induced axonal growth [72]. Early growth response (Egr) proteins – Egr1 and Egr3 are induced by NGF signaling in sympathetic neurons with inhibition of Egr1 *in vitro* using a dominant negative and Egr3 knockout *in vivo* show decreased neurite outgrowth and target innervation [49, 73, 74]. Recent studies have suggest a role of non-coding RNAs and post-translational modifications downstream of NGF signaling during axonal growth [75, 76]. Untranslated axonal mRNA Tp53inp2 upregulates NGF-TrkA signaling during axonal growth [75] and NGF-dependent prenylation of proteins such as Rac GTPase appears to be important for receptor trafficking to promote axonal growth [76].

Once the axons reach the target, NGF-TrkA signaling increases the expression of Coronin-1, a protein that interacts with the actin cytoskeleton [77]. Coronin-1

acts as a molecular switch to convert downstream effectors of NGF-TrkA from the PI-3 K pathway to calcium signaling, leading to the suppression of axonal growth and branching [77, 78].

2.3.2 Neurotrophin 3 (NT-3)

In addition to NGF, neurotrophin-3 is expressed in sympathetic neurons, although its main receptor TrkC is expressed at low levels in neonatal sympathetic neurons [44, 79–81]. NT-3 mutant mice show severe defects in their sympathetic nervous system with 50% fewer neurons, and defects in axonal branching and axonal innervation of target tissues such as the pineal gland and cardiac myocytes [82–84]. In addition, neurotrophin-3 (NT-3) promotes axonal growth and branching in sympathetic neurons *in vitro* [41, 84]. Overexpression of NT-3 in adipose tissue leads to increased sympathetic innervation through its activation of TrkC receptors [85]. However, NT-3's effects on axonal growth are mediated by activation of TrkA receptors as opposed to TrkC, with NT-3 selectively promoting neurite outgrowth rather than for survival in neonatal sympathetic neurons [41]. Although both NGF and NT-3 signal using the same receptor, unlike the NGF-TrkA complex, NT-3-TrkA complex does not mediate retrograde signaling [61]. Recent studies also suggest that NT3-TrkA complex prevents axons from branching into intermediate targets and enables larger growth cones in the absence of Coronin-1, through activation of Ras-MAPK and PI3K-Akt pathways [86].

2.3.3 Brain-derived neurotrophic factor (BDNF)

Similar to other neurotrophins, BDNF is expressed in sympathetic neurons and sympathetic neuron targets [79, 87], and serves as target-derived growth factor for pre-ganglionic sympathetic neurons [88]. Unlike NGF and NT-3, BDNF null mutants show a slight increase in the number of sympathetic neurons compared to wildtype animals, indicating that BDNF is not important for survival of sympathetic neurons [89]. Addition of exogenous BDNF inhibits axonal growth and inhibiting BDNF activity using antibodies against BDNF promotes axonal growth in sympathetic neurons *in vitro* [79]. Also, BDNF ^{+/-} and BDNF ^{-/-} mice show hyperinnervation of the target tissues [87]. Although Trk B (the main BDNF receptor) is not present in sympathetic neurons [41], the sympathetic axons express p75^{NTR} during target innervation [87] and BDNF's effects on axonal growth are mediated through its interaction with this receptor. BDNF-p75^{NTR} signaling inhibits the activity of NGF-TrkA complex leading to axonal growth inhibition *in vitro* and axon pruning *in vivo* [87, 90].

2.4 Tumor necrosis factor superfamily

Multiple members of the tumor necrosis factor superfamily (TNFSF) are known to regulate axonal growth in sympathetic neurons. Members of the TNFSF act as either as membrane-bound ligands or soluble ligands once cleaved from the membrane and bind to receptors belonging to the TNF superfamily (TNFRSF) [91, 92]. These molecules can also serve as reverse signaling molecules with TNFRSF acting as ligands and membrane-bound TNFSF functioning as receptors [93].

TNF α protein is present in postnatal SCG neurons throughout the cell body and neurites with strong immunoreactivity for TNF receptors R1 (TNFR1) in the cell body and in target tissues [94]. *tnfa*^{-/-} and *tnfr*^{-/-} mice show decreased innervation of

sympathetic targets, with no effect on neuronal numbers [94]. While soluble TNF α inhibits NGF-induced axonal growth *in vitro* through activation of NF- κ B [95], the reverse signaling mediated by TNFR1 at the axon terminal enhances axonal growth and target innervation through elevation of opening of T-type calcium channels leading to rapid activation of protein kinase C, ERK1 and ERK2 [94, 96]. Another TNF superfamily member – receptor-activator of NF- κ B (RANK, also known as TNFRSF11A)) is expressed in embryonic and early postnatal sympathetic neurons, while its ligand RANKL is expressed in target tissues [97]. Similar to TNF α , local activation of RANKL-RANK signaling is necessary for axonal growth effects, and addition of soluble RANKL or activation of RANK signaling inhibits NGF-induced axonal extension and branching, through activation of NF- κ B signaling [97]. The glucocorticoid induced tumor necrosis factor receptor related protein (GITR) and its ligand GITRL are also expressed in sympathetic neurons [98]. The activation of GITR by its ligand GITRL leads to activation of ERK signaling and the downregulation of NF- κ B signaling pathways and regulation of both of these pathways are necessary for NGF-induced axonal growth [98, 99]. A recent study showed that *TWE-PRIL*, an alternative spliced form that combines extracellular domain of one TNFSF member APRIL (TNFSF13) and the transmembrane and cytoplasmic domains of another member TWEAK (TNFSF12), is expressed in developing SCG neurons [100]. *April*^{-/-} mice show increased axonal growth in the presence of NGF, that can be rescued by overexpression of TWE-PRIL. TWE-PRIL reverse signaling leads to axonal growth inhibition by preventing NGF-dependent activation of ERK [100]. Similarly, CD40 (TNFRSF5) and its ligand CD40L are expressed in embryonic and early postnatal SCG neurons [101]. While CD40 by itself does not affect axonal growth, the reverse autocrine signaling mediated by CD40-CD40L enhances NGF induced axonal growth in these neurons, especially when there is low NGF with high levels of NGF inhibiting CD40 and CD40L expression [102].

Interestingly, two TNF family members have differential effects on paravertebral and prevertebral ganglia. Unlike SCG targets which showed hypoinnervation in *tnfa*^{-/-} and *tnfr*^{-/-} mice, the targets of the prevertebral sympathetic ganglia showed no change in innervation and reverse signaling mediated by TNFR1 did not alter axonal growth from prevertebral ganglia neurons [103]. Similarly, CD40 null mutants show hyperinnervation in targets of prevertebral ganglia and CD40-CD40L reverse signaling inhibits axonal growth in prevertebral ganglia neurons [101].

2.5 Extracellular matrix proteins

As axons extend from the sympathetic ganglia to the target, they are exposed to a complex environment composed of extracellular matrix molecules such as laminin, collagen, fibronectin and thrombospondin. Laminin, collagen IV and thrombospondin promote axonal growth in perinatal superior cervical ganglia neurons *in vitro* and mediate their effects on axonal growth through activation of specific classes of integrin receptors [104–107]. Exposure of SCG neurons to laminin leads to formation of multiple axons, whereas neurons exposed to collagen IV extend only a single axon suggesting distinct signaling pathways downstream of integrin activation [104, 105, 108]. In addition, exposure to laminin causes bundling of microtubules, leading to rapidly growing axons [109]. Conversely, chondroitin sulfate proteoglycans inhibit axonal growth in cultured neonatal SCG neurons and may be responsible for lack of sympathetic reinnervation of the heart during ischemia-reperfusion injury [110].

2.6 Other signaling pathways involved in axonal growth

Interleukin 1b (IL-1b) and Interleukin 1 receptor (IL-1R) are expressed in neonatal sympathetic neurons with IL-1R1 being present in the cell body and axons, and IL-1b being expressed in the sympathetic neurons and target tissues [111, 112]. IL-1b inhibits axonal growth in cultured sympathetic neurons by promoting the nuclear translocation of NF- κ B [112].

Ceramide, a lipid second messenger, generated from glycosphingolipid metabolism or sphingomyelin metabolism is known to be important for cell proliferation or cell death downstream of extracellular agents such as TNF, interleukins and other molecules [113, 114]. Although newly synthesized glycosphingolipids are not important for axonal growth, when added to the distal axons ceramide inhibits neuronal outgrowth, possibly by decreasing the uptake of NGF by the distal axons [113, 114].

3. Growth factors and signaling pathways involved in dendritic growth regulation

Dendritogenesis in post-ganglionic sympathetic neurons begins around E14, with maturation of dendritic arbor continuing into postnatal development [13, 115]. Sympathetic neurons extend multiple dendrites with complex branching patterns. The size of the dendritic arbor is dependent on size of the target field and neuronal activity, suggesting that dendritic complexity is determined by the needs of the targets [116–120]. Similar to axonal growth, dendritogenesis can be divided into 3 stages – initiation of dendrites, elongation and branching of dendrites, and maturation coupled with pruning of the dendritic tree. In this section, we will explore the current understanding of the various growth factors, their signaling pathways and interactions between them to influence dendritic arborization in sympathetic neurons.

3.1 Bone morphogenetic proteins (BMPs)

Members of the bone morphogenetic protein (BMP) family are important for dendritic growth initiation in sympathetic neurons *in vitro* and *in vivo*. BMPs bind and activate a heterotrimeric receptor complex of transmembrane serine/threonine kinase receptors made of type I receptor – BMP receptor type I A (BMPR1a), also known as activin receptor-like kinase-3 (ALK-3) or BMP receptor type IB (BMPR1b), also known as ALK-6, and one of the three type II receptors – BMPRII, Activin type II or IIB (Act II or ActRIIB). The activation of these kinases leads to phosphorylation of receptor Smads (Smads 1, 5 and/or 8), which complex with Smad 4 to translocate to the nucleus and regulate gene expression [121–123].

Sympathetic neurons and glial cells in the SCG from embryonic and postnatal ganglia express mRNA and protein for BMP-5, BMP-6 and BMP-7 [108, 124, 125]. Also, BMPR1a, BMPRIIB, ActRII and BMPRII are present in mouse SCG through later stages of embryonic development into postnatal life [126, 127], suggesting that BMP signaling pathway is functional in sympathetic neurons during periods of dendritogenesis. BMP-5, BMP-6, BMP-7 initiate dendritic growth in cultured perinatal sympathetic neurons by activation and translocation of the Smad complex and regulating gene expression [108, 128, 129]. Conditional knockouts of BMPR1a or both BMPR1a/1b show a decrease in dendritic length and branch complexity compared to congenic wildtype animals but do not show complete absence of

dendrites [130]. Also, BMP receptor knockouts showed a dramatic decrease in total dendritic length, branching and soma size later in postnatal development suggesting that BMP signaling may be important for maintenance of dendrites, rather than initiation of dendrites *in vivo* [130]. This difference in BMP function *in vitro* and *in vivo* may stem from the presence of other receptors such as the activin receptors to mediate BMP signaling [131]. Interestingly, although transfection of Smad1 dominant negative mutant blocks BMP-7-induced dendritic growth *in vitro*, the SCG neurons in conditional Smad 4 knockout mice show an increase in dendritic length and total dendritic arbor [130], suggesting that Smad 4 may play a limiting role *in vivo* and BMPs may be signaling through Smad-dependent and Smad-independent pathways for dendritic growth regulation.

Transcriptome and miRNome analyses have identified over 250 genes and over 40 microRNAs whose expression are altered in response to BMP-7 treatment in cultured sympathetic neurons during the period of dendritic growth initiation [132, 133]. Of the genes, p75^{NTR} mRNA and protein are strongly upregulated by BMP-7 signaling in cultured SCG neurons. BMP-mediated effects on dendritic growth are not observed in p75^{NTR} knockout mice, with p75^{NTR} knockout mice showing stunted dendritic arbor compared to wildtype. Conversely, overexpression of p75^{NTR} phenocopies the dendritic growth effects of BMP-7, suggesting that this is an important target of BMP-7 during dendritic growth regulation [132, 134]. However, p75^{NTR} ligands, interplay between neurotrophins and BMP in activating p75^{NTR} and downstream effectors of p75^{NTR} signaling responsible for dendritogenesis in sympathetic neurons still need to be elucidated. Of the microRNAs identified, three miRNAs – miR-21, miR-23b and miR-664-1* may regulate dendritic growth downstream of BMP-7 in sympathetic neurons *in vitro* [133]. Also, signaling pathways mediated by ubiquitin-proteasome system and by reactive oxygen species are suggested to be downstream of Smad signaling in sympathetic neurons *in vitro* with proteasome inhibitors and antioxidants inhibiting BMP-7 induced dendritic growth [135, 136].

3.2 Neuronal activity dependent dendritic growth

Electric field stimulation or treatment of sympathetic neurons with potassium chloride can lead to neuronal depolarization and this neuronal activity triggers dendritic growth in postganglionic sympathetic neurons by the activation of calcium calmodulin dependent kinase II (CaMKII) [137]. Also, inhibition of integrin-linked kinase (ILK) using an siRNA prevents activity-dependent dendritic growth in sympathetic neurons *in vitro*, whereas pharmacological inhibition of glycogen synthase kinase-3 β (GSK-3 β) enhances activity-dependent dendritic growth in these neurons [138, 139].

3.3 Nerve growth factor and fibroblast growth factor

NGF was one of the earliest growth factors recognized as important for dendritic growth with NGF injections leading to enhanced dendritic growth in sympathetic ganglia [116]. However, NGF, by itself, is unable to induce dendritic growth in cultured perinatal SCG neurons, but is required for BMP-7 induced dendritic growth [129, 140]. One of the downstream targets of NGF for dendritic growth appears to be Egr3 with Egr3^{-/-} mice showing significant decrease in the number of primary dendrites, total dendritic length and maximum extent of dendritic arbor [74].

Fibroblast growth factor receptor 1 (FGFR1) is expressed in adult SCG neurons and its nuclear localization increases in perinatal sympathetic neurons upon BMP-7 exposure [141, 142]. Also, expression of mutant FGFR1 decreases the dendritic growth induced by BMP-7 in sympathetic neurons, through the activation of the integrative nuclear FGFR1 signaling pathway [142].

Interestingly, stimulation of the MAPK signaling pathways has differential effects on activity-dependent dendritic growth and BMP-7 induced dendritic growth. While pharmacological inhibition of ERK activity using PD98059 inhibits activity-dependent dendritic growth, the treatment with the same inhibitor enhances BMP-7-induced dendritic growth [137, 139, 143]. Stimulation of the MAPK signaling through overexpression of MEK1 leads to inhibition of BMP-7 induced dendritic growth and the inhibition of MAPK signaling pathway with dominant negative MEK1 or ERK2 mutant increases the number of dendrites and total dendritic arbor in BMP-7 treated [143]. Further studies are needed to understand the opposing roles of ERK in BMP-induced vs. activity-dependent dendritic growth.

3.4 Cytokines

Several members of the cytokine family have been shown to regulate dendritic growth in sympathetic neurons. These growth factors function through the activation of the Janus kinase (JAK), leading to the nuclear translocation of proteins known as signal transducers and activators of transcription (STAT) [144]. In perinatal sympathetic neurons, interferons gamma (IFN γ), leukemia inhibitory factor (LIF) and ciliary neurotrophic factor (CNTF) decrease the number of primary dendrites and total dendritic arbor, without affecting axonal growth and neuronal survival. In addition, these cytokines can lead to retraction of pre-existing dendrites through the activation of STAT proteins [145–147]. In addition to activating STATs, IFN γ activates Rit, (a small GTPase related to Ras GTPase) and p38-MAPK pathway to effect the dendritic retraction observed in these neurons [148]. Rit is expressed in sympathetic neurons and has opposite effects on axonal and dendritic growth. Dominant negative Rit transgenes decrease axonal elongation but enhance BMP-7 induced dendritic growth in an ERK-signaling dependent manner and constitutively active Rit enhances number of axons and axonal branching in sympathetic neurons while inhibiting dendritic growth [149].

3.5 Cytoskeletal proteins

Dendritic growth and remodeling requires changes to the actin and microtubule cytoskeleton [150, 151]. Signaling pathways downstream of Rho GTPases act as intermediates to connect extracellular signals and actin cytoskeletal remodeling during dendritic growth [152]. In cultured sympathetic neurons, BMP-7 treatment increases the GTP bound RhoA [153] and decreases GTP-bound Rit [149], with no effects on other small GTPases. In cultured SCG neurons, BMP-7 induced dendritic growth requires the activation of RhoA [153], suggesting that activation of this GTPase may be the link to actin cytoskeleton remodeling necessary for dendritic growth.

The microtubule polarity in axons is different from that in dendrites. Unlike microtubules in axons, which have a uniform polarity, microtubules in dendrites have a mixed orientation that is driven by the different motor proteins [154, 155]. A kinesin related motor protein kinesin 6 (also known as CHO/MKLP1) mRNA and protein are

expressed in cultured embryonic sympathetic neuron, with CHO/MKLP1 protein extending from the cell body to the newly formed dendrites [156, 157]. Two other kinesin related motors – Kinesin 5 (also known as Eg5 or Kif11) and kinesin 12 (also known as Kif15) – are also expressed in embryonic sympathetic neurons [158, 159], with kinesin 5 associating only with the microtubule cytoskeleton and kinesin 12 being enriched in the dendrites and associating with both actin and microtubule cytoskeleton [158–160]. Treatment with antisense oligonucleotides against kinesin 6 lead to an increase in axonal length but a decrease in dendritic width and inhibition of BMP-7- induced dendritic growth in these neurons [156, 157]. Knockdown of kinesin 12 in cultured embryonic SCG neurons using an siRNA lead to longer axons that are less branched than control neurons and decrease in dendritic width [157, 160]. Both kinesin 6 and 12 appear to be important for the mixed polarity of microtubules in the dendrites with a decrease in these kinesins leading to fewer minus-end directed microtubules in the dendrites and increased frequency of microtubule transport. Similar to the others kinesins, inhibition of kinesin 5 leads to increase in axonal length, however a decrease in kinesin5 also leads to axons being non-responsive to navigational cues [161, 162]. In addition to a decrease in dendritic width like other kinesins, a reduction in kinesin 5 causes a decrease in dendritic length, a small decrease in number of dendrites and a significant effect on dendritic morphology especially during dendritic maturation stages [163]. In contrast to other kinesin mutants, a decrease in kinesin 5 leads to more minus-end microtubules in the dendrites [163]. Interestingly, kinesin5 appears to be regulated by phosphorylation with more phosphorylated kinesin5 being localized to the dendrites, suggesting that kinesin5 could be a potential link between signaling pathways and the cytoskeletal remodeling during dendritogenesis [163].

3.6 Other signaling pathways involved in dendritic growth

Retinoic acid synthesis enzymes and signaling pathway components are expressed in embryonic sympathetic neurons and activation of retinoic acid signaling in embryonic SCG neurons *in vitro* inhibits BMP-7 induced dendritic growth [164]. Similarly, pituitary adenylate cyclase 38 (PACAP 38) and vasoactive intestinal peptide (VIP) are released by the preganglionic neurons and in cultured perinatal sympathetic neurons, PACAP38 and VIP decrease the number of dendrites and the total dendritic arbor of BMP-7 treated neurons. This effect is mediated through activation of the PAC1 receptor leading to the phosphorylation and nuclear translocation of cyclic AMP response element binding (CREB) protein, with inhibition of adenylate cyclase activity leading to enhanced dendritic growth [165].

4. Limitations of current research and the path forward

Sympathetic neurons have been long regarded as an important model system for studying neuronal differentiation. Due to increased recognition of the importance of sympathetic nervous system dysregulation in many diseases, there has been a renewed interest in understanding the mechanisms controlling neuronal differentiation, target innervation and neuronal survival in these neurons. Significant strides have been made in understanding axonal growth over the past 70 years *in vitro* and *in vivo* but there are still questions that need further exploration. While we understand the importance of individual growth factors for axonal growth, many of the null mutants show some innervation of target tissues. That still leaves the question of how

much each of these growth factors contribute to initiation and elongation of axons during normal development and how their signaling pathways are coordinated to regulate final axonal growth in different paravertebral and prevertebral ganglia.

In comparison to axonal growth, our understanding of dendritic growth in these neurons is much more limited. Most of the studies on sympathetic neurons have been limited to cultured SCG neurons, which leaves the question of whether similar signals are important for regulation of dendritic growth in other paravertebral and prevertebral ganglia. Even in the SCG, many disparate signaling pathways including BMP, NGF, cytokine, ROS, ubiquitin-proteasome, etc. have been shown to control the dendritic tree *in vitro*. However, it is unclear which of these interactions are crucial for dendritic arborization *in vivo* in the SCG and how these pathways coordinately regulate dendritogenesis.

Finally, additional whole genome analysis looking at transcripts, proteins and non-coding RNAs is needed to fully understand the downstream mediators of both axogenesis and dendritogenesis to identify the common regulators controlling neuronal polarity and function in these neurons.

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Author details

Vidya Chandrasekaran
Saint Mary's College of California, Moraga, CA, USA

*Address all correspondence to: vc5@stmarys-ca.edu

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