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Molecular Control of the Neural Crest and Peripheral Nervous System Development

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Abstract

A transient and unique population of multipotent stem cells, known as neural crest cells (NCCs), generate a bewildering array of cell types during vertebrate development. An attractive model among developmental biologists, the study of NCC biology has provided a wealth of knowledge regarding the cellular and molecular mechanisms important for embryogenesis. Studies in numerous species have defined how distinct phases of NCC specification, proliferation, migration, and survival contribute to the formation of multiple functionally distinct organ systems. NCC contributions to the peripheral nervous system (PNS) are well known. Critical developmental processes have been defined that provide outstanding models for understanding how extracellular stimuli, cell–cell interactions, and transcriptional networks cooperate to direct cellular diversification and PNS morphogenesis. Dissecting the complex extracellular and intracellular mechanisms that mediate the formation of the PNS from NCCs may have important therapeutic implications for neurocristopathies, neuropathies, and certain forms of cancer.

1. INTRODUCTION

Neural crest cells (NCCs) are a stem-cell population that generate much of the peripheral nervous system (PNS) during development (Le Douarin & Kalcheim, 1999; Le Douarin & Smith, 1988). A tightly regulated balance between extrinsically derived cues and intrinsic regulators is required for the appropriate specification, growth, and function of NCCs during PNS formation. Evidence suggests that the early NCC population is comprised of both fate-restricted and multipotent progenitors (Bronner-Fraser & Fraser, 1988; Coelho-Aguiar, Le Douarin, & Dupin, 2013; Crane & Trainor, 2006; Fraser & Bronner-Fraser, 1991; Greenwood, Turner, & Anderson, 1999; Krispin, Nitzan, & Kalcheim, 2010; Le Douarin & Dupin, 2003; Ziller, Dupin, Brazeau, Paulin, & Le Douarin, 1983). During the course of development *in vivo* most NCCs undergo progressive fate restriction. However, some derivatives retain a level of plasticity and self-renewal potential and neural crest-like stem cells have been extracted from the sciatic nerve and dorsal root ganglia (DRG) of adult organisms (Bixby, Kruger, Mosher, Joseph, & Morrison, 2002; Greenwood et al., 1999; Li, Say, & Zhou, 2007; Morrison, White, Zock, & Anderson, 1999; Nagoshi et al., 2008; Stemple & Anderson, 1992; White et al., 2001). Since cranial PNS structures are derived from both NCCs and placode cells, the focus of this review is primarily on the development of the DRG and the peripheral nerves which are derived solely from trunk NCCs. The study

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of PNS development continues to shed light on the role of distinct molecular mediators of complex cell and tissue interactions.

2. NEURAL CREST SPECIFICATION

NCC arises from the dorsal lip of the developing neural tube at early stages of embryogenesis. Briefly, extracellular cues derived from the ectoderm, mesoderm, and adjacent neuroepithelium play an active role in the process of NCC specification. The inductive cues and fate potentials of NCCs along the neuraxis are diverse and a number of canonical patterning systems participate in this process, including Wnt/β-catenin, FGFs, BMPs, retinoic acid, and Delta/Notch signaling (Cheung et al., 2005; Mead & Yutzey, 2012; Milet & Monsoro-Burq, 2012; Stuhlmiller & Garcia-Castro, 2012). Many of these same signals act at later stages of NCC and PNS differentiation as well. The tightly regulated expression of various transcription factors is important during this transition; Pax7, Snail/Slug, FoxD3, and Sox9 are but a few that are especially critical at this early stage (Betancur, Bronner-Fraser, & Sauka-Spengler, 2010; Bhatt, Diaz, & Trainor, 2013).

Once specified, NCCs separate from the neuroepithelium and undergo an epithelial to mesenchymal transition (EMT) before initiating migration toward distant sites (Lim & Thiery, 2012). Live cell imaging has revealed significant heterogeneity in the sequence of detachment, division, polarization, and migration during EMT, indicating that highly complex and plastic interactions between multiple cellular subprograms regulate this process (Ahlstrom & Erickson, 2009). Modulation of cadherins, integrins, and multiple extracellular matrix (ECM) components is vital for modulating NCC delamination (Perris & Perissinotto, 2000). For example, a regulated switch from N-cadherin to cadherin-6 expression and noncanonical Wnt/planar cell polarity signaling play a key role in delamination and early migration (Carmona-Fontaine, Matthews, & Mayor, 2008; Clay & Halloran, 2014; De Calisto, Araya, Marchant, Riaz, & Mayor, 2005; Mayor & Theveneau, 2014; Nakagawa & Takeichi, 1995, 1998; Ulmer et al., 2013). Wnt/β-catenin signaling also acts as a potent instructive cue that promotes PNS specification. Activation of β-catenin drives the formation of DRG sensory neurons at the expense of many other NCC derivatives, while inhibition of Wnt or β-catenin attenuates DRG and sympathetic ganglia (SG) formation (Armstrong, Ryu, Chieco, & Kuruvilla, 2011; Hari et al., 2002; Ikeya, Lee, Johnson, McMahon, & Takada, 1997; Lee et al., 2004). The effect of Wnt/β-catenin signaling on DRG fate is most effective at the premigratory stage; however, Wnts continue to have important functions during later stages of neuronal development (Bodmer, Levine-Wilkinson, Richmond, Hirsh, & Kuruvilla, 2009; Hari et al., 2012).

NCCs are induced along the entire neuraxis and can be divided into specific groups with distinct migratory routes and competencies. The PNS arises primarily from trunk NCC, which is derived from the neural tube caudal to the fourth somite. Unlike cranial NCCs, trunk NCCs are generally restricted from generating ectomesenchymal tissues such as bone and cartilage *in vivo* (Coelho-Aguiar et al., 2013). However, exceptions have been observed in turtle carapace and plastron development (Cebra-Thomas et al., 2013). NCCs from the vagal and sacral regions generate the enteric nervous system (ENS), while the cranial and sacral NCCs make important contributions to the parasympathetic nervous system.

Outstanding advances have been made in defining mechanisms of ENS morphogenesis that are reviewed elsewhere (Sasselli, Pachnis, & Burns, 2012).

3. MIGRATORY PATTERNS OF TRUNK NEURAL CREST

NCCs exiting the dorsal neural tube first migrate ventrally in a non-segmental fashion before traveling along a set of well-characterized routes (Fig. 1). Cooperative cell interactions, control of cytoskeletal activity, and an array of positive and negative cues directly influence the complex pattern of NCC migration (Friedl & Gilmour, 2009; Mayor & Carmona-Fontaine, 2010). NCCs often migrate in chains, an interaction that is critical for regulating the directionality of migration (Erickson, 1985; Rorth, 2009). Migratory routes are lined with a number of permissive ECM components, such as laminins, versican, and fibronectin, which help guide the path of NCCs (Dutt, Kleber, Matasci, Sommer, & Zimmermann, 2006; Perris & Perissinotto, 2000; Rorth, 2009). Typically, trunk NCCs migrate ipsilaterally; however, some NCCs are capable of crossing the dorsal midline and migrating into the contralateral DRG (George, Chaverra, Todd, Lansford, & Lefcort, 2007).

The timing and choice of migratory pathway is tightly linked to subsequent fate decisions. An early bifurcation occurs when migratory NCCs choose a dorsolateral path along the ectoderm or a ventromedial course in between the neural tube and developing somites (Gammill & Roffers-Agarwal, 2010; Serbedzija, Bronner-Fraser, & Fraser, 1989; Thiery, Duband, & Delouvee, 1982). Trunk NCCs that enter the ventromedial pathway contribute to the peripheral and autonomic nervous system in addition to other trunk derivatives, such as adrenal chromaffin cells, while the dorsolateral pathway mostly generates the pigment cell lineage including melanocytes (Kelsh, Harris, Colanesi, & Erickson, 2009; Serbedzija, Fraser, & Bronner-Fraser, 1990; Shtukmaster et al., 2013). The choice of pathway is also related to the timing of emigration; early NCCs primarily enter the ventromedial pathway, while later waves of NCCs are biased toward the dorsolateral pathway. Interestingly, late-born NCCs transplanted into younger embryos still enter the dorsolateral pathway, showing that the timing of NCC birth is critical for subsequent migratory path and fate choices (Erickson & Goins, 1995; Reedy, Faraco, & Erickson, 1998). NCCs generally show a bias toward populating target organs in a ventral to dorsal order, though variation between chick and mouse has been observed (Krispin, Nitzan, Kassem, & Kalcheim, 2010; Serbedzija, Bronner-Fraser, & Fraser, 1994, Serbedzija et al., 1989).

The developing somites provide an additional critical source of patterning cues that initiate segmental migration and direct the metameric organization of the developing DRG, SG, and peripheral nerves (Bronner-Fraser, 1986; Bronner-Fraser & Stern, 1991; Keynes & Stern, 1984; Krull, 2001). Rotation or ablation of the early somites leads to aberrant PNS segmentation and altered NCC migratory patterns (Bronner-Fraser & Stern, 1991; Kalcheim & Teillet, 1989). The early wave of trunk NCCs migrates ventrally along intersomitic blood vessels in between the somites (Bronner-Fraser, 1986; Schwarz, Maden, Davidson, & Ruhrberg, 2009; Thiery et al., 1982). NCCs entering the intersomitic path will generate neurons and glia within the SG and are stimulated by chemoattractant and instructive cues from the dorsal aorta (DA), such as SDF1/CXCR4, BMPs, and neuregulin-1 (Nrg1), as well as blood vessel-derived artemin (Belmadani et al., 2005; Britsch et al., 1998; Honma et al.,

2002; Kasemeier-Kulesa, McLennan, Romine, Kulesa, & Lefcort, 2010; Reissmann et al., 1996; Saito, Takase, Murai, & Takahashi, 2012; Schneider, Wicht, Enderich, Wegner, & Rohrer, 1999; Shah, Groves, & Anderson, 1996; Yip, 1986). As the somite differentiates into the sclerotome and dermomyotome (DM), another wave of NCCs migrates segmentally into the space between the developing structures, often along the basement membrane of the DM (Krull, 2001; Tosney, Dehnbostel, & Erickson, 1994). Importantly, the caudal somite produces factors that repel migrating NCCs, while the rostral half provides attractive cues (Bronner-Fraser & Stern, 1991; Goldstein, Teillet, & Kalcheim, 1990; Koblar et al., 2000; Krull et al., 1997; Wang & Anderson, 1997). A subpopulation of NCCs migrate through the developing sclerotome and provide an additional source of SG progenitors. NCCs that arrest migration adjacent to the neural tube generate the DRG and subsequent derivatives.

4. MOLECULAR REGULATORS OF NEURAL CREST MIGRATION

A number of secreted factors act in conjunction with intrinsic regulators to control NCC migration, proliferation, and multipotency during the early migratory stage of development. Extracellular signaling through secreted trophic factors helps promote migratory NCC survival and/or proliferation (Britsch et al., 1998; Kalcheim, 1996; Meyer & Birchmeier, 1995; Murphy, Reid, Ford, Furness, & Bartlett, 1994; Shah, Marchionni, Isaacs, Stroobant, & Anderson, 1994; Sommer, 2006). FGF2, Nrg1, the neurotrophin-3 (NT-3) receptor TrkC, and the thrombospondin/EGF domain-containing factor NELL2 can be detected in a subset of migrating trunk NCCs, all of which promote NCC proliferation and may act as instructive cues (Henion, Garner, Large, & Weston, 1995; Kahane & Kalcheim, 1994; Kalcheim, Carmeli, & Rosenthal, 1992; Murphy et al., 1994; Nelson, Claes, Todd, Chaverra, & Lefcort, 2004; Rifkin, Todd, Anderson, & Lefcort, 2000). The transcription factors Sox2, Sox10, and FoxD3 play well-defined roles in maintaining the stem cell-like features and self-renewal capacity of early migratory NCCs (Kim, Lo, Dormand, & Anderson, 2003; Mundell & Labosky, 2011; Sonnenberg-Riethmacher et al., 2001; Southard-Smith, Kos, & Pavan, 1998; Teng, Mundell, Frist, Wang, & Labosky, 2008). Sox10 increases the expression of the neuregulin receptor ErbB3, providing a specific mechanistic example of a precise intrinsic cue that modulates extrinsic responsiveness (Britsch et al., 2001; Paratore, Goerich, Suter, Wegner, & Sommer, 2001; Prasad et al., 2011). The mechanism of interaction between many other critical extrinsic and intrinsic cues has yet to be fully elucidated.

Importantly, somite-derived factors that direct NCC migration have been defined. The caudal half of the developing somite provides local cues that inhibit NCC migration, while the rostral half appears to produce attractive and mitogenic factors (Goldstein et al., 1990; Koblar et al., 2000; Krull, 2001; Krull et al., 1997; Wang & Anderson, 1997). Repulsion from the caudal somite is mediated by semaphorins and ephrins that act in concert with Neuropilin and Eph-expressing neural crest (Gammill, Gonzalez, Gu, & Bronner-Fraser, 2006; Kawasaki et al., 2002; Krull, 2001; Krull et al., 1997; Maden et al., 2012; Schwarz et al., 2009; Wang & Anderson, 1997). These signaling cues are critical for directing the segmental migration and final pattern of PNS morphogenesis. F-spondin expression in the caudal sclerotome provides an additional repulsive cue for migrating NCCs while thrombospondin in the rostral domain has been shown to act as an attractant (Debby-

Brafman, Burstyn-Cohen, Klar, & Kalcheim, 1999; Tucker et al., 1999). Furthermore, a similar role for Delta expression in the caudal somite has been proposed (Bettenhausen, Hrabe de Angelis, Simon, Guenet, & Gossler, 1995). Deletion of *Delta1* results in disruption of the metameric pattern of DRG formation; however, a reduced number of progenitors indicate multiple functions for Delta/Notch signaling that clearly extend beyond strict migratory control (De Bellard, Ching, Gossler, & Bronner-Fraser, 2002; Hrabe de Angelis, McIntyre, & Gossler, 1997; Mead & Yutzey, 2012).

Long-range, local, and contact-dependent molecules have been identified that regulate diverse aspects of NCC migration. These signals are capable of activating numerous intracellular pathways; however, convergent regulation of common downstream components, such as Rho and Rac, serves as a key integration point (Berndt, Clay, Langenberg, & Halloran, 2008; Clay & Halloran, 2014; Liu & Jessell, 1998; Shoval & Kalcheim, 2012; Theveneau & Mayor, 2012). Newly developed high-resolution imaging techniques and genetic tools will continue to provide unique insight into how entire populations of cells are guided into distinct migratory routes and destinations during embryogenesis (Clay & Halloran, 2010).

In vivo clonal analyses suggest that early migratory NCCs contain both multipotent progenitors capable of generating cells within the DRG, SG, and nerve, in addition to progenitors restricted to a specific lineage (Bronner-Fraser & Fraser, 1988, 1989; Frank & Sanes, 1991; Krispin, Nitzan, Kassem, et al., 2010; Serbedzija et al., 1989; Shtukmaster et al., 2013). A disruption in migratory guidance occurs in *Nrp1* and *EdnRB2* mutants that leads precociously misrouting of NCCs into the dorsolateral pathway (Krispin, Nitzan, Kassem, et al., 2010; Schwarz et al., 2009). Interestingly, neuronal markers are detected in the dorsolateral pathway of these mutants. Thus, NCCs can be specified to the neurogenic lineage in the absence of interactions with sclerotome-derived signals (Krispin, Nitzan, Kassem, et al., 2010; Schwarz et al., 2009). Even though DRG-restricted NCCs have been identified, these cells produce both neurons and glia *in vivo* (Greenwood et al., 1999; Zirlinger, Lo, McMahon, McMahon, & Anderson, 2002). Overall, these data provide support for the notion that some migratory NCCs are specified to the DRG or the autonomic lineage prior to choosing between a neuronal or glial fate (Anderson, 2000; Crane & Trainor, 2006; Krispin, Nitzan, Kassem, et al., 2010; Morrison et al., 1999).

5. BOUNDARY CAP

An intermediate population of NCC-derived stem cells, known as the boundary cap, form on the border of the spinal cord and DRG along both the dorsal and ventral roots, known as the dorsal root entry zone (DREZ) and the motor exit point (MEP), respectively (Altman & Bayer, 1984; Golding & Cohen, 1997). NCCs migrating along the ventromedial pathway generate the boundary cap after the initial wave of DRG progenitors is established (Niederlander & Lumsden, 1996). The boundary cap progenitors form a critical boundary between the CNS and the PNS (Bron et al., 2007; Coulpier et al., 2010, 2009; Hjerling-Leffler et al., 2005; Maro et al., 2004; Mauti, Domanitskaya, Andermatt, Sadhu, & Stoeckli, 2007; Vermeren et al., 2003). This cell impermeable barrier relies, in part, on boundary cap-derived, membrane-bound Semaphorin6A (Sema6A; Bron et al., 2007; Mauti et al., 2007).

Sema6A expression may play two roles in this process, the first being to appropriately aggregate boundary cap cells along the CNS/PNS boundary and the second to inhibit PlexinA or Neuropilin2-expressing CNS-derived cell types from migrating into the PNS (Bron et al., 2007; Kucenas, Wang, Knapik, & Appel, 2009; Mauti et al., 2007). Ablation of the boundary cap by multiple techniques has been shown to result in the ectopic presence of CNS-derived motor neurons and oligodendrocytes in the proximal peripheral nerve (Bron et al., 2007; Mauti et al., 2007; Vermeren et al., 2003). DREZ- and MEP-associated boundary cap cells have distinct molecular profiles and slightly different temporal relationships with outgrowing axons (Coulpier et al., 2009; Fraher, Dockery, O'Donoghue, Riedewald, & O'Leary, 2007). These data suggest that potentially distinct specific functions of the boundary cap at these two sites have yet to be discovered.

During normal development, boundary cap progenitors produce a small subset of neurons in the DRG followed by the production of satellite glia and Schwann cells (Aquino et al., 2006; Hjerling-Leffler et al., 2005; Maro et al., 2004). *Egr2/Krox-20* serves as an important molecular identifier *in vivo* and is required for boundary cap barrier functions, as is *Sox10* expression (Coulpier et al., 2010; Frob et al., 2012; Maro et al., 2004; Vermeren et al., 2003; Wilkinson, Bhatt, Chavrier, Bravo, & Charnay, 1989). Boundary cap progenitors maintain a state of pluripotency somewhere between that of early NCCs and a Schwann cell progenitor (SCP), though *in vitro* studies have shown that these cells can even generate multiple CNS subtypes (Coulpier et al., 2009; Zujovic et al., 2010, 2011). These characteristics have led to a number of studies seeking to utilize boundary cap progenitor transplantation in spinal cord, peripheral nerve, and dorsal root injury paradigms (Aldskogius et al., 2009; Aquino et al., 2006; Trolle, Konig, Abrahamsson, Vasylovska, & Kozlova, 2014; Zujovic et al., 2010, 2011).

6. SENSORY NEUROGENESIS IN THE DRG

Sensory neurons in the PNS relay information into the CNS from a number of specific exteroceptive, proprioceptive, and interoceptive structures, including Merkel's discs, Meissner's and Pacinian corpuscles, Ruffini's end organs, Golgi tendon organs, muscle spindles, and free nerve endings in the skin. Dedicated neurons transmit information of distinct somatosensory modalities; proprioceptive neurons provide spatial information regarding limb position, mechanoreceptive neurons mediate touch, nociceptive neurons respond to painful stimuli or itch, and thermoreceptive neurons relay information regarding temperature (Liu & Ma, 2011; Marmigere & Ernfors, 2007). The importance of trophic factor signaling during the development of PNS neurons has long been recognized, particularly the neurotrophin ligand/receptor components NGF/TrkA, BDNF/TrkB, and NT-3/TrkC (Cowan, 2001; Ernsberger, 2009). The discovery that functionally related neuronal subtypes require specific neurotrophic factors has provided a crucial molecular handle for analyses of PNS development. Dozens of different neuronal subtypes have been characterized based on the expression of specific molecular components and peripheral/central innervation targets (Abraira & Ginty, 2013; Li et al., 2011; Liu & Ma, 2011).

DRG sensory neurons are generated in a number of waves that derive from temporally distinct NCC populations (Carr & Simpson, 1978; Frank & Sanes, 1991; Lawson & Biscoe,

1979; Marmigere & Ernfors, 2007; Rifkin et al., 2000). The initial production of sensory neurons from postmigratory NCCs follows a stereotyped pattern where large-diameter *TrkC*/*TrkB*$^+$ proprio- and mechanoreceptive neurons are produced first, while small-diameter *TrkA*$^+$ nociceptive neurons are subsequently generated (Carr & Simpson, 1978; Lawson & Biscoe, 1979; Liu & Ma, 2011; Marmigere & Ernfors, 2007). Boundary cap progenitors and contralaterally migrating NCCs also generate a small population of *TrkA*$^+$ nociceptive sensory neurons that populate the DRG (George et al., 2007; Maro et al., 2004). NCCs that first migrate into the nascent DRG generate a core domain of differentiated postmitotic sensory neurons, while subsequent NCCs tend to encapsulate and proliferate in the perimeter region surrounding the core (George, Kasemeier-Kulesa, Nelson, Koyano-Nakagawa, & Lefcort, 2010). Activity-dependent BDNF production from active neurons in the core and protocadherin-1 expression in the perimeter are necessary for proper DRG formation (Bononi, Cole, Tewson, Schumacher, & Bradley, 2008; Wright & Ribera, 2010). Inhibition of either mechanism leads to less NCCs localizing within the DRG and an increase in ventrally migrating NCCs that expand the SG. Lastly, contact-mediated interactions between immature neurons in the core domain and undifferentiated NCCs regulate neuronal specification and subsequent lineage diversification, in part through Delta/Notch signaling (Hagedorn, Suter, & Sommer, 1999; Maynard, Wakamatsu, & Weston, 2000; Wakamatsu, Maynard, & Weston, 2000).

The sequence of transcriptional changes that occurs during sensory neuron specification has been well studied (Lallemend & Ernfors, 2012). The downregulation of factors that maintain NCC multipotency, such as Sox10, Sox2, and FoxD3, is important for NCC differentiation into postmitotic neurons (Montelius et al., 2007; Nitzan et al., 2013; Wakamatsu, Endo, Osumi, & Weston, 2004). The coordinated upregulation of proneural transcription factors, *Neurogenin-1* and *-2*, can be detected in a subset of migrating NCCs shortly after exiting the neural tube (Greenwood et al., 1999; Ma, Fode, Guillemot, & Anderson, 1999; Perez, Rebelo, & Anderson, 1999). *Neurogenins* are potent promoters of DRG specification; however, they do not necessarily drive NCCs toward a specific subtype of sensory neuron or glia (Zirlinger et al., 2002). The subsequent upregulation of neuron-specific transcriptional regulators, *Brn3a* and *Islet1*, is involved in the transition of neurogenic progenitors into sensory neurons (Dykes, Tempest, Lee, & Turner, 2011; Fedtsova & Turner, 1995; McEvilly et al., 1996; Sun et al., 2008). *Brn3a* and *Islet1* also direct the expression of factors important for sensory neuron maturation, such as the Runx family of transcription factors and specific neurotrophin receptors (Chen et al., 2006; Dykes et al., 2011; Kramer et al., 2006; Marmigere et al., 2006). Loss of *Brn3a* leads to an increased number of aberrantly differentiated sensory neurons that express multiple neurotrophin receptors and decreased levels of *Runx1* (Zou, Li, Klein, & Xiang, 2012). Runx1 is critical for the continuing differentiation of nociceptive neurons, while Runx3 primarily regulates proprioceptive maturation (Chen et al., 2006; Inoue et al., 2007; Kramer et al., 2006; Lallemend et al., 2012).

7. NEUROTROPHIC FACTORS IN SENSORY NEURON DEVELOPMENT

Peripheral innervation targets, central neurons, and associated glia produce neurotrophic cues that direct the development of receptive neuronal subtypes at distinct stages (Davies,

Thoenen, & Barde, 1986; Kawaja et al., 2011; Lumsden & Davies, 1983; Patapoutian, Backus, Kispert, & Reichardt, 1999; Usui et al., 2012). Neurotrophic factor responsiveness is highly dynamic during development. This mechanism is likely important for generating diverse neuronal characteristics that are necessary for responding to a wide range of sensory stimuli. The transient pan-neuronal expression of *TrkC* is rapidly restricted to a small subset of proprioceptive neurons, while *TrkA* and *TrkB* expression is upregulated in nociceptive and mechanoreceptive neurons, respectively (Farinas, Wilkinson, Backus, Reichardt, & Patapoutian, 1998; Lefcort, Clary, Rusoff, & Reichardt, 1996; Martin-Zanca, Barbacid, & Parada, 1990; Mu, Silos-Santiago, Carroll, & Snider, 1993; Rifkin et al., 2000; Wright & Snider, 1995). Genetic deletion mutants have clearly demonstrated that NT-3/TrkC is critical for the survival of large-diameter proprioceptive neurons, while NGF/TrkA maintains small-diameter nociceptive neuron number (Crowley et al., 1994; Ernfors, Lee, Kucera, & Jaenisch, 1994; Farinas, Jones, Backus, Wang, & Reichardt, 1994; Klein et al., 1994; Ruit, Elliott, Osborne, Yan, & Snider, 1992; Smeyne et al., 1994; Tessarollo, Vogel, Palko, Reid, & Parada, 1994). As embryogenesis continues, a subset of *TrkA*-expressing nociceptive neurons develop responsiveness to GDNF by upregulating the GDNF receptors *Ret/GFR*α (Molliver & Snider, 1997; Molliver et al., 1997).

The p75 low-affinity neurotrophin receptor ($p75^{NTR}$) is also activated by a number of trophic factors (Simi & Ibanez, 2010). $p75^{NTR}$ can bind all of the neurotrophins, but when compared to the Trks, striking differences in structure and intracellular signal transduction have been discovered (Charalampopoulos et al., 2012). Different deletion mutants of $p75^{NTR}$ exhibit complex sensory and sympathetic abnormalities that vary depending on the precise mutation (Davies, Lee, & Jaenisch, 1993; Dhanoa, Krol, Jahed, Crutcher, & Kawaja, 2006; Lee et al., 1992; Majdan, Walsh, Aloyz, & Miller, 2001; Petrie et al., 2013; von Schack et al., 2001). Conditional NCC-specific $p75^{NTR}$ mutants show effects consistent with a disruption in PNS development (Bogenmann et al., 2011). Many of these studies have focused upon the role of $p75^{NTR}$ in neuronal survival and innervation. However, the onset of $p75^{NTR}$ expression occurs in premigratory neural crest and $p75^{NTR}$ has been used to isolate neural crest stem cells (Stemple & Anderson, 1992; Wilson, Richards, Ford-Perriss, Panthier, & Murphy, 2004). It will be interesting to further evaluate whether $p75^{NTR}$ modulates early neural crest migration or patterning events that might also contribute to PNS phenotypes (Hapner, Boeshore, Large, & Lefcort, 1998).

As neurons transition into a postmitotic state, they begin to grow neurites that fasciculate with outgrowing spinal motor axons in the forming ventral root *en route* to the periphery or project centrally into the spinal cord via the dorsal root and innervate CNS targets. Once again somite-derived patterning cues direct the stereotyped position of early sensorimotor projections into the periphery and coordinate alignment with the developing vertebrae (Keynes & Stern, 1984; Koblar et al., 2000; Krull, 2010). Trophic factor regulation of postmitotic sensory and motor neuron survival is well known. Mouse mutants that block the neuronal death associated with trophic factor deletion, by simultaneously deleting the prodeath Bcl-2 family member, *Bax*, are an important tool for defining the additional vital functions of trophic factors in neurons (Deckwerth et al., 1996; Patel, Jackman, Rice, Kucera, & Snider, 2000). For example, mouse mutants that lack both *Bax* and *NGF*/*TrkA* do

not exhibit a loss of sensory neurons; however, nociceptive neurons fail to innervate the peripheral cutaneous field (Patel et al., 2000). With this approach, the multifunctional effects of various trophic factors on target innervation, subtype specification, and synapse formation have been definitively evaluated (Deppmann et al., 2008; Glebova & Ginty, 2004; Guo et al., 2011; Luo et al., 2007; Patel et al., 2003; Sharma et al., 2010).

8. GLIOGENESIS IN THE PNS

After neurogenesis has commenced, a subset of NCCs begin to generate distinct populations of nonneuronal cells. These include satellite glia within the peripheral and enteric ganglia, in addition to SCPs in the developing peripheral nerve. Satellite glia in the DRG can be detected prior to SCPs in the nerve (Woodhoo, Dean, Droggiti, Mirsky, & Jessen, 2004). Moreover, the satellite glia lineage shows a number of differences from the SCP lineage, such as the expression of *Erm* (Hagedorn et al., 2000). SCPs maintain a close association with developing axons in the nerve and undergo additional lineage diversification into nonmyelinating and myelinating glial subtypes (Jessen & Mirsky, 2005). Myelinating Schwann cells form a myelin sheath around a single axon crucial for nerve transmission, while non-myelinating Schwann cells ensheath multiple axons in a Remak bundle.

Delta/Notch signaling acts as a critical module for driving gliogenesis in undifferentiated and neurogenic NCCs. Evidence suggests that newly born DRG neurons in the core domain upregulate *Delta1*, which acts on neighboring *Notch*-expressing NCCs to promote the onset of gliogenesis and maintenance of gliogenic precursors (Morrison et al., 2000; Tsarovina, Schellenberger, Schneider, & Rohrer, 2008; Wakamatsu et al., 2004). NCC-specific deletion of *Notch* or the canonical downstream effector, *Rbpj*, results in a profound reduction in gliogenic precursors in the DRG, while *Notch* overactivation drives premature and increased gliogenesis *in vivo* and *in vitro* (Hu et al., 2011; Mead & Yutzey, 2012; Morrison et al., 2000; Taylor, Yeager, & Morrison, 2007). *Sox2* is a critical intrinsic factor important for gliogenesis that is regulated by Notch (Wakamatsu et al., 2004). Sox2 is required for maintaining the gliogenic state of SCPs while also preventing melanocyte specification (Adameyko et al., 2012; Wakamatsu et al., 2004). As in migratory NCCs, Sox10 continues to be vital for maintaining the SCP pool and glial differentiation (Britsch et al., 2001; Kim et al., 2003; Paratore et al., 2001). The functional requirement for Sox10 and Notch persists in developing Schwann cells; both regulate later stages of Schwann cell differentiation and development (Bremer et al., 2011; Britsch et al., 2001; Finzsch et al., 2010; Paratore et al., 2001).

SCPs are distinct from migrating NCCs in that they are dependent on axonal-derived cues for survival (Jessen et al., 1994; Woodhoo et al., 2004). Axonally derived Nrg-1 is a crucial component of the neuron-derived signal that instructs gliogenic neural crest toward a glial fate, promotes SCP survival, and is required for lineage progression and myelination (Dong et al., 1999; Meyer et al., 1997; Michailov et al., 2004; Shah et al., 1994; Taveggia et al., 2005). *ErbB2*, *ErbB3*, and *Nrg1* mutant mice exhibit a near complete absence of SCPs in the developing peripheral nerve (Lin et al., 2000; Meyer & Birchmeier, 1995; Morris et al., 1999; Riethmacher et al., 1997; Woldeyesus et al., 1999). Importantly, these mutants also exhibit profound sensory and motor neuron death and abnormally fasciculated axons in the

peripheral nerve. Moreover, SCP-derived trophic factors have been found to be potent stimulators of Nrg1 release from neurons (Esper & Loeb, 2004, 2009; Hapner et al., 2006; Ma, Wang, Song, & Loeb, 2011). These data suggest that Schwann cells and axons form reciprocal trophic feedback loops that support the development of the neuroglial unit and appropriate nerve function.

Nrg1/ErbB and Delta/Notch are critical extracellular modulators of a core transcriptional network necessary for subsequent Schwann cell development and myelination. These transcriptional regulators exhibit complex interactions with some factors promoting (*Sox10, Oct6, Egr2/Krox-20, YY1, NF-κB*) and others inhibiting (*Sox2, Nab, c-Jun, Id2*) lineage progression in developing Schwann cells (Pereira, Lebrun-Julien, & Suter, 2012). Unlike terminally differentiated neurons, mature Schwann cells can dedifferentiate into a progenitor-like state following nerve injury and help promote efficient peripheral nerve regeneration (Glenn & Talbot, 2013; Napoli et al., 2012). Developmental regulators of lineage progression often continue to act as important factors in Schwann cell dedifferentiation and remyelination.

It is important to note that SCPs generate cell types other than Schwann cells. SCPs have been shown to generate melanocytes and endoneurial fibroblasts that line the peripheral nerve sheath (Adameyko et al., 2009; Joseph et al., 2004). Recent exciting work has shown that SCPs can even generate neurons *in vivo* (Dyachuk et al., 2014; Espinosa-Medina et al., 2014). In these studies, elegant whole mount labeling and 3D imaging demonstrate that parasympathetic neurons are derived from SCPs in the developing cranial nerves (Dyachuk et al., 2014; Espinosa-Medina et al., 2014). Thus, the developing cranial nerve appears to serve as both a guide and source of progenitors for the parasympathetic ganglia it will eventually innervate. Further research is clearly necessary to precisely evaluate the mechanisms that balance fate restriction and multipotency in the SCP pool.

9. TROPHIC SIGNALING MECHANISMS DURING PNS DEVELOPMENT

The study of trophic factor functions in PNS neurons and glia has served as a classic system for dissecting the biochemical pathways that mediate cellular development (Cowan, 2001; Dekkers, Nikoletopoulou, & Barde, 2013; Harrington & Ginty, 2013). The intracellular signaling cascades downstream of ErbBs and Trks have been well studied and provide a model for other receptor tyrosine kinases (RTKs; Lemmon & Schlessinger, 2010). Even though there are dozens of RTKs, a number of common core pathways are repeatedly implicated, including extracellular signal-regulated kinase 1/2 (Erk1/2), phosphatidylinositol-3-kinase (PI3K), phospholipase C, and protein kinase C (Lemmon & Schlessinger, 2010). Tight control of the activity of signaling pathways is likely an important mechanism to obtain specific responses in certain neural crest populations. For example, substantial gene dose-dependent defects in cranial and cardiac neural crest derivatives are observed following deletion of *Erk1* and *Erk2*, whereas the initial formation of the DRG from trunk neural crest is relatively intact (Newbern et al., 2008). At later stages of PNS development, neurons appear to utilize distinct intracellular pathways to achieve precise patterns of inner-vation. Signaling through ERK1/2 is critical for promoting nociceptive cutaneous innervation *in vivo*, possibly via disruption of SRF and ETS family

transcription factors downstream of NGF (Arber, Ladle, Lin, Frank, & Jessell, 2000; Fontanet, Irala, Alsina, Paratcha, & Ledda, 2013; Newbern et al., 2011; Patel et al., 2003; Wickramasinghe et al., 2008). In contrast, SAD kinase signaling has little effect on NGF-dependent nociceptive neurons, but strongly regulates NT-3-dependent proprioceptive innervation (Lilley, Pan, & Sanes, 2013).

The study of glial development has provided important insight into the functional requirement and regulatory features of trophic signaling mechanisms. The PI3K/Akt pathway has repeatedly been implicated in the control of Schwann cell myelination in response to Nrg1 and ECM signaling (Heller et al., 2014; Maurel & Salzer, 2000). A number of findings suggest that Nrg1-mediated activation of the ERK1/2 pathway is also crucial for development of the Schwann cell lineage *in vivo*. Neural crest-specific deletion of *Shp2* or *Erk1/2* led to a profound absence of SCPs in the developing mouse peripheral nerve without a substantial alteration in the initial stages of neurogenesis (Grossmann et al., 2009; Newbern et al., 2011). Moreover, hyp-eractivation of ERK1/2 signaling is sufficient to rescue mature Schwann cell defects in *ErbB3* mutants and even results in hypermyelination (Ishii, Furusho, & Bansal, 2013; Sheean et al., 2014). Interestingly, robust reactivation of the ERK1/2 cascade in adult myelinating Schwann cells following injury induces reversion to a SCP-like state *in vivo* (Napoli et al., 2012). Thus, the level of ERK1/2 kinase activity appears to be tightly linked to the state of glial progenitor differentiation.

In the traditional model, neurotrophic receptors activate intracellular signaling pathways after ligand binding and often support neuronal survival in the PNS (Lemmon & Schlessinger, 2010; Reichardt, 2006). Recent findings have shown that in the *absence* of ligand, some receptors promote death. These receptors have thus been termed “dependence receptors.” TrkA and TrkC have been shown to act as dependence receptors in the developing nervous system (Dekkers et al., 2013; Nikoletopoulou et al., 2010; Tauszig-Delamasure et al., 2007). DRG and spinal cord neurons induced to over-express TrkA and TrkC will undergo death unless the associated ligands, NGF or NT-3, are simultaneously increased (Nikoletopoulou et al., 2010; Tauszig-Delamasure et al., 2007). Furthermore, a comparison of $TrkA^{-/-}$ and $NGF^{-/-}$ mutant mouse embryos revealed that deletion of TrkA protects NGF-dependent E11.5 DRG neurons from death *in vivo* (Nikoletopoulou et al., 2010). Current findings suggest that the death-promoting effect of dependence receptors in the PNS involves complex interactions with p75 and possibly the generation of proapoptotic receptor fragments (Dekkers et al., 2013; Ichim et al., 2013; Nikoletopoulou et al., 2010; Tauszig-Delamasure et al., 2007). Notably, the sensory and sympathetic neuron loss in E13.5 $TrkA^{-/-}$ mutants can be significantly rescued by simultaneous inhibition of $p75^{NTR}$ (Majdan et al., 2001; Nikoletopoulou et al., 2010). It is not yet clear why some receptors act as dependence receptors and others do not. For example, the GDNF receptor, c-Ret, can act as a dependence receptor, while TrkB does not appear to share this property (Bordeaux et al., 2000; Canibano et al., 2007; Nikoletopoulou et al., 2010). Indeed, the rules governing the death-promoting effect of dependence receptors deserve further attention. Future studies will undoubtedly illuminate additional critical functions of RTK signaling and dependence receptors in NCC and PNS development.

10. CONCLUSIONS

The formation of the PNS from trunk NCCs provides a rich developmental process to study how cell–cell interactions, secreted cues, and transcriptional networks contribute to embryogenesis. Additional molecules that regulate key cellular events during NCC development certainly await discovery. Nonetheless, many extracellular cues and transcription factors have been characterized that are necessary for specific stages of trunk NCC development. It will be important to continue to define the intracellular signaling mechanisms that link these two fundamental processes. Relative to the extremely complex repertoire of cellular and subcellular changes in the developing trunk NCCs, the number of known extracellular regulatory cues might seem limiting. Furthermore, many of these cues act at multiple stages of development. The mechanism of cellular response specificity likely depends upon the interaction between distinct canonical cues (Finelli, Murphy, Chen, & Zou, 2013). Dissecting these and many other key issues will yield important insight into the control of NCC development and assist in defining the pathogenesis of various developmental abnormalities.

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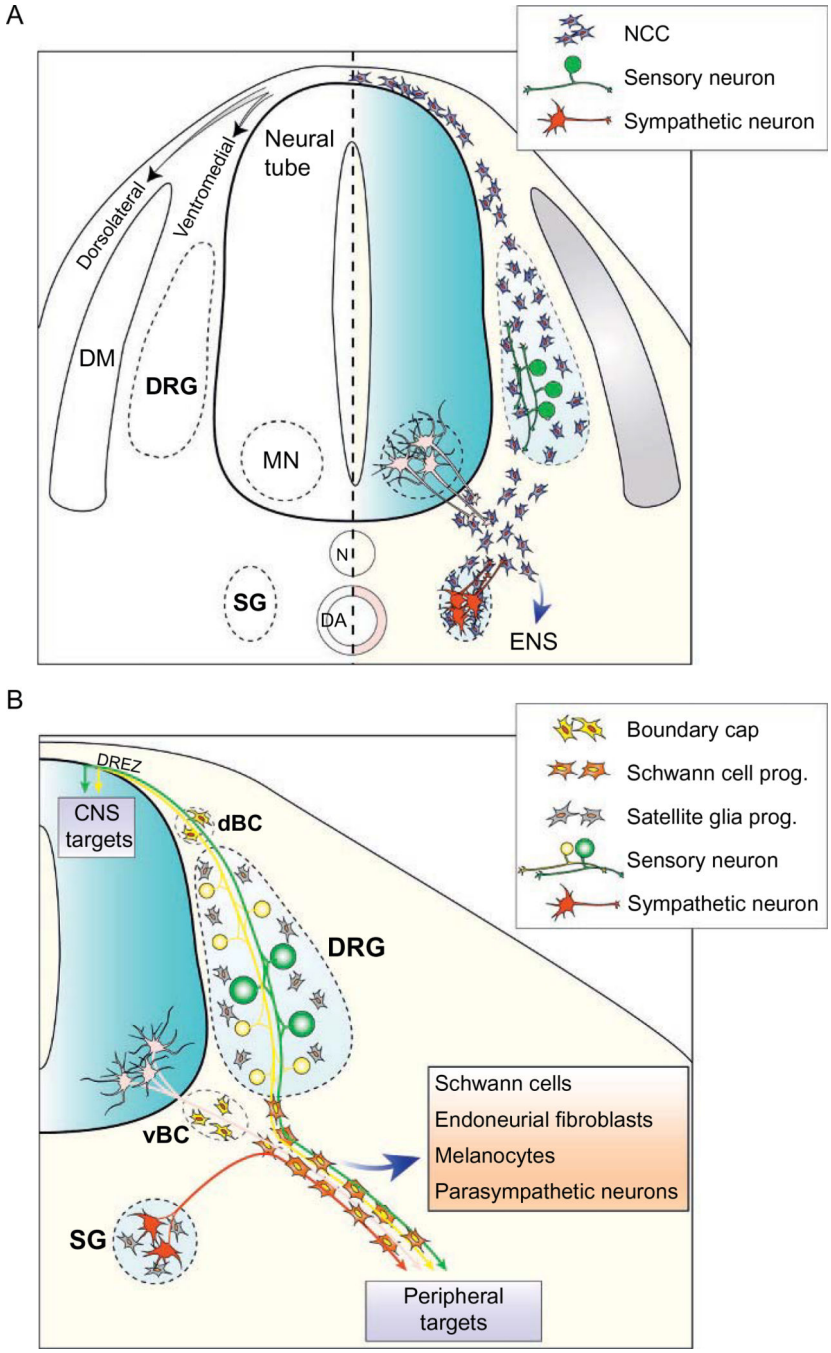

Figure 1.

The initial formation of the PNS from NCCs. (A) After undergoing EMT in the roof plate of the neural tube, migratory trunk NCCs are guided by a combination of attractive, repulsive, and instructive cues derived from the developing dermomyotome (DM), sclerotome, dorsal aorta (DA), and notochord (N). NCCs that generate the PNS migrate ventromedially between the neural tube and developing somite, while the dorsomedial NCCs primarily generate melanocytes. Some NCCs migrate to distant sites in the trunk, such as the enteric nervous system (ENS) and adrenal glands. A population of NCCs cease migration at sites of

peripheral ganglia formation and enter a phase of neurogenesis that produces sensory neurons in the dorsal root ganglia (DRG) and sympathetic neurons in the sympathetic ganglia (SG). (B) Axons from NCC-derived SG and DRG neurons and neuroectodermally derived lower motor neurons begin growing into the periphery. The sites where axons enter and exit the spinal cord are populated by the boundary cap, a transient NCC-derived stem-cell niche. The ventral boundary cap (vBC) is localized along outgrowing lower motor neurons axons at CNS/PNS boundary, while the dorsal boundary cap (dBC) is found along fibers near the dorsal root entry zone (DREZ) where sensory afferents enter the spinal cord. TrkC expressing, large-diameter proprioceptive neurons (green) are among the first neurons to be produced in the nascent DRG, followed by small-diameter, TrkA-expressing DRG neurons (red). Subsequent to the onset of neurogenesis, NCCs and boundary cap generate satellite glia progenitors that reside in the ganglia and Schwann cell progenitors (SCPs) that migrate along axons in the developing nerve. SCPs can ultimately differentiate into various cell types that contribute to peripheral nerve function, including myelinating and nonmyelinating Schwann cells and endoneurial fibroblasts. SCPs also generate melanocytes and have even been shown to produce parasympathetic neurons in cranial nerves.