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Specification of neural crest into sensory neuron and melanocyte lineages

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Abstract

Elucidating the mechanisms by which multipotent cells differentiate into distinct lineages is a common theme underlying developmental biology investigations. Progress has been made in understanding some of the essential factors and pathways involved in the specification of different lineages from the neural crest. These include gene regulatory networks involving transcription factor hierarchies and input from signaling pathways mediated from environmental cues. In this review, we examine the mechanisms for two lineages that are derived from neural crest, the peripheral sensory neurons and the pigment producing melanocytes. Insights into the specification of these cell types may reveal common themes in the specification processes that occur throughout development.

Keywords

neural crest; dorsal root ganglion; melanocyte

Introduction

Neural crest cells (NCCs) arise as an apparently homogeneous population of cells along the dorsal aspect of the neural tube that migrate extensively into the periphery to generate diverse structures. They differentiate into a wide variety of cell types: neurons and glia of the peripheral sensory and autonomic nervous system, pigment cells, neuroendocrine cells and craniofacial mesenchyme that forms bones and cartilage of the head. The neural crest (NC) has thus been a favorite system for developmental biologists to understand the process of specification: the acquisition of distinct characteristics that allow differentiating cells to carry out their appropriate functions.

The process of developmental specification is also often referred to cell fate acquisition, where fate simply refers to the future outcome of a cell or, for a dividing cell, its progeny or lineage. Here we use the term specification without assumption of the limits on a cell's potential, the range of possible fates a cell could undertake given the appropriate environmental stimuli. Cells that can respond to new environments are said to display plasticity; cells with limited plasticity are deemed restricted. As development proceeds, cells

often undergo lineage restriction, changing in their potential to become capable of giving rise to a more limited number of cell types.

In this review we compare the processes regulating the specification of two cell types, peripheral sensory neurons and pigment cells. While these cells have clearly distinct characteristics, the process of their specification shares some common themes. They are both regulated by a set of transcription factors that appear to define nodal points in their development. Both are also regulated by receptor tyrosine kinases and their ligands, signaling systems that both control their survival and influence their differentiation. Insights into the specification of these cell types may reveal common themes in the specification processes that occur throughout development.

Development of sensory neurons and melanocytes from the neural crest

Peripheral sensory neurons are the afferent nervous system cells that are responsive to external stimuli, and then transmit this information to the central nervous system; these include the sensory neurons of the dorsal root ganglia (DRG) in the trunk and a subset of the neurons of the trigeminal ganglia of the head. The NC origin of peripheral sensory neurons has been known since Wilhelm His's original study of the NC (His, 1868; Horstadius, 1950). Ablation, transplantation and vital dye labeling experiments in amphibian embryos by Harrison, Detwiler, Raven and others confirmed these initial observations (reviewed in (Horstadius, 1950; Weston, 1970). In contrast, neurons of the trigeminal ganglion have a dual origin from both NC and placode (Hamburger, 1961; Johnston, 1966; Noden, 1978). Here we will focus mainly on the DRG neurons derived from trunk NC.

Sensory neurons can be divided into several categories depending on the type of stimulus they respond to: mechanoreceptors that respond to mechanical touch, proprioceptors that respond to limb and muscle movement, thermoreceptors that respond to temperature, nociceptors that respond to painful or pruritic (itch) stimuli (see (Delmas et al., 2007; Han and Simon, 2011; Schepers and Ringkamp, 2010; Woolf and Ma, 2007) for review). Cells can be further distinguished by their sensitivity to the relative qualities of stimuli and the speed of response (Vallbo et al., 1979). Evidence is emerging for distinct labeled lines for different submodalities (reviewed in (Ma, 2010)). For example, at least four different types of peripheral thermoreceptors have been described that respond to cold temperatures, some of which also convey painful sensation or respond to heat (Campero and Bostock, 2010). These functional sensory subtypes may be distinguished by expression of different transient receptor potential (TRP) channel subtypes (Dhaka et al., 2008; Hjerling-Leffler et al., 2007). Distinct nociceptors are also distinguishable by the Mas-related G protein coupled receptor (Mrgpr) family (Dong et al., 2001). Similarly, distinct populations of neurons may detect different qualities of mechanical stimuli. For example, four distinct subtypes of low threshold mechanoreceptors have been identified by genetic labeling techniques (Li et al., 2011). These findings suggest that there may be dozens of distinct sensory neuron subtypes with possible overlapping responses to stimuli.

Sensory neurogenesis follows a precise schedule. NCCs that will form DRG sensory neurons migrate on a ventral path between somite and neural tube to coalesce into the segmentally reiterated ganglia. Sensory neurons are added to the DRG in overlapping waves that produce neurons of distinct function (Carr and Simpson, 1978; George et al., 2007; Kitao et al., 1996; Lawson and Biscoe, 1979; Ma et al., 1999). The first wave of neurogenesis gives rise to large diameter mechanoreceptive and proprioceptive neurons, while the second wave additionally generates smaller diameter mechanoreceptive, thermoreceptive and nociceptive neurons. Specialized glial cells at the junction between CNS and PNS called boundary cap cells give rise to a third wave of neurogenesis, forming

largely nociceptive neurons (Hjerling-Leffler et al., 2005; Maro et al., 2004). Additionally, neurons continue to be added to the DRG from precursors that lie amongst the satellite glia that surround the ganglia (George et al., 2010).

Sensory neurons continue to mature through postnatal periods, acquiring characteristics that allow them to respond to distinct stimuli. The steps involved in maturation have best been characterized for a subset of nociceptors. As these nociceptors mature, they divide into two groups: peptidergic nociceptors that respond to the neurotrophin NGF and express the neuropeptide CGRP, and nonpeptidergic nociceptors that respond to the neurotrophin GDNF and often bind the lectin IB4 (Averill et al., 1995; Bennett et al., 1998; Molliver and Snider, 1997; Molliver et al., 1997; Stucky and Lewin, 1999; Zwick et al., 2002). The challenges for understanding sensory neuron development are thus two-fold: determining how NC cells are initially specified to this lineage, and how sensory neurons become distinct from one another to respond to different stimuli.

It has been known for over 60 years that, like the sensory neurons, the specialized pigment cells known as melanocytes also arise from the NC (Rawles, 1947, 1948). For most of these years, it was thought that during embryonic development, NC-derived melanocyte precursors, known as melanoblasts, undergo a relatively uniform developmental process, all migrating solely along a dorsolateral pathway beneath the ectoderm, and subsequently invade the overlying epidermis to colonize skin and hair follicles. While this is indeed a major migratory path used by melanoblasts, additional evidence is emerging that perhaps not all melanocytes are equivalent, due to differences in embryonic melanoblast development. For example, epidermal melanoblasts can also arise from NCCs that migrate along a ventral pathway, coming from precursors previously thought to give rise solely to Schwann cells (Adameyko et al., 2009). Ventrally migrating melanoblasts also give rise to melanocytes that are not located in the skin and hair follicles; melanocyte populations exist in the eye (iris, choroid, ciliary body and Harderian gland), the inner ear, heart, and the leptomeninges of the brain. Consistent with different subsets of melanocytes, oncogenic transformation of melanocyte lineages (melanoma) acquire distinct molecular defects depending on the site and type of melanoma, perhaps due to differences in embryonic origins (Whiteman et al., 2011).

Prior to their extensive migration, the earliest developmental stages of NC-derived melanocyte precursors in the trunk include the generation of premigratory NC cells at the dorsal neural tube, the initial migration of these cells dorsal to the neural tube, and then their movement to the Migration Staging Area (MSA), a region between the neural tube and somite where melanoblasts destined for the dorsolateral pathway pause before migration (Weston, 1991). At these first developmental stages, signals directing early specification events are generated, including those needed for dorso-lateral migration and for the expression of melanocyte-specific genes. Evidence from several studies indicates that the specification of melanocytes occurs prior to emigration (Raible and Eisen, 1994), and recent lineage tracing studies in chick indicate it occurs within the dorsal neural tube from a regionally defined population of cells located dorsal to roof plate cells (Krispin et al., 2010).

Species-specific differences are apparent in early melanoblast specification from NC (Kelsh et al., 2009). In the mouse, both dorsolateral and ventral migrating cells begin to migrate at embryonic day (E) 8.5, while in avian and zebrafish systems, NC dorsal-lateral migration occurs later than ventral migration (Erickson et al., 1992; Loring and Erickson, 1987; Raible et al., 1992). Mouse melanoblasts migrating along the dorsolateral pathway express melanoblast markers beginning at E9.0, leave the MSA from E10.5 onward, and then begin to invade the developing epidermis at E11.5-12 (Luciani et al., 2011; Mayer, 1973; Nakayama et al., 1998; Serbedzija et al., 1990; Wilson et al., 2004; Yoshida et al., 1996). In

contrast, zebrafish melanoblasts show early migration along both DL and ventral pathways, as measured by Tyrosinase (Tyr) and Dopachrome tautomerase (Dct) expression (Camp and Lardelli, 2001; Kelsh and Eisen, 2000). Transplantation and single-cell labeling studies in avians have been instructive in elucidating details of early melanoblast specification/migration (Erickson et al., 1992; Reedy et al., 1998a, b).

Subsequent to their migration throughout the embryo, melanoblasts complete differentiation into mature melanocytes, which includes the establishment of extensive dendritic connections with numerous epidermal keratinocytes (in human epidermis), colonization of hair follicles (in mammals), and production of melanin pigment. Synthesis of the two forms of melanin, brown/black eumelanin and red/yellow pheomelanin, occurs within unique melanocyte organelles known as melanosomes. The melanin is transferred (Erickson et al., 1992; Loring and Erickson, 1987; Raible et al., 1992) via melanocyte dendritic processes to skin keratinocytes and hair. Melanocytes exhibit complex subcellular trafficking of melanosomes, and also exhibit numerous signaling pathways that affect pigment production in response to extracellular cues, including ultraviolet radiation (UVR) (Miyamura et al., 2007).

Specification of sensory neurons and melanocytes by WNT signaling

Both sensory neuron and melanocyte lineages are developmentally regulated by WNT proteins, a family of secreted signaling glycoproteins essential for development. WNTs act as ligands for 7-transmembrane G-protein coupled receptors of the Frizzled family, and are also able to act as ligands for single transmembrane receptors in some cell types (Kikuchi et al., 2009). Both WNT and Frizzled proteins are conserved across many metazoan species, and WNT proteins regulate a wide variety of downstream pathways at many different stages during development (van Amerongen and Nusse, 2009). WNT signaling is complex, given the large number of WNT and Frizzled proteins, their overlapping developmental expression patterns, and the crosstalk that can occur among various WNTs and their receptors (Kikuchi et al., 2009). Additional complexity exists because WNT signaling (along with additional signaling from FGF and BMPs) directs early NC formation, and this signaling is temporally distinct from actions at later stages of melanoblast specification (Garcia-Castro et al., 2002; LaBonne and Bronner-Fraser, 1998; Lewis et al., 2004; Monsoro-Burq et al., 2005; Yanfeng et al., 2003).

Evidence for WNT signaling promoting sensory neuron differentiation comes from studies of mouse NC (Lee et al., 2004). In these studies, conditional expression of activated beta-catenin (β-catenin), an effector molecule downstream of WNT that when activated translocates to the nucleus and activates gene transcription, promotes sensory neuron differentiation in vivo while preventing differentiation of other NC cell types. Treatment of stem cell cultures derived from NC with WNT1 also promotes sensory neuron differentiation (Lee et al., 2004). However in zebrafish and in avian NC cultures, WNT signaling does not appear to promote sensory neurogenesis (Dorsky et al., 1998; Jin et al., 2001).

WNT1 and WNT3a act to specify melanocytes in mouse, chick, zebrafish, and Xenopus NC. NC-specific overexpression of WNT1 or activated β-catenin causes increased melanocytes in zebrafish and in mouse NC explant cultures respectively (Dorsky et al., 1998; Dunn et al., 2000). Similarly, melanoblast formation is increased by WNT3a overexpression in avian NC cultures (Jin et al., 2001) and by WNT3a and β-catenin overexpression within mouse NC (Dunn et al., 2005). While WNT1 and WNT3a appear to act through distinct mechanisms (Dunn et al., 2005), they also show redundancy, as independent mutants appear unaffected, yet combined absence of both WNT1 and WNT3a signaling causes severe defects in the

expansion of NC cells, including melanocytes and neurons derived from cranial and dorsal root ganglia (Ikeya et al., 1997).

The pathways downstream of WNT and β-catenin in melanoblast development are complex, and experimental manipulation suggests that their effects vary depending on the presence of other extracellular factors or the melanocyte developmental stage. For example, in mouse, β-catenin blockage in NC inhibits melanocyte formation, as well as sensory neuron formation (Hari et al., 2002), yet β-catenin overexpression leads to sensory neuron formation, but not melanocyte formation (Lee et al., 2004). This may reflect multiple stages of WNT-β-catenin regulation of NC specification, and a two-stage model has been proposed in which a developmental stage promoting sensory neuron formation precedes a stage controlling melanocyte formation (Sommer, 2011). Melanoblast development in mouse appears sensitive to any perturbation in β-catenin levels, because melanocyte proliferation and subsequent cutaneous melanocyte number were reduced when active β-catenin was either reduced or increased in NC melanoblast precursors (Delmas et al., 2007; Luciani et al., 2011). This sensitivity to both high and low β-catenin levels may in fact reflect levels of the transcription factor MITF (detailed below), as β-catenin combines with Tcf/Lef to activate *Mitf* expression (Dorsky et al., 2000; Takeda et al., 2000) and MITF has been shown to activate melanoblast proliferation at low levels, yet repress it at high levels, respectively (Carreira et al., 2006).

Transcription factor regulation of sensory neuron and melanocyte specification

Not surprisingly, cell fate specification is driven by the regulation of gene transcription. Cell fate restriction of NCCs to the sensory neuron or melanocyte lineages is achieved by activation of specific transcription factors. A compelling model for this process involves integration of signals at a “nodal point”, with activation of a transcription factor or factors that acts as a master regulator that in turn controls downstream differentiation genes (Weintraub et al., 1991). Such transcription factors may act as pioneer factors, promoting access to chromatin for other factors that allow differentiation to proceed (Zaret and Carroll, 2011).

The earliest steps of sensory neuron specification are controlled by basic helix-loop-helix transcription factors of the *neurogenin (neurog)* family. These transcription factors have been well studied in their regulation of neurogenesis, and play important roles in the specification of neurons in the CNS and PNS (Kageyama et al., 2005; Morrison, 2001; Sommer et al., 1996). Forced expression of *neurog* genes is sufficient to produce ectopic neurons in Xenopus (Ma et al., 1996) or zebrafish (Blader et al., 1997). Expression of *neurog* promotes neurogenesis, inhibits gliogenesis and regulates cell migration through a variety of different mechanisms (Ge et al., 2006; Hand et al., 2005; Sun et al., 2001).

Ample evidence supports the idea that *neurogs* initiate sensory neurogenesis. They are the earliest known markers of the sensory neuron lineage, and are expressed in migrating NC before overt neurogenesis in a subset of crest cells that may correspond to fate-restricted precursors (Greenwood et al., 1999; Ma et al., 1999). Overexpression of *neurog* in chick premigratory NCCs biases them to localize to the DRG (Perez et al., 1999). Ectopic expression of *neurog* drives expression of DRG neuronal markers in a heterologous tissue, the dermamyotome (Perez et al., 1999). Both *neurog1* and *neurog2* are needed for DRG neuron development (Ma et al., 1999). Targeted inactivation of either locus alone resulted in loss of subsets of DRG neurons, some only transiently. By contrast when both genes are mutated, DRG development was completely blocked.

Zebrafish have only a single *neurog* gene used in sensory neuron specification (Andermann et al., 2002; Cornell and Eisen, 2002). In mouse, *neurog1* and *neurog2* each play a different role in the development of a subset of cranial sensory neurons: *neurog 1* is necessary for proximal ganglion differentiation, while *neurog2* is necessary for distal (epibranchial) ganglion formation (Fode et al., 1998; Ma et al., 1998). Loss of zebrafish *neurog1* function completely blocks all cranial ganglion formation in addition to disrupting DRG development, demonstrating that it assumes the role of both mammalian genes. In the absence of *neurog1*, cells that would normally form sensory neurons instead differentiate as glial cells, suggesting that it controls the fates of neuroglial-restricted precursors (McGraw et al., 2008). A similar role for *neurog* in directing binary cell fate decisions between neurons and glia has been suggested to occur in the central nervous system (Bertrand et al., 2002; Miller and Gauthier, 2007; Nieto et al., 2001; Ross et al., 2003).

Does *neurog* act as a master regulatory gene for sensory neuron specification? Several lines of evidence refute this idea, and suggest additional factors are needed. Expression of *neurog* alone within NCCs is not sufficient to distinguish cells as DRG sensory neurons. Introduction of *neurog* into NCCs promotes general neurogenesis, but cells can form sensory or sympathetic neurons depending upon the addition of exogenous factors (Lo et al., 2002). Recombination of *neurog* into the *mash1* locus allows cells that would normally express *mash1* to continue with autonomic neurogenesis rather than being diverted to sensory lineages (Parras et al., 2002). Genetic lineage marking techniques using *cre* recombinase and the ROSA26 *lacZ* reporter strain have demonstrated plasticity of cells expressing *neurog2*: cells are strongly biased towards DRG contribution, but both neurons and glia are labeled (Zirlinger et al., 2002). Thus *neurog* expression alone may not be sufficient to specify DRG neuron cell type, and suggests that it works in combination with other transcription factors as it does in the CNS (Helms et al., 2005; Nieto et al., 2001).

Two factors that might function in conjunction with *neurog* are Brn3a and Isl1, homeobox transcription factors that are co-expressed in early postmitotic sensory neurons (Fedtsova and Turner, 1995). Targeted inactivation of either factor results in sensory neuron death (Eng et al., 2001; Huang et al., 1999; McEvilly et al., 1996; Sun et al., 2008; Xiang et al., 1996), and loss of both together show additive effects (Dykes et al., 2011). Brn3a and Isl1 perform several functions to regulate the transition from progenitor to differentiated neuron. Both factors are required for repression of early neurogenic factors (Dykes et al., 2010; Eng et al., 2007; Lanier et al., 2007; Sun et al., 2008). These factors also block alternate differentiation pathways; ectopic expression of central nervous system genes occurs in their absence (Lanier et al., 2009; Sun et al., 2008). In addition, Brn3a and Isl1 directly promote the expression of differentiation genes (Dykes et al., 2010; Eng et al., 2007; Eng et al., 2004; Sun et al., 2008). In some cases this synergy comes about by their ability to bind to common regulatory regions (Dykes et al., 2011). Taken together, these studies support a model where Brn3c and Isl1 regulate the transition from neurogenic precursor to differentiating sensory neuron.

Although sensory neurons share common developmental aspects, such as their positioning in the DRG and gross aspects of central and peripheral projections, it is their distinct characteristics that define their functions to detect particular sensations. These characteristics are acquired during the maturation of sensory neurons, a process that is regulated by the Runx family of transcription factors. Related to Drosophila Runt, Runx proteins were identified as transcription factors with oncogenic potential (Ito, 2004). These transcription factors are regulated by Brn3a (Dykes et al., 2010), and are expressed in different subsets of sensory neurons: Runx1 in nociceptors and Runx3 in proprioceptors (Inoue et al., 2002; Levanon et al., 2002; Levanon et al., 2001). Runx1 is required for proper maturation of nociceptive neurons, refining the differences between peptidergic and

nonpeptidergic classes (Chen et al., 2006b; Kramer et al., 2006; Marmigere et al., 2006; Yoshikawa et al., 2007). Loss of Runx1 results in loss of the nonpeptidergic Ret+ nociceptors, resulting in insensitivity to thermal and neuropathic pain. Overexpression of Runx1 results in increased neuropeptide expression (Kramer et al., 2006). Runx1 is also necessary for expression of genes necessary for nociceptor functions, including different classes of the Mrgpr receptors (Chen et al., 2006b; Liu et al., 2008). Runx3 is required for differentiation of proprioceptors (Chen et al., 2006a; Inoue et al., 2002; Kramer et al., 2006; Levanon et al., 2002). Loss of Runx3 results in mistargeting of axons, and eventual loss of neurons. Overexpression of Runx3 results in increase in proprioceptors at the expense of TrkB+ mechanoreceptors (Inoue et al., 2007; Kramer et al., 2006).

Similar to sensory neurons, melanocyte differentiation is also influenced by the interplay of transcription factors and growth factors influencing fate restriction. Just as one or more *neurogs* are key factors for sensory neuron development, melanocyte specification and differentiation is due to regulated expression of another basic helix loop helix transcription factor, microphthalmia associated transcription factor (MITF). MITF expression is seen in cells of the dorsal neural tube and early emigrating melanoblasts, and continues throughout melanocyte differentiation (Lister et al., 1999; Nakayama et al., 1998; Opdecamp et al., 1997; Thomas and Erickson, 2009). MITF regulates expression of many early genes that regulate aspects of melanocyte development and survival, including but not limited to Silver/Pmel17, Dopachrome tautomerase, Tyrosinase, Tyrosinase-related protein 1, Mlana, and Slc45a2, and it has been suggested that the earliest expression of MITF marks specification of the melanoblast lineage (Thomas and Erickson, 2008, 2009). Animals containing null mutations for *Mitf* lack melanocytes in mice, fish and man, and misexpression of MITF can promote pigmentation in mouse fibroblasts in culture (Tachibana et al., 1996) and in zebrafish embryos in vivo (Lister et al., 1999) suggesting that MITF expression specifies crest cells to a melanocytic fate. While MITF is required for survival of melanocytes in rodents, zebrafish, and avians (Hodgkinson et al., 1993; Hughes et al., 1993; Lister et al., 1999; Mochii et al., 1998; Opdecamp et al., 1997), detailed analysis of *Mitf* mutant mice that do not produce MITF protein yet still express *Mitf* mRNA demonstrates that *presumptive* melanoblasts are observed in early migrating crest but only transiently, and are thought to undergo apoptosis (Hou et al., 2000; Nakayama et al., 1998; Opdecamp et al., 1997). Consistent with this notion, lineage-tracing studies have indicated that melanoblasts, along with other crest derivatives, are specified prior to emigration within defined locations in the dorsal neural tube (Krispin et al., 2010). The subset of cells from which melanoblasts will form in the neural tube exhibit low levels of FOXD3, SNAIL and SOX9, implicating reduced expression of these transcription factors is needed for melanoblast specification.

The reduced FOXD3 expression in presumptive melanoblasts is consistent with studies demonstrating it having a repressive role in melanocyte specification and being a key regulator in a melanocytic versus glial fate. FOXD3 is expressed in emigrating crest but is not expressed in melanoblasts or melanocytes. Misexpression of FOXD3 in late emigrating avian crest results in reduced MITF expression, reduced numbers of melanocytes and increased numbers of glial cells (Thomas and Erickson, 2009). FOXD3 mutant zebrafish have an expanded MITF expression domain, and FOXD3 has been shown to directly repress the transcription of *mitf* in zebrafish (Curran et al., 2009). This repression of FOXD3 via HDAC1 is required for MITF expression in avian melanocytes (Thomas and Erickson, 2009). Murine knockout studies, while confirming early roles in NC formation (Teng et al., 2008), have yet to address these functions of FOXD3 in mouse melanocytes.

Additional transcription factors that may play a role in specification of melanocytes are the SOXE family of HMG box transcription factors--SOX8, 9 and 10--that are all expressed in

the dorsal neural tube around the time of NC formation (Figure 2; reviewed in Hong and Saint-Jeannet, 2005). SOX9 is downregulated in trunk NCCs in mouse, chick, Xenopus and zebrafish (Cheung et al., 2005; McKeown et al., 2005; Spokony et al., 2002; Yan et al., 2005). In Xenopus (Spokony et al., 2002), knockdown of SOX9 function affects cranial crest but does not cause a loss of pigment cells. Similarly in zebrafish, lack of Sox9b expression causes craniofacial defects with limited alterations of pigment cells, restricted to reduction of iridophores and altered pigmentation within melanocytes (Yan et al., 2005). Gain of function studies with SOX9 in Xenopus (Taylor and LaBonne, 2005) and chick (Cheung and Briscoe, 2003) demonstrate its ability to promote melanocyte differentiation, however this action may only occur early via promotion of increased NC, as ectopic, prolonged expression of SOX9 in melanoblasts of transgenic mice results in a hypopigmented state (Qin et al., 2004). Consistent with this, overexpression studies have shown that SOX9 can induce the expression of SOX10 in frog, fish and chick (Aoki et al., 2003; Cheung and Briscoe, 2003; Yan et al., 2005).

In contrast to SOX9, SOX10 is required for melanocyte development in mouse (Britsch et al., 2001; Lane and Liu, 1984; Southard-Smith et al., 1998), *Xenopus* (Honore et al., 2003), and zebrafish (Dutton et al., 2001; Kelsh and Eisen, 2000). In mouse and zebrafish SOX10 null mutants, *Mitf* and an additional early melanoblast marker, *Kit,* are both absent, suggesting a key involvement of SOX10 in specifying melanocyte fate (Dutton et al., 2001; Hou et al., 2006). Additional studies in vitro have demonstrated that SOX10 directly binds the MITF promoter to direct transcription, therefore its role in pigmentation may be through the upregulation of *Mitf,* which in turn proceeds to direct melanocyte migration and differentiation. Interspecies differences are apparent, as SOX10 but not SOX9 expression is maintained in melanocytes in mice (Hou et al., 2006; Osawa et al., 2005), SOX10 is lost in human melanocytes in concert with a reactivation of SOX9 (Passeron et al., 2007), and in zebrafish SOX9 is downregulated and then, after initial melanocyte specification, SOX10 is also downregulated in all NC cells except glial cells (Dutton et al., 2001). Even though interspecies differences are noted in SOXE expression patterns, it is still likely that gene relationships in regulatory loops will be conserved. An elegant series of experiments and modeling has further dissected the initial specification of melanocytes in zebrafish (Greenhill et al., 2011). This work supports a more refined model, where SOX10 is only needed for initiation of *Mitf* expression, and then acts as a feed forward inhibitor to block melanocyte differentiation genes, perhaps as a mode for maintaining plasticity. In this model SOX10 is no longer needed for differentiation, and in fact MITF in conjunction with HDAC is involved in downregulation of SOX10 to overcome its inhibitory effects on melanocyte differentiation. Additional studies are needed to assess how this gene regulatory network functions in mice, and also in human melanomas that exhibit co-expression of SOX10 and MITF.

Growth factor regulation of sensory neuron and melanocyte specification

While the expression of combinations of transcription factors may set a cell's potential, configuring the genome to interpret environmental cues, the expression of growth factor receptors is critical for enabling a cell to respond to these cues. For the development of sensory neurons and melanocytes, growth factor receptors play important roles in cell type specification. In addition, these receptors regulate cell survival, as both melanocyte and sensory neuron differentiation is sculpted by cell death.

The influences of growth factors on sensory neuron development have a long history; Levi-Montalcini and Hamburger identified the first growth factor (nerve growth factor, NGF) studying the survival of DRG neurons (Hamburger and Levi-Montalcini, 1949). The neurotrophins NGF, BDNF, NT3 and NT4 are target-derived growth factors that promote

sensory neuron survival (reviewed in (Ernsberger, 2009)). The receptor tyrosine kinases TrkA, TrkB and TrkC respond to each neurotrophin respectively. TrkC is expressed very early in dividing sensory precursors (Henion et al., 1995; Rifkin et al., 2000). Expression of TrkA, TrkB and TrkC are refined to distinct sensory neuron types within the DRG (Farinas et al., 1998; Kashiba et al., 1996; Li et al., 2010; McMahon et al., 1994; Mu et al., 1993; Rifkin et al., 2000; Wright and Snider, 1995; Zhang et al., 1994): TrkA expression overlaps with nociceptor markers, TrkB is expressed in a subset of mechanoreceptors, and TrkC is expressed in cells corresponding to proprioceptors. Targeted inactivation of Trk receptors and their ligands confirmed that they function in specific DRG neuron subtypes. When TrkC receptors or NT3 were functionally inactivated, large proprioceptors were selectively lost (Ernfors et al., 1994; Farinas et al., 1994; Klein et al., 1994; Minichiello et al., 1995; Tessarollo et al., 1994). In contrast, when trkA receptors or NGF were inactivated, smaller nociceptors were lost (Crowley et al., 1994; Minichiello et al., 1995; Smeyne et al., 1994).

The well-established roles of neurotrophins and their receptors in neuron survival confounded interpretations of whether these signals play additional roles in cell specification. Prevention of cell death by inactivation of the proapoptotic gene BAX revealed roles for NGF/TrkA in maturation of nociceptor subtypes and NT3/TrkC for maturation of proprioceptors, including proper axonal projections (Genc et al., 2004; Guo et al., 2011; Luo et al., 2007; Patel et al., 2000; Patel et al., 2003). These studies supported the idea that neurotrophin signaling played critical roles in the definition of sensory neuron cell type. When TrkC coding sequence is used to replace the TrkA locus, a small fraction of cells acquire proprioceptor characteristics (Moqrich et al., 2004), supporting the idea that receptor activation has an effect on lineage choice. While factors that regulate the initiation of Trk receptors are largely unknown, both Runx factors and Brn3a are required for their continued expression and dynamic refinement (Dykes et al., 2010; Inoue et al., 2007; Lei et al., 2006; Ma et al., 2003).

The receptor tyrosine kinase Ret acts a receptor for GDNF family ligands along with the GFRalpha co-receptors (reviewed in (Ernsberger, 2008)). As mentioned earlier, Ret expression distinguishes differentiated subtypes of sensory neurons, including nonpeptidergic nociceptors from peptidergic nociceptors (Bennett et al., 1998; Molliver et al., 1997). Ret function is required for the differentiation and maintenance of nonpeptidergic nociceptors from TrkA+ precursors (Luo et al., 2009; Luo et al., 2007). Ret is also expressed in a distinct subset of early differentiating sensory neurons (Kramer et al., 2006). Ret function is necessary in these cells for the development of a subset of rapidly adapting mechanosensory cells (Luo et al., 2009). In contrast to Trk family receptors, Ret appears to have little control of cell survival, with the majority of its effects directed towards maturation of sensory neurons.

A variety of mouse studies have shown that the type III receptor protein-tyrosine kinase Kit oncogene (KIT) is required during defined critical portions of melanocyte development between E9.5 and E15.5 for migration, survival, proliferation, and later on for differentiation (Botchkareva et al., 2001; Cable et al., 1995; Ito et al., 1999; Mackenzie et al., 1997; Nishikawa et al., 1991; Yoshida et al., 1996). Similarly, the zebrafish Kit ortholog Kita is required for melanocyte migration and survival at two different developmental timepoints (Rawls and Johnson, 2003), and also for melanocyte differentiation (Mellgren and Johnson, 2004). However, these are all functions that would be executed after melanoblast specification, suggesting KIT does not play a role in this process. In support of this idea, NC cultures derived from KIT null embryos still exhibit MITF+ cells at early NC developmental stages (Hou et al., 2000). Also, Kit expression in avian systems occurs in melanoblast precursors, not glial-melanoblast precursors, suggesting Kit expression may be coincident with melanoblast lineage restriction (Lecoin et al., 1995; Luo et al., 2003).

The G protein-coupled Endothelin receptor type B (EDNRB) is a 7 transmembrane domain membrane protein that is expressed in melanoblasts and required for normal development of melanocytes and enteric ganglia (Hosoda et al., 1994). EDNRB is regulated by Endothelin 3 (EDN3) signaling, and is required for embryonic melanocyte development from E10-12.5, a time period when the melanoblast precursors reach the migration staging area (MSA) and E12.5, when they have migrated away from the MSA (Lee et al., 2003; Pavan and Tilghman, 1994; Shin et al., 1999). Overexpression of the chick EDNRB ortholog Ednrb2 directs cells that would normally migrate medially (and not become melanocytes) to migrate dorsolaterally; this suggests that, at least in avians, the Ednrb2 signals that direct dorsolateral migration can be experimentally separated from those signals regulating specification (Harris et al., 2008). Collectively, these studies suggest EDNRB is essential for later stages of melanoblast development, and not for melanoblast specification, and in support of this, EDNRB does not appear to be necessary for initial protein expression of the melanoblast genes SOX10, MITF, and KIT (Hou et al., 2004). This requirement for EDNRB for later melanoblast developmental stages does not preclude its influence on earlier NC development. Rather, murine and avian NC culture studies hint that EDN3/EDNRB signaling may regulate survival, proliferation, differentiation, and migration of a bipotent glial-melanocyte NC derivative (Dupin et al., 2000; Dupin and Le Douarin, 2003; Lahav et al., 1998; Lahav et al., 1996; Opdecamp et al., 1998; Reid et al., 1996; Trentin et al., 2004).

Conclusions

Detailed analyses of individual NC lineages provide insights into the specific cellular pathways that are involved both during development and in disease states. Additionally, much can be learned from comparison of these pathways, both between species and between specific lineages. Many of the genetic factors essential for cell fate specification in NC-derived sensory neurons and melanocytes are well characterized. The bHLH transcription factors *Neurog* and *Mitf* play central roles in cell fate specification of sensory neurons and melanocytes, respectively. The initial expression of these two markers appears to coincide with specification of each lineage, although following their expression, plasticity remains that is subject to signaling input. Future studies in other NC cell lineages will determine if other transcription factors play similarly central roles in specification.

Signaling pathways play an essential part in NC lineage specification. To date, only WNT factors have been identified as common signals regulating the earliest steps in sensory neuron and melanocyte specification upstream of *Neurog* and *Mitf*. Although both lineages can be specified by WNT signaling, each clearly responds with different transcriptional and biochemical downstream pathways that result in distinct lineages. Thus many questions remain regarding which molecular mechanisms at the earliest stages of specification direct such a precise outcome. While the timing of WNT signals may provide a mechanism for specificity, temporal changes imply an alteration in the internal state of NCCs, so that the WNT signals are interpreted in a different context over time. The mechanism by which there are changes in NCC competence to respond to WNT signals remains unknown.

NC lineage specification also involves overcoming transcriptional repressors at appropriate developmental stages, and many questions remain regarding this process. For example, FOXD3 is essential for early stages of NC development, yet its expression acts to repress the melanocyte lineage (Kos et al., 2001; Wang et al., 2011). Thus at some point prior to or coincident with melanocyte lineage specification, FOXD3 expression must be downregulated. Future studies will be required to determine what mechanisms overcome FOXD3 repression in melanocyte lineage precursors, and what maintains its expression in other lineages; the existence of other transcriptional repressors functioning in NC specification may await discovery as well.

Finding these novel factors governing early NC lineage specification is not trivial, and studies on these earliest stages of NC lineage specification are technically difficult. Reliance on markers is problematic, as this requires gene expression robust enough for visualization. Lineage tracing is becoming more informative, such as moving from LacZ-based expression tracing to real-time fluorescence markers in fish and mice (Shibata et al., 2010), yet one still needs the ability to reliably identify lineages.

Still broader questions remain regarding spatial differences in NC development. For example, cranial crest appears to show differences in development and plasticity as compared to trunk NC. In the trunk, specific anatomical sub-regions or different migratory pathways may influence NC development. Understanding the molecular differences that contribute to these regional subtypes may reveal essential factors that act in different embryonic regions. Recent work studying both dorsolaterally-migrating melanocytes and those that arise from regions adjacent to developing nerves in the trunk, head, and neck has begun to shed light on these differences (Adameyko et al., 2009; Adameyko et al., 2012). In summary, comparing and contrasting common themes governing individual cell types, such as the melanocytes and sensory neurons, we are able to gain insights into basic developmental pathways involved in specification of lineages. These findings will be applicable when elucidating the specification of other neural crest lineages.

Highlights

Sensory neurons and melanocytes are derived from neural crest.

Transcription factors control the process of sensory neuron and melanocyte specification.

Growth factors influence neural crest cell fate specification.

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