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CONCISE REVIEW

STEM CELLS TRANSLATIONAL MEDICINE

Adult tissue–derived neural crest-like stem cells: Sources, regulatory networks, and translational potential

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Abstract

Neural crest (NC) cells are a multipotent stem cell population that give rise to a diverse array of cell types in the body, including peripheral neurons, Schwann cells (SC), craniofacial cartilage and bone, smooth muscle cells, and melanocytes. NC formation and differentiation into specific lineages takes place in response to a set of highly regulated signaling and transcriptional events within the neural plate border. Premigratory NC cells initially are contained within the dorsal neural tube from which they subsequently emigrate, migrating to often distant sites in the periphery. Following their migration and differentiation, some NC-like cells persist in adult tissues in a nascent multipotent state, making them potential candidates for autologous cell therapy. This review discusses the gene regulatory network responsible for NC development and maintenance of multipotency. We summarize the genes and signaling pathways that have been implicated in the differentiation of a postmigratory NC into mature myelinating SC. We elaborate on the signals and transcription factors involved in the acquisition of immature SC fate, axonal sorting of unmyelinated neuronal axons, and finally the path toward mature myelinating SC, which envelope axons within myelin sheaths, facilitating electrical signal propagation. The gene regulatory events guiding development of SC in vivo provides insights into means for differentiating NC-like cells from adult human tissues into functional SC, which have the potential to provide autologous cell sources for the treatment of demyelinating and neurodegenerative disorders.

KEYWORDS

demyelinating disorders, gene regulatory network, neural crest, Schwann cells

1 | INTRODUCTION TO THE NEURAL CREST CELLS

Often referred to as the "fourth germ layer," the neural crest (NC) is a multipotent and migratory stem cell population that contributes to a wide array of organs and tissues in the vertebrate embryo, including autonomic ganglia, sensory neurons, adrenal and thyroid glands, cartilage and bone of the face, smooth muscle cells of some major arteries, and melanocytes in the skin.[1,2] NC formation is first observed at stage 9 of human embryogenesis and extends till stage 20 as per the Carnegie staging system.[3] Neural crest stem cells (NCSC) were first identified in rodents by Stemple and Anderson and isolated using cell sorting for NC-specific cell surface protein $p75^{NTR}$ (neurotrophin receptor [NTR]). These $p75^{NTR+}$ cells could self-renew and generate

neurons and glia of the PNS as well as myofibroblasts.[4] The high degree of self-renewal and regenerative capacity of NC makes it a very attractive source for stem cell-based therapies.

During embryonic development, formation of NC stem cells originates in response to a set of signaling events between neural and non-neural ectoderm, a region termed as the neural plate border.[5] Induction is initiated at the plate border by signals including fibroblast growth factor (FGF), bone morphogenetic protein (BMP), and Wnt.[5,6] On establishment of the neural plate border territory, new signaling events are established for specification of bona fide NCSCs. This process results in expression of NC specifiers (Snail2, Sox8, Sox9, Sox10, FoxD3, c-Myc, and Id family members) that in turn mediate changes in shape, motility, and adhesive properties leading to delamination of NCSCs from the neuroepithelium and initiating cell lineage decisions.[6] NC precursor cells within the dorsal neural tube then undergo epithelial to mesenchymal transition and migrate along precise pathways,[7] eventually settling and differentiating into specialized cell types, according to their axial origin as well as environmental cues encountered during the process.[8] Cranial NCSCs form craniofacial structures of the head including cartilage and bone tissue of the skull and face, as well as cranial neurons, glia, and connective tissue of the face. Trunk NCSCs differentiate into dorsal root ganglia (DRG), containing sensory neurons and satellite glial cells, endocrine cells of the adrenal glands, and Schwann cells (SC) along the spinal nerves. Some of these NCSCs also differentiate into melanocytes in the skin. Finally, vagal NCSCs populate the enteric nervous system (ENS) along the length of the gut and contribute to the connective tissues of the arteries, septation of the outflow tract and cardiac ganglion.[1]

Significance statement

Neural crest (NC) cells have attracted attention for their multipotent nature and ease of isolation from adult tissues. This concise review reports the advantages of using NCs for the treatment of demyelinating disorders and spinal cord injury (SCI), over other cell sources such as induced pluripotent stem cells and embryonic stem cells. Adult tissue-derived NCs are easy to expand in vitro and can be derived from autologous sources. Moreover, differentiation of NCs to Schwann cells (SC) can be easily achieved without genetic mutation, making them safe for translation from a laboratory to a clinical setting. Adult NC-derived SC are functional and can myelinate neurons in vitro and spinal cord in vivo in mice. Hence, NCs derived from adult tissue are a promising cell source for the treatment of demyelinating disorders and SCI. Furthermore, this technology can also be used for disease modeling and drug testing, making way for personalized therapeutics for neurological disorders.

2 | SOURCES OF NC-LIKE STEM CELLS IN ADULT TISSUES

2.1 | NC characteristics are retained postembryonically in adult tissues

Although NC cells are often referred to as stem or stem-like cells, they are a transient population in the embryo that becomes progressively restricted in developmental potential during the course of development and rapidly lose their multipotency. Nevertheless, recent evidence suggests that many NC derivatives, including skin, cornea, gut, and peripheral nerves, contain stem or precursor cells with the ability to give rise to multiple NC derivatives.[1,9] These tissues provide potential sources for obtaining multipotent neural crest-like stem cells (NCISCs) for the purpose of regenerative medicine and cell therapy, and consequently, they are under study in several laboratories. Whether NC-like cells from the adult tissue come from embryonic NCs and remain dormant in a multipotent state or they attain a specialized fate and dedifferentiate to their NC progeny in specific culture conditions has not been established yet. The answers to these questions can only be attained by lineage-tracing experiments tracking migration and differentiation of NCs starting from embryo development and throughout adulthood.

NCISCs have been isolated from mouse bone marrow and DRG. Nagoshi et al used double-transgenic mouse strains P0 and Wnt1-Cre/Floxed-EGFP to map and isolate NCISCs from bone marrow, DRG, and whisker pad using cell-sorting. P0 and Wnt1 are marker genes expressed in NC cells in mouse embryos.[10] Interestingly, DRG-derived NCISCs generated more primary and secondary spheres compared with bone marrow and whisker pad–derived cells and showed increased expression of NC markers p75NTR, Sox10, Nestin, and Musashi1. Additionally, 75% of DRG-derived spheres showed tri-lineage differentiation to neurons, glia, and myofibroblasts, compared with only 7.3% of spheres derived from whisker pad and 3.3% in spheres derived from bone marrow.[10] These results highlight the tissue-dependent differences in the abundance and self-renewal capacity of adult NCISCs, which may ultimately determine the suitability for cellular therapies. Furthermore, bone marrow–derived NCs could be differentiated into SC that showed myelination around DRG neuronal axons in vitro, indicating their potential for use in peripheral nerve regeneration.[11]

During development, NCs also migrate to the cornea, where their derivatives remain throughout adulthood. The cornea is a transparent avascular structure that covers the front of the eye and helps to focus light on the retina. The cornea consists of three major cellular components: a stratified epithelium, a collagenous stroma containing keratocytes, and a layer of endothelium.[1] Experiments with chick-quail chimeras demonstrated that cranial NC cells form the corneal endothelium and keratocytes.[12–15] Lineage tracing experiments demonstrated that upon transplantation from late into early chick embryos quail NC-derived keratocytes followed normal migratory routes giving rise to smooth muscle cells, myofibrils, keratocytes, and endothelial cells but failed to differentiate into neurons or cartilage, suggesting restricted plasticity of these NC-derived progenitors.[16] Another study however demonstrated differentiation of corneal progenitor cells into keratocytes, fibroblasts, myofibroblasts, adipocytes, chondrocytes, and neural cells, indicating similar differentiation potential to NCSC.[17]

Stem cell derivatives of NC origin persist in the adult rodent gut from which they can be isolated based on CD49b expression. Sorted cells showed expression of NC marker genes, such as p75NTR, Sox10, and Nestin, along with markers specific to enteric glia such as S100B and glial fibrillary acidic protein.[18] Multipotent progenitors from fetal gut exhibited more plasticity and degree of self-renewal compared with those derived from adult gut. In addition, upon transplantation into chick embryos, fetal progenitors gave rise primarily to neurons, whereas postnatal gut progenitors turned predominantly into glia.[19] In vivo grafting experiments suggest therapeutic potential of these progenitors for the treatment of ENS disorders.[20,21]

Cardiac NC cells play a role in septation of cardiac outflow tract into pulmonary and aortic branches.[1] In vitro clonal expansion of NCISCs isolated from cardiac tissue suggested that only a small fraction of them were capable of self-renewal and generation of NC derivatives.[22] Stem cells from neonatal rodent heart demonstrate a "NC-like" behavior, and when grown as cardiospheres, they could differentiate into PNS neurons, glia, smooth muscle cells, and cardiomyocytes, as well as migrate to tissues characteristic for NC derivatives in ovo.[23] Interestingly, cardiac *resident Nestin+* progenitors migrated to areas damaged by infarction and contributed to reparative vascularization, indicating their potential for the treatment of various heart diseases.[24]

Although the presence of NCISCs in developed tissues provides evidence of an alternative cell source for cell therapy, most studies of this type have been limited to rodents, due to inaccessibility of human NCs in organs such as gut, heart, DRG and spine, as shown in Figure S1. Interestingly though, NCISCs have also been isolated from adult human tissues such as skin and dental pulp. The isolation of NCISCs from skin tissue enhances their therapeutic potential, mostly because of the accessibility and size of skin tissue that can provide autologous cells for cell therapies.[25–28] Fernandes et al showed that endogenous adult dermal precursors residing in the papillae of hair and whisker follicles could give rise to multipotent NCISCs.[25] Similarly, Sieber-Blum et al reported the presence of multipotent NCISCs in the adult mammalian hair follicle, which could give rise to neurons, melanocytes, smooth muscle cells, SC, and chondrocytes in vitro. These multipotent cells were termed epidermal neural-crest cells,[26] and when grafted in a mouse model of SCI, they integrated into the host spinal tissue yielding improvements in touch perception and sensory connectivity.[29]

2.2 | Multipotent NCISCs from interfollicular epidermis

Recently, in our laboratory, Bajpai et al devised a method to reprogram postnatal human epidermal keratinocytes (KCs) to NCISC (termed KC-NC) by mimicking signaling events that occur at the neural plate border. Transcriptomic analysis confirmed that epidermally derived NCISCs were similar to those generated from human embryonic stem cells (ESCs) and maintained the multilineage differentiation potential into melanocytes, neurons, SC, and mesenchymal cells in vitro and in ovo.[30] In a subsequent study, we identified the factors that promote expansion of KC-NC and maintain the NC phenotype. Specifically, we showed that FGF2 was necessary and sufficient for expression of Sox10, but both FGF2 and IGF1 worked synergistically to upregulate FoxD3. In addition, inhibition of TGF-β1 further enhanced Sox10 expression.[31] We also demonstrated that the same signaling factors can be used to obtain multipotent and functional NCISCs from cultures of human inter-follicular KC isolated from elderly donors.[32] Interestingly, NCISC from older donors exhibited significantly younger epigenetic age than epidermal KC, perhaps indicating greater potential for cell therapies. Given the accessibility, high proliferative capacity, and ease of reprogramming without genetic modification, KC-NC represent an abundant, autologous source of functional therapeutic cells for regenerative medicine. They can also provide an excellent culture system for studying human disease, similar to induced pluripotent stem cells (iPSCs) but without the need for genetic modification or reprogramming to the pluripotent state.

2.3 | Schwann cell precursors contribute to NC derivatives

Recent evidence suggests that NC cells that become associated with peripheral nerves acquire a partial glial phenotype, assuming the characteristics of a "Schwann cell precursor" (SCP). Intriguingly, it has been shown that late embryonic stages, many melanocytes originate from nerve-associated SCPs.[33] This occurs well after NC cells destined to form melanocytes have emigrated from the neural tube. Similarly, lineage analysis in mice has shown that cranial parasympathetic ganglia as well as a subpopulation of enteric neurons arise from this cell population.[34–36] This is consistent with the possibility that later NC derivatives may arise from an SCP population that represents a nascent stem cell population associated with peripheral nerves. These SCPs express characteristic marker genes that are different from those expressed by migratory NCSC but similar to markers expressed by immature SC. For example, SCPs express genes encoding myelin basic protein (MBP), peripheral myelin protein 22 (PMP22), desert hedgehog, Cadherin 19, Connexin 29, GAP43, BFABP, and other Schwann cell markers, many of which are also associated with differentiation into myelinating SC.[37–41] However, rather than being restricted to differentiate into SC, SCPs remain multipotent and appear to have the ability to contribute to numerous lineages at much later times in embryogenesis than normally associated with NC migration. In fact, recent studies also suggest that SCPs may give rise to chromaffin cells of the adrenal medulla, as evidenced by single cell RNA sequencing (scRNA-seq) of the developing adrenomedullary cells in mice.[42] This raises the intriguing possibility that these may represent true stem cells with remarkable multipotency and regenerative ability.

The transition from migratory NC cell to SCPs likely occurs when NC cells approach and/or become associated with peripheral nerves emanating from sensory and autonomic ganglia. At this point, the NC-derived cells upregulate genes typically associated with SC while downregulating more typical NC markers, thus assuming a more glial like state.[38,43] Although these cells may be biased toward glial lineages, they remain multipotent and we speculate that perhaps they "dedifferentiate" similar and give rise to other NC fates similar to radial glia which are neuronal progenitors in the central nervous system. Whether SCPs maintain their

multipotency into adulthood and the full range of cell types into which they can differentiate remain open questions.

3 | GENE REGULATION IN NC CELLS: FATE ACQUISITION AND MULTIPOTENCY MAINTENANCE

3.1 | An NC gene regulatory network controls lineage diversification into neuronal, melanocytic, and glial, including Schwann cell lineages

The NC is an excellent model system for studying questions of stem cell biology due to its multipotency, motility, and ability to form a broad array of derivatives. These are as diverse as neurons and SC of the peripheral nervous system, craniofacial cartilage, and bone, as well as skin melanocytes. These inherent stem cell properties have potentially important implications in regenerative medicine to treat disorders like familial dysautonomia, cleft palate, and NC-related heart conditions such as Persistent Truncus Arteriosus, as well as to understand anomalies in differentiation that lead to cancers such as melanomas and Schwannomas.

The recent expansion of molecular biological techniques including single-cell RNA-seq, ChIP-seq, and ATAC-seq have facilitated the dissection of the genetic program controlling NC development. These genomic approaches have provided important insights into gene regulatory mechanisms and uncovered new regulatory factors involved in control of NC formation and diversification.[44,45] It is now clear that an intricate array of transcription factors and signaling molecules act in concert to imbue NC cells with its broad multipotency and migratory ability. These factors have been proposed to act via a multistep NC gene regulatory network (GRN) that integrates transcriptional inputs and diverse environmental signals.[2,5,46,47] The NC GRN consists of a series of hierarchically arranged regulatory steps, including induction of the prospective NC at the neural plate border, specification of multipotent NC cells within the dorsal neural tube, control of their delamination via an epithelial to mesenchymal transition to produce a migratory population, and finally, diversification into distinct cell lineages.

The NC GRN posits that the process of NC formation is comprised of a logical series of distinct regulatory steps that flow seamlessly from one to the other. First, signaling molecules, including Wnts, FGFs, and BMPs, in the gastrula stage embryo initiate the process of NC induction by inducing transcription factors like *Msx*, *Pax3/7*, *Zic1*, and *Dlx3/5* at the border between the neural plate and nonneural ectoderm. The region where these genes are coexpressed defines the neural plate border—a domain primed to form bona fide NC cells. These in turn function in combination with signaling molecules to regulate "NC specifier genes" like *Snail/Slug*, *AP-2*, *FoxD3*, *Twist*, *Id*, *cMyc*, and *Sox8/9/10*. The NC GRN itself can be envisioned as a series of sequential binary decisions leading to differentiation into derivative fates. Recently *Twist1* has been reported to play a critical role as a regulator of NC fate decision, and it biases NC commitment toward a mesenchymal fate.[45] Conversely, *FoxD3* represses the mesenchymal program of delaminating NCs.[48] The postmigratory program begins following the downregulation of transcription factors associated with the neural tube program such as *Zic3* and *Pax8*.

Expression of the Sox family genes initiates within the dorsal neural tube and defines cells with the potential to emigrate from the neural tube and form migratory NC cells. In particular, the SoxE transcription factors (Sox8/9/10) are critical regulators of most NC lineages.[5,49,50] Specifically, Sox8 and Sox9 are expressed early in the newly induced NC, preceding Sox10, which serves as a nearly pan migratory NC marker. At later developmental stages, Sox9 and Sox10 persist in specific NC subpopulations. Whereas Sox9 is maintained in NC-derived chondrocytes, Sox10 persists in neuronal, glial, and melanocyte lineages and controls their specification in combination with different cofactors in each lineage.

Sox10 regulates differentiation of sensory and autonomic lineages by regulating expression of achaete-scute homolog 1 and the paired homeodomain (Phox2b) transcription factors that are essential for neurogenesis in the autonomic lineage.[51] In the DRG, transient expression of Sox10 regulates expression of neurogenin.[52] Sox10 also binds to endothelin receptor-B (EDNRB) to regulate development of the ENS, and disruption in this binding has been shown to cause Hirschsprung disease.[53] Sox10 also is critical for emergence of the glial lineage by regulating Oct6 and Krox20 (Egr2) transcription factors, which are critical for myelination.[54–56] Its expression persists through subsequent stages of terminal differentiation,[49] regulating expression of myelin proteins, including protein zero (P0)[57], MBP, PMP22, and the gap junction protein connexin 32.[58]

3.2 | Diverse signaling pathways govern NC cell fate during embryogenesis

Many studies have focused on discovering the regulatory pathways that control NC fate acquisition in order to better understand cell fate specification during embryonic development in vivo and develop bioinspired strategies to differentiate NC into different lineages in vitro.

After formation of the neural tube, NC cells separate from the neuroepithelium and migrate to distant anatomic locations, while making cell lineage decisions in response to multiple morphogenetic signals.[59,60] However, some NCs remain unspecified and retain their stemness and multipotency.[9,61] In general, there is significant heterogeneity with respect to the differentiation capacity of NCs, with some giving rise to multiple derivatives while others differentiating into a subset of cell types,[62,63] depending on anatomic location and the presence of fate specifying signals. NCs from all axial levels give rise to neurons, glia, and pigment cells, but mesenchymal cell specification depends on axial position. Cranial NCs give rise to skeletal mesenchyme; trunk NCs give rise to dorsal fin mesenchyme in amphibians and fish; and vagal NCs contribute to smooth muscle cells of the cardiac outflow tract.[64,65]

One of the earliest NC markers includes the family of receptor tyrosine kinases (RTK), which plays an important role in cell migration and survival. The RTK family are critical for development of NC

derivatives in vivo.[66] At migratory stages, the neurotrophin factor NT-3 binds to the trkC receptor and induces sensory neurogenesis.[67] GDNF binds to the RET receptor during ENS development.[66] Neuregulin binds to receptor ErbB3 and is required for glia formation in the peripheral nervous system.[68] Binding of steel factor to the c-kit receptor promotes formation of melanocyte precursors,[60] whereas cartilage precursors express platelet-derived growth factor receptor α.[69]

The timing of NC migration during development also affects the fate they attain as cell specific genes are expressed at different times during migration. Early-migrating cells express transcription factors Brn3 or neurogenin-2 and commit to sensory neuron lineage.[70,71] Late-migrating cells express melanocytic-specific markers in the migration staging area after departure of the early-migrating NCs.[72] These signals contribute to the molecular heterogeneity of the premigratory NCs.

Three main classes of signals, namely Wnts, BMP2/4, and TGFβ1/2/3, influence NC cell fate during and following migration (Figure 1).[73,74] Their interplay, timing, and relative intensity determine the proportion of various derivatives generated during development. Wnts and the downstream β-catenin pathway have been found to promote pigment cell formation in zebrafish embryo, possibly through activation of *Nacre* (*Mitfa*), a gene necessary and sufficient for pigment cell formation; conversely, inhibition of Wnt signaling leads to generation of neurons at the expense of pigment cells.[75,76] Conditional deletion of β-catenin in mice prevented sensory ganglion formation, whereas constitutive activation led to formation of sensory neurons at the expense of other NC derivatives.[77,78] The second class of signaling molecules, BMP2/4 are known to induce autonomic neurogenesis via expression of Ascl1 (MASH1), a basic helix-loop-helix transcription factor expressed in autonomic neuron precursors prior to differentiation. Interestingly, continuous BMP signaling is required for commitment of NCs to neuronal fate.[79] Although BMP2/4 have been identified as factors promoting specification of NCs to an autonomic lineage, it does not prevent sensory neurogenesis in NCs prespecified to a sensory fate in vivo.[70]

The members of TGFβ superfamily—1/2/3 are also able to specify NC cell fates, through a different mechanism than BMP2/4, since they signal through a separate receptor complex and have different downstream effectors.[75] TGFβ1/2/3 were shown to promote cardiac smooth muscle specification of rat NCs, as evidenced by the expression of smooth muscle actin.[74] TGFβ1/2/3 are also expressed in the developing heart and thought to be active during the induction of cardiomyogenesis in NCs, as well as at final stages of cardiac cushion tissue formation.[80]

The development of SC from NCs results from exposure of NCs to neuregulin-1 (NRG1, also known as Glial Growth Factor), an inductive signal of the neuregulin family. NRG1 has been found to suppress neuronal differentiation and specify NCs to a Schwann cell fate.[81] The molecular mechanisms governing differentiation of NCs to SC are elaborated later in this review. The interplay of signaling pathways and their effect on different transcription factors are summarized in Figure 1.

4 | MOLECULAR MECHANISMS UNDERLYING DIFFERENTIATION OF NC CELLS TO SC

During development, NCSC) delaminate from the neural tube and translocate to various regions of the embryo. Some localize adjacent to the developing nerves, where they differentiate into SCPs, which in turn give rise to a variety of peripheral glial cells that ultimately perform a plethora of functions linked to myelination, neuronal support, regulation of synaptic connectivity and sensory function. ErbB3/Nrg1

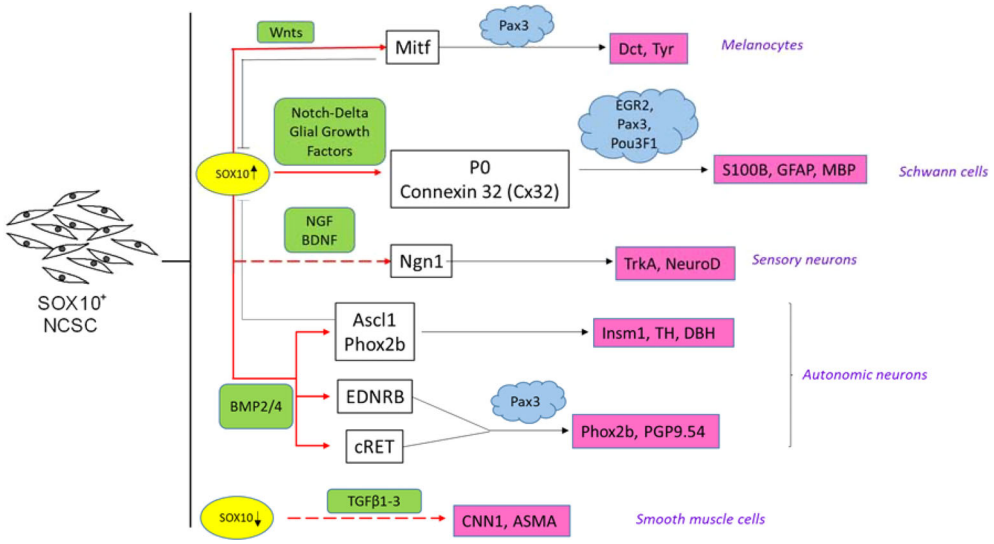

FIGURE 1 Role of Sox10 in differentiation to neural crest (NC)-specific lineages. Sox10 is required for differentiation of NCs to neurons, melanocytes, and Schwann cells, but downregulated for smooth muscle cell differentiation. Red arrows represent direct binding sites of Sox10 to lineage specific transcription factors. Dashed red lines indicate no evidence for direct binding of Sox10. Green boxes represent extrinsic signals during differentiation. Factors that act synergistically with Sox10 are depicted in blue clouds. Downstream targets of gene regulation by Sox10 are depicted in pink boxes

interactions and the transcription factor Zeb2 are involved in lineage specification and myelination[82–84]; however, the precise mechanisms dictating the fate acquisition from NC to SCP and mature myelinating or nonmyelinating SC, as well as the role of metabolic pathways in SC development and myelination, are not yet completely understood.

4.1 | The role of Sox10, Pax3, and HDAC1 in NC lineage specification to SCP

The transcription factors Sox10 and Pax3 are responsible for maintenance of NC multipotency and for differentiation into SC and melanocytes. Although Sox10 is an important NC specifier,[85] it is not the sole transcription factor setting the lineage specification and differentiation mechanisms in motion. Peripheral glial lineage specification is abolished when HDAC1/2 knockout mice (flanked by LoxP)[86] are crossed with mice expressing Cre recombinase (Cre) under the control of Wnt1 promoter (Wnt1-Cre).[87,88] Furthermore, HDAC1/2 has been shown to interact with Sox10 and activate two promoters,[89,90] the early lineage marker Myelin Protein Zero (MPZ or P0)[61] and Pax3. In turn, a positive feedback loop is set in motion, where Pax3 and Sox10 activate the Sox10 MCS4 enhancer, to maintain high levels of Sox10 but also upregulate expression of Fabp7, another early SCP marker.[90,91] Interestingly, Sox10 expression precedes neuronal differentiation[92,93] but is downregulated during neurogenesis. In addition to Sox10 and Pax3, another key transcription factor FoxD3 plays a key role in glial fate acquisition, by biasing migrating NC against alternative melanocytic fate.[94–96] Considering that Sox10 is also necessary for melanocytic differentiation and survival, the combined action of Sox10 and FoxD3 is necessary for commitment of NC to peripheral glial fate acquisition.

4.2 | Path to myelination—Signaling during radial axonal sorting dictates lineage specification

Following HDAC1/2-Sox10-Pax3-related signaling events, SCPs become immature SC, where the process of radial sorting takes place. Radial sorting refers to the process by which SC choose which axons to myelinate during development.[97] It relies on the establishment of Schwann cell polarity and cytoskeletal remodeling through Schwann cell-axon interactions, ultimately resulting in deposition of extracellular matrix (ECM), terminal Schwann cell differentiation, and myelin production. As expected, a variety of signals are necessary for these processes. ECM components like Laminin 211 and 411, Collagen XV and associated integrins $\alpha6\beta1$, $\alpha7\beta1$, as well as dystroglycan glycosylation enzymes play a pivotal role in attachment and sorting.[98–105] Intracellular signaling regulates cytoskeletal remodeling and radial sorting through molecules such as ILK, FAK, RhoGTPases, Rac1, Cdc42, Profilin, Merlin/NF2, and N-WASp[106–112], as summarized in Figure S2.

In addition, cell-cell communications between neurons and SC regulate axonal myelination. Such interactions are mediated through Neuregulin 1 (Nrg1) type III on the surface of axons and ErbB2/3 on the surface of SC.[98] Indeed inhibition of the ErbB pathway impaired axonal sorting in zebrafish nerves,[113] strongly suggesting that ErbB2/3-Nrg1 is necessary for Schwann cell radial sorting.[114–116] Furthermore, the Erk/Akt signaling pathways downstream of Nrg1 were implicated in formation of abnormal Remak bundles containing unsorted large caliber axons, possibly through the inactivation of Gab1 (Grb2 associated binder 1), which in turn indirectly decreases Erk but not Akt phosphorylation.[117] Finally, the Wnt/β-catenin signaling has also been implicated in axonal radial sorting,[118] as conditional inactivation of β-catenin resulted in mild radial sorting defects and impaired lamellipodia formation.[119]

4.3 | Metabolic signaling pathway networks in Schwann cell development and myelination

Recent studies revealed an increasingly important role for metabolism in neuronal and glial biology. Accumulating evidence supports the role of key metabolic pathways in SCP development[120,121]; the importance of metabolic crosstalk between SC and axons[122–124]; and the contributions of metabolic abnormalities to the etiology of axonal degradation and myelin related disorders.[125–129] Specifically, mTORC1, a multiprotein complex and major integrator of several growth factor (e.g., IGF-1) signaling pathways such as PI3K/AKT and MAPK,[130,131] drives Schwann cell proliferation or myelin production, in a context-specific manner that depends on developmental stage. On the one hand, mTORC1 impeded myelin production by promoting proliferation of immature SC and inhibiting their terminal differentiation and nerve development.[132–134] On the other hand, myelin production was arrested in mTOR core kinase knockout mice and mTORC1 was identified as the cause of the deficiency due to its prime role in lipid formation and protein biosynthesis.[135] In addition, LKB1, a serine threonine kinase upstream of AMPK, a key regulator of cellular energetics,[136–138] plays a pivotal role in myelin production and axonal sorting in SC, with significant repercussions for PNS myelination. Collectively, these studies shed light on the etiology of myelopathies by providing links between metabolism and signaling during development, thereby providing valuable insights for development of therapeutic strategies that may involve the use of NC derived SC for cellular therapies.[139–141]

5 | NCSCs: A CELL SOURCE FOR THE TREATMENT OF DEMYELINATING DISORDERS

Demyelinating disorders are generally defined as diseases resulting in loss of myelin from neuronal cells with relative preservation of axons. These disorders are a result of damage to myelin sheaths or to the cells that produce them. Demyelinated axons tend to degenerate, resulting in decrease or loss of neurological function. Demyelinating disorders affect both the CNS and PNS and can be caused by auto-immunity, certain infectious agents, or genetic factors.[142] Demyelinating diseases affecting the CNS include in multiple sclerosis (MS), acute-disseminated encephalomyelitis, acute haemorrhagic leucoencephalitis, and progressive

multifocal leukoencephalopathy, with MS being the most common disabling neurological illness affecting young and middle-aged adults in North America and Europe.[143] Demyelinating diseases affecting the PNS include the Guillain-Barré syndrome, Charcot-Marie-Tooth disease, progressive inflammatory neuropathy, and copper deficiency. These diseases often result from loss of function of cells responsible for myelination—oligodendrocytes in the CNS or SC in the PNS. Although the causes and pathology of each of these diseases have been extensively studied, the likelihood of reoccurrence is high and treatment options are limited. Peripheral nerve injuries are also known to result in loss of myelin in and around the site of injury. The incidence of peripheral nerve injuries is fairly high, with a conservative estimates placing it between 13 and 23 per 100,000 people per year.[144] Although nerve grafts have dominated the field of experimental treatment for peripheral nerve injuries, their use is often limited by technical difficulties, invasiveness, and mediocre outcomes.[145]

The last few decades have seen attempts to use SC expanded in culture for neural repair.[146] SC play a central role in nerve repair—they become activated after a nerve injury and assume a primitive phenotype, upregulating genes encoding for the production of neurotropic factors and stimulating axonal regeneration. Additionally, once activated, SC produce ECM molecules such as collagen and laminin creating guided tunnels for axonal growth and regeneration.[145] Various stem cell sources have been examined for the purpose of generating SC for the treatment of neurological diseases and peripheral nerve injury. Here, we provide a brief review of the therapeutic potential of these stem cells and discuss NCISC as an alternate cell source for Schwann cell engineering.

5.1 | Stem cells for generation of autologous SC

Multipotent stem cells isolated from various adult sources may serve as an autologous source of SC. Multipotent mesenchymal stem cells (MSCs) have dominated this field, given their abundance and accessibility via minimally invasive procedures. Adipose tissue has been shown to be a rich source of MSCs that could be coaxed to generate SC in vitro and myelinate axons in the spinal cord in vivo.[147–152] However, these cells have limited in vitro expansion capacity, which hinders their clinical usefulness. Adult neural stem cells isolated from the brain have been shown to differentiate to S100/p75^{NTR} positive SC and improve axonal regeneration in mouse models of peripheral nerve injury.[153,154] However, neural tissue may not be an ideal source of stem cells due to its limited accessibility, invasive procurement, and frequent contamination with fibroblasts that may overpopulate the cultures upon cell expansion in vitro.[155] Moreover, the potency and regenerative potential of neural stem cells may be affected by the neurodegenerative disease affecting the patient, calling the effectiveness of this cell source into question.

Since the discovery of the reprograming factors by Yamanaka et al,[156] the focus of cell engineering has drastically shifted to reprogramming patient-specific somatic cells to pluripotent stem cells). These iPSCs can then be coaxed to differentiate to any cell type by exposing them to signals that mimic embryonic development. In this regard, iPSCs have been considered as a potentially unlimited source of SC,[157–159] which have been shown to induce axonal regrowth and facilitate myelination in mouse models of SCI.[160,161] ESCs derived from blastocyst stage embryos can also be used to produce SC, but significant ethical concerns are plaguing their clinical use. Clinical cases with patients undergoing cell-based therapies for SCI have been evaluated in detail by Harrop et al.[162] Though there has been considerable progress in the treatment of SCI and other neurodegenerative diseases, there clearly is a need of more accessible and easily expandable adult stem cell sources for derivation of myelinating SC.

5.2 | Adult tissue–derived NCISCs for Schwann cell therapy

NC cells give rise to SC in vivo during development, thus making them one of the most suitable candidates as an autologous cell source of SC. ESCs and iPSCs go through an intermediate NC fate when coaxed to differentiate into SC, and some of these studies were discussed previously.[157] Although most studies establish differentiation of pluripotent cells to mature SC, as evidenced by expression of S100β and MBP, few have demonstrated Schwann cell function in vivo.

As discussed above, several adult human tissues can also serve as potential sources of NCISCs. In one of the first studies, adult skin-derived precursor cells (SKPs) were shown to have the potential to generate SC. SKPs are multipotent cells that are present in the skin dermis and express NC markers including Pax3, Snail, Slug, and NGFR.[28] However, SKPs do not express the key NC transcription factors, SOX10 and FOXD3, and they have not been reported to give rise to melanocytes, chondrocytes, or osteocytes, all cells known to be derived from NCs. More recently, lineage tracing studies showed that murine SKPs are of mesodermal origin, in contrast to NCSC that originate from the ectoderm. Nevertheless, mesodermal SKPs gave rise to myelinating SC in the presence of signaling cues such as heregulin β, FGF, and forskolin, suggesting plasticity of developmentally defined lineage boundaries[163] (Table 1). Furthermore, SKP-derived SC were shown to myelinate axons as efficiently as CNS-derived precursors, thus establishing them as a potent cell source for the treatment of SCI.[169] Similarly, rat-derived SKP-SCs aided sensory,[171] motor,[175,176] and behavioral recovery,[172] and enhanced peripheral nerve regeneration compared with acellular nerve grafts.[174,177] Finally, SC generated from SKPs were used successfully for the treatment of incomplete cervical SCI.[170,175,178]

Recently, NCISCs were isolated from the bulge of hair follicles and coaxed to differentiate into SC, a process that required NRG1 and micro-RNA miR-21.[165] These SC expressed SOX10, p75NTR (NGFR), KROX20, MBP, and S100β and interacted with axons in a DRG coculture model, thus providing evidence of their functionality. Dental pulp stem cells derived from human wisdom teeth have also been shown to resemble NCSC and were capable of differentiating into S100β-expressing SC.[166] Finally, human and rat bone marrow–derived NC-like cells were also capable of differentiating into SC in vitro.[11,167]

Recently, our laboratory showed that cultures of KC from interfollicular epidermis could be the source of NClSCs (termed KC-NC),

TABLE 1 Studies describing differentiation of adult-tissue derived neural crest (NC) cells to Schwann cells (SC)

Source	Culture conditions	NC markers expressed	SC markers	Functionality	References
Human epidermal neural crest cells isolated from hair follicles	Alpha-modified MEM containing retinoic acid (RA) (35 ng/mL), SB431542 (10 μM), rhFGF2 (10 ng/mL), PDGF-BB (5 ng/mL), forskolin (5 μM) and neuregulin-1 (200 ng/mL)	SOX10, p75	SOX10, KROX20, p75NTR, MBP and S100B	Coculture with primary dorsal root ganglion (DRG) neurons	Sakaue and Sieber-Blum[164]
Human-derived hair follicle cells	MesenPRO medium containing neuregulin-1 (20 ng/mL), transfection with miR-21 agonist agomir-21	p75	S100β, GFAP		Ni et al[165]
Human neonatal foreskin	EBM2 basal medium, FBS (2%), ciliary neurotrophic factor (100 ng/mL), NRG1 (100 ng/mL), FGF2 (4 ng/mL), ascorbic acid (200 mg/mL), Glutamax (0.5X), SB431542 (10 mM)	SOX10, FOXD3, PAX3/7, SNAI2, TFAP2A, MSX1/2, cMYC, and SOX9	S100β, GFAP, MPZ, PLP1	NC migration toward DRG in chicken embryo	Bajpai et al[30]
Human-derived dental pulp cells	αMEM supplemented with forskolin (5 μM), bFGF (10 ng/mL), PDGF (5 ng/mL), recombinant human neuregulin-β1 (200 ng/mL)	CD271, SOX10, nestin	S100β		Al-Zer et al[166]
Human bone marrow	DMEM/F12 supplemented with N2 supplement, CNTF (10 ng/mL), l bFGF (10 ng/m), dbcAMP (1 mM), neuregulin-1β (20 ng/mL)	Nestin, Sox9, TWIST, SLUG, p75, SNAIL1, Brn3a, MSI1	S100β, MBP, P0	NC migration toward DRG in chicken embryo	Coste et al[167]
Human skin mesenchymal stem cells	Alpha-MEM containing FBS (10%), RA (35 ng/mL), forskolin (5 μM), rh-FGF-2 (10 ng/mL), rhPDGF-AA (5 ng/mL) and neuregulin-1β (200 ng/mL)	p75NTR, Sox10, Notch1, integrin-4α, Ap2α and Pax6	S100β, MBP	BDNF secretion by ELISA	Saulite et al.[168]
Postnatal rat bone marrow	DMEM/F12 supplemented with FBS (5%), all-trans-retinoic acid (tRA) (35 ng/mL), forskolin (5 mM), βheregulin-1 (HRG-1b) (200 ng/mL), FGF2 (10 ng/mL), PDGF-AA (10 ng/mL), and N2 (1%)	p75, nestin	S100β, GFAP, CNPase p75	Coculture with primary dorsal root ganglion (DRG) neurons	Shi et al[11]
Human skin–derived precursors	Neurobasal medium containing 1% FBS plus 1% N2 supplement, 4 μM forskolin, and 10 ng/mL heregulin β	Pax3, snail, slug and NGFR	S100β, p75	—	Toma et al[28]
Mice skin–derived precursors	—	Nestin	MBP, GFAP	Myelination of spinal cord in mice	Mozafari et al[169]
Neonatal SKPs	—	—	—	Myelination of spinal cord in rats	Vasudeva et al[170]
Rodent/human skin mesenchymal precursors	DMEM/F12 at 3:1, N2 supplement (2%), neuregulin-1β (10 ng/mL), and forskolin (4 μM)	—	GFAP, S100β, P0, p75NTR, and NECL4	Alignment of MBP expressing Schwann cells in vivo	Krause et al.[163]
Rat SKPs	—	—	p75	Sensory (thermal) recovery, axonal regeneration	Shakhbazau et al[171]

(Continues)

TABLE 1 (Continued)

Source	Culture conditions	NC markers expressed	SC markers	Functionality	References
Rat SKPs	DMEM/F12, Neuregulin (50 ng/mL), forskolin (5 μM), N2 supplement (1%)	–	p75, nestin, MBP	Integration and ensheathment of regenerating axons and myelination, behavioral recovery	Khuong et al[172]
Mouse SKPs	Serum-free DMEM/F12 supplemented with dibutyryl cyclic AMP (10 mM), bFGF (10 ng/mL), and neuregulin (20 ng/mL)	–	GFAP, S100β	–	Kanget al[173]
Rat SKPs	DMEM/F12 media with forksolin (4 μM), neuregulin-1 (10 ng/mL), N2 supplement (1%)	–	S100β, p75	Secretion of bioactive neurotrophins, axonal regeneration	Walsh et al[174]
Rat SKPs	DMEM/F-12 (3:1) containing forskolin (5 μM), neuregulin-1 (50 ng/mL), N2 supplement (1%)	–	S100β, p75, P0	Axonal growth and myelination	Biernaskie et al[175]

Abbreviations: BDNF, brain-derived neurotrophic factor; DMEM, Dulbecco's Modified Eagle Medium; ELISA, enzyme-linked immunosorbent assay; FGF, fibroblast growth factor; GFAP, glial fibrillary acidic protein; MBP, myelin basic protein; NRG1, neuregulin-1; SKP, skin-derived precursor cell.

after induction with specific chemical cues.[30] KC-derived NCISCs could be coaxed to differentiate into functional neurons, SC, melanocytes, osteocytes, chondrocytes, adipocytes, and smooth muscle cells in vitro. Most notably, upon transplantation into chick embryos, KC-NCs migrated along stereotypical pathways and gave rise to multiple NC derivatives, providing strong support of their NC-like phenotype. Specifically, these cells gave rise to BLBP+ glial cells in ovo and were localized around the axon bundles. Interestingly, KC-NC from aged donors maintained the same differentiation potential in vitro and in ovo,[32] indicating the potential of adult epidermis as a source of KC-NC for the treatment of neurodegenerative diseases. Current studies in our laboratory employ the hypomyelinating *Shiverer/Rag2−/−* mouse—a model of congenital hypomyelinating disease that has become the gold standard for the assessment of myelinating cell preparations—to examine whether KC-NC or SC derived from them can be used to myelinate axons and rescue the *shiverer* phenotype. Table 1 depicts studies describing differentiation of adult tissue–derived NCISCs to SC.

6 | CONCLUSION AND FUTURE PERSPECTIVES

NC cells have attracted great interest due to their ability to differentiate into multiple cell types.[156] Although NC stem cells are a transient cell population in developing embryos, multiple investigators have isolated cells with NC-like characteristics, including transcriptional profile and differentiation potential, from a variety of adult tissues like DRG, bone marrow, skin, carotid body, whisker pad, heart, gut, and cranial tissues like cornea, iris, hard palate, dental pulp, and oral mucosa.[1] Regardless of source, NC-like cells have been coaxed to differentiate into SC, neurons, chondrocytes, smooth muscle cells, and even cardiomyocytes,[2,179,180] providing a multipotent stem cell source for the treatment of demyelinating and other neurodegenerative disorders. Patient-derived NCISCs harboring mutations for neurogenic diseases may also be used to study disease pathogenesis as well as provide a platform for drug screening further increasing their clinical potential.[1]

The use of SC derived from adult tissue–derived NCISCs for the treatment of SCI has gained momentum in recent years, after demonstration of successful myelination of axons in vitro and in vivo. Though these results are very promising, most studies use cells derived from mice or rats, which are implanted in a mouse contusion model of SCI. However, the potential of these cells for the treatment of demyelinating disease in large animal models or humans has yet to be established. Furthermore, most studies have focused on myelination after SCI and not treatment of demyelinating disorders of the CNS or PNS, leaving the field fairly unexplored in this domain. Finally, isolation of NCISCs from patients suffering from neurodegenerative disorders and their differentiation to SC and neurons may help identify abnormalities in myelin production and nerve conduction, aiding in better disease diagnosis and development of patient-specific therapies.

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CONFLICT OF INTEREST

The authors indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

P.M. wrote the manuscript, specifically parts on introduction to the topic, sources of neural crest and their genetic regulation, their application for treatment of demyelinating disorders and made the manuscript figures. G.T. wrote the manuscript, specifically mechanisms underlying differentiation of neural crest cells to Schwann cells and made the manuscript figures. M.E.B. wrote the manuscript, specifically content on how Schwann cell precursors contribute to neural crest derivatives, and gene regulatory networks controlling lineage diversification. S.T.A. conceived overall review content, writing, and editing the manuscript and project supervision.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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