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REVIEW ARTICLE

Schwann cell precursors in health and disease

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Abstract

Schwann cell precursors (SCPs) are frequently regarded as neural crest-derived cells (NCDCs) found in contact with axons during nerve formation. Nevertheless, cells with SCPs properties can be found up to the adulthood. They are well characterized with regard to both gene expression profile and cellular behavior —for instance, proliferation, migratory capabilities and survival requirements—. They differ in origin regarding their anatomic location: even though most of them are derived from migratory NCCs, there is also contribution of the boundary cap neural crest cells (bNCCs) to the skin and other tissues. Many functions are known for SCPs in normal development, including nerve fasciculation and target innervation, arterial branching patterning and differentiation, and other morphogenetic processes. In addition, SCPs are now known to be a source of many neural (glia, endoneural fibroblasts, melanocytes, visceral neurons, and chromaffin cells) and non-neural-like (mesenchymal stromal cells, able e.g., to generate dentine-producing odontoblasts) cell types. Until now no reports of endoderm-like derivatives were reported so far. Interestingly, in the Schwann cell lineage only early SCPs are likely able to differentiate into melanocytes and bone marrow mesenchymal stromal cells. We have also herein discussed the literature regarding their role in repair as well as in disease mechanisms, such as in diverse cancers. Moreover, many caveats in our knowledge of SCPs biology are highlighted all through this article. Future research should expand more into the relevance of SCPs in pathologies and in other regenerative mechanisms which might bring new unexpected clinically-relevant knowledge.

KEYWORDS

peripheral glia progenitors, multipotency, plasticity, development, function, disease

Abbreviations: AP-2α, activator protein-2α; Ascl1, achaete-scute homolog 1; Atg, autophagy related; BAC, benzalkonium chloride; bFABP, brain fatty acid binding protein; bFGF, fibroblast-growth factor-2; basic FGF; BMP-4, bone morphogenetic protein 4; bNCCs, boundary cap neural crest cells; bNCSCs, boundary cap neural crest stem cells; bNCD, boundary cap neural crest-derived; CD90, cluster of differentiation 90; CNS, central nervous system; Cre, CRE (causes recombination) recombinase; CreERT2, CRE recombinase fused to a mutant form of the human estrogen receptor ligand binding domain; Cxcl12, chemokine (C-X-C motif) ligand 12; Cxcr4, chemokine (C-X-C motif) receptor 4; Fc, fragment, crystallizable; Dhh, desert hedgehog; DRG, dorsal root ganglia; DTA, diphtheria toxin A; E, embryonic day; EdnrB, endothelin receptor type B; EGFR, epidermal growth factor receptor; ENCCs, enteric neural crest cells; ErbB, avian erythroblastosis oncogene B; fl, flox; Foxd3, forkhead box D3; GAP-43, growth associated protein-43; GFAP, glial fibrillary acidic protein; GFP, green fluorescent protein; GFRα, glial cell line-derived neurotrophic factor family receptor-α; HB9, homeobox protein 9; HDAC, histone deacetylases; HMB-45, human melanoma black-45; HSCs, hematopoietic stem cells; Id4, inhibitor of differentiation 4; IGF-1, insulin-like growth factor 1; Isl2, insulin related protein 2; Krox20, early growth response 2; Krox24, early growth response 1; Kv1.1, potassium voltage-gated channel, shaker-related subfamily, member 1; LSL, LoxP-transcription stop-LoxP; Mbp, myelin basic protein; Mitf, microphtalmia associated transcription factor; MSCs, mesenchymal stem/stromal cells; MZ, mantle zone; N-CAM, neural cell adhesion molecule; NCCs, neural crest cells; NCD, neural crest-derived; NCDCs, neural crest-derived cells; NF1, neurofibromin-1; NFATc, nuclear factor of activated T-cells; Npn-1, neuropilin-1; NPY, neuropeptide Y; NRGs, neuregulins-1β; O4, lipid surface antigen O4; Oct6, organic cation/carnitine transporter 6; OSM, oncostatin M; P, passage; P_0, protein zero; P75 o $p75^{NTR}$, neurotrophin receptor p75; PAC, phage artificial chromosome; Pax3, paired box 3; PDGF, platelet-derived growth factor; PDGF-AA, platelet-derived growth factor isoform AA; Phox2, paired-like homeobox 2; PKC, protein kinase C; PLP1, proteolipid protein; PMP-22, peripheral myelin protein 22; Prss56, protease, serine 56; R26R, Rosa 26 reporter strain; REB, rat homologue of the human HeLa E-box binding protein; Ret, RET (rearranged during transfection) receptor tyrosine kinase; Rlbp, retinaldehyde binding protein; S1P1, Sphingosine-1-phosphate receptor 1; SC/s, Schwann cell/s; SCPDCs, Schwann cell precursor-derived cells; SCP/s, Schwann cell precursor/s; Sema3A, semaphorin-3A; Sox 2/10, SRY-related HMG-box 2/10; TAM, tamoxifen; TdT, tdTomato; TH, tyrosine hydroxylase; Thy1, thymus cell surface antigen-1; TPA, 12-O-tetradecanoyl phorbol acetate; VEGF, vascular endothelial growth factor; Wnt1, wingless-type MMTV integration site family, member 1; YFP, yellow fluorescent protein.

1 | INTRODUCTION

Schwann cell precursors (SCPs) are described as neural crest-derived cells which populate nerves at embryonic day (E)12–E13 in mouse, E14–E15 in rats and in 12 week-old human embryos, during the process of axonal elongation into the limb and peripheral target innervation (see review by Jessen & Mirsky, 2002). They can be identified by using specific antigenic markers (see below), and by their ability of growing in pavement-like arrays and their incapacity to survive without trophic support from neighbor axons. In addition, SCPs show similar rates of migratory capacity than neural crest cells (NCCs), although by cell-to-cell rather than cell-to-extracellular matrix interactions (Jessen et al., 1994).

At first stages of nerves formation, they are composed by few packed axons surrounded by SCPs with flattened sheet-like processes (Jessen et al., 1994; Jessen & Mirsky, 2005). They lack from connective tissue and blood supply, features that arise once axons have reached their target tissues. SCPs would keep proliferating and in the next 2–3 days gradually give rise to immature Schwann cells (immature SCs), with higher proliferative (Stewart, Morgan, Jessen, & Mirsky, 1993) but lower motile (Jessen & Mirsky, 1998) capacities. Cellular proliferation in SCPs and immature SCs might eventually be linked to the expression of Kv1.1, a shaker-like potassium channel (Hallows & Tempel, 1998). In the meantime, new dorsal root ganglia (DRG) and motorneurons axons grow and get recruited into forming nerves; therefore, some peripheral glia progenitors start appearing in between bundles. This is followed by axonal re-arrangements and sorting. Indeed, immature SCs associate with separate groups of axons, a process which is followed by a series of orderly events. Such events include: axonal loss (due to competition for target-derived survival factors), neural connective tissue development, axonal segregation, cessation of immature Schwann cell division (from E20 in rat), and myelination (as reviewed in Jessen & Mirsky, 1991; Jessen & Mirsky, 1992). Immature SCs express significant levels of the calcium-binding protein S100, start forming an external lamina, and acquire the capacity to survive independently of axon-derived signals in serum-containing culture media (Jessen et al., 1994; Meier, Parmantier, Brennan, Mirsky, & Jessen, 1999).

Neuregulins-1β (NRGs) are the key components in the axonal survival signals for SCPs and were also involved in the transition from neural crest cells (NCCs) to SCPs, and in SCPs survival, maturation and subsequent differentiation into immature SCs (Aquino et al., 2006; Dong et al., 1995; Dong et al., 1999; Leimeroth et al., 2002); an issue that was previously reviewed (Birchmeier & Nave, 2008; Garratt, Britsch, & Birchmeier, 2000). Since NRGs promote SCPs survival and proliferation, they are regarded as selective signals. In addition, NRGs were also found to exert instructive roles by inhibiting NCC differentiation into neurons and pigment cells and/or outcompeting signals diverging their differentiation (Adameyko et al., 2009). Moreover, boundary cap neural crest stem cells (bNCSCs) incubated in serum-free medium supplemented with NRGs were able to produce SCPs in a time-course similar to the *in vivo* process (Aquino et al., 2006). Furthermore, only the axonal membrane-bound NRG isoform (Type III) was shown to induce S100 and Oct-6 expression in rat embryonic dorsal root ganglia non-neuronal cells (Leimeroth et al., 2002). And while mice lacking NRG isoforms I and II show normal SC development, inactivation of the isoform III results in the depletion of SCPs in peripheral nerves (Woodhoo & Sommer, 2008).

Endothelins have also been involved in SCPs differentiation and they seem to negatively regulate SCPs-to-Schwann cell transition (Brennan et al., 2000), while fibroblast-growth factor-2 (FGF-2; basic FGF, bFGF; known to be synthesized by peripheral axons) was shown to accelerate the generation of SCs in the context of NRGs (Dong et al., 1999). In addition, bFGF was found to be mitogenic for mouse but not for rat SCPs, and to induce proliferation in immature SCs of both animal species (Dong et al., 1999). Finally, Notch signalling has been reported to stimulate differentiation of SCPs into SCs; moreover, it was shown to induce SC proliferation and to inhibit myelination (Woodhoo et al., 2009). NRGs and Notch were seen to suppress fibroblastic differentiation in the neural crest lineage (Morrison et al., 2000; Shah, Marchionni, Isaacs, Stroobant, & Anderson, 1994).

1.1 | SCPs expression profile

Many specific markers have been characterized for early SC lineage (Figure 1). Multipotent NCCs, SCPs, and immature SCs share some markers such as: A5E3 (Jessen et al., 1994; Jessen, Morgan, Stewart, & Mirsky, 1990); the NRG receptors, mainly ErbB3 but also ErbB2 and ErbB4 (Garratt et al., 2000); the growth associated protein-43 (GAP-43, more weakly expressed in NCCs; Jessen et al., 1994); L1 (Jessen et al., 1994); nestin (Aquino et al., 2008; Stemple & Anderson, 1992); the neurotrophin receptor p75 ($p75^{NTR}$; p75; LNGFR; Shah et al., 1994; Stemple & Anderson, 1992; Stewart, 1995); the SRY-related HMG-box 2 (Sox2; Aquino et al., 2006); Sox10 (Aquino et al., 2006; Britsch et al., 2001), and vimentin (Jessen et al., 1994). In addition, other NCC and SCP markers are downregulated in immature SCs, such as α4-integrin (Joseph et al., 2004), AP-2α (Stewart et al., 2001) and N-cadherin (Wanner et al., 2006a). The latter, known to be induced by NRG signalling, is also expressed in axons at the same developmental stage (Wanner et al., 2006a). Whether or not N-cadherin needs to be expressed simultaneously in both cell types for axonal extension and SCPs migration remains to be elucidated. Other markers first appearing within neural crest lineage in SCPs such as the brain fatty acid-binding protein (BFABP; in mouse but not in rat; Britsch et al., 2001), cadherin 19 (downregulated in immature SCs and thus restricted to SCPs; Takahashi & Osumi, 2005), connexin 29 (Altevogt, Kleopa, Postma, Scherer, & Paul, 2002; Li et al., 2007), desert hedgehog (Dhh; Bitgood & McMahon, 1995; Parmantier et al., 1999), fibronectin (Aquino et al., 2006), laminin (Furlan et al., 2017), the zinc-finger transcriptional factor Krox-24 (downregulated in immature SCs, but re-expressed after birth together with Krox20 and further downregulated in the myelinating Schwann cell lineage; Topilko et al., 1997), neurotrypsin (downregulated in mature Schwann cells; Wolfer, Lang, Cinelli, Madani, & Sonderegger, 2001), peripheral myelin protein 22 (PMP-22; Blanchard et al. 1996; Hagedorn, Suter, & Sommer, 1999) and proteolipid protein 1 (PLP1; Griffiths et al., 1998). It is believed that the downregulation of N-cadherin and cadherin 19 in immature SCs plays a key role in changes in their cell-cell interaction pattern and in the reduction of

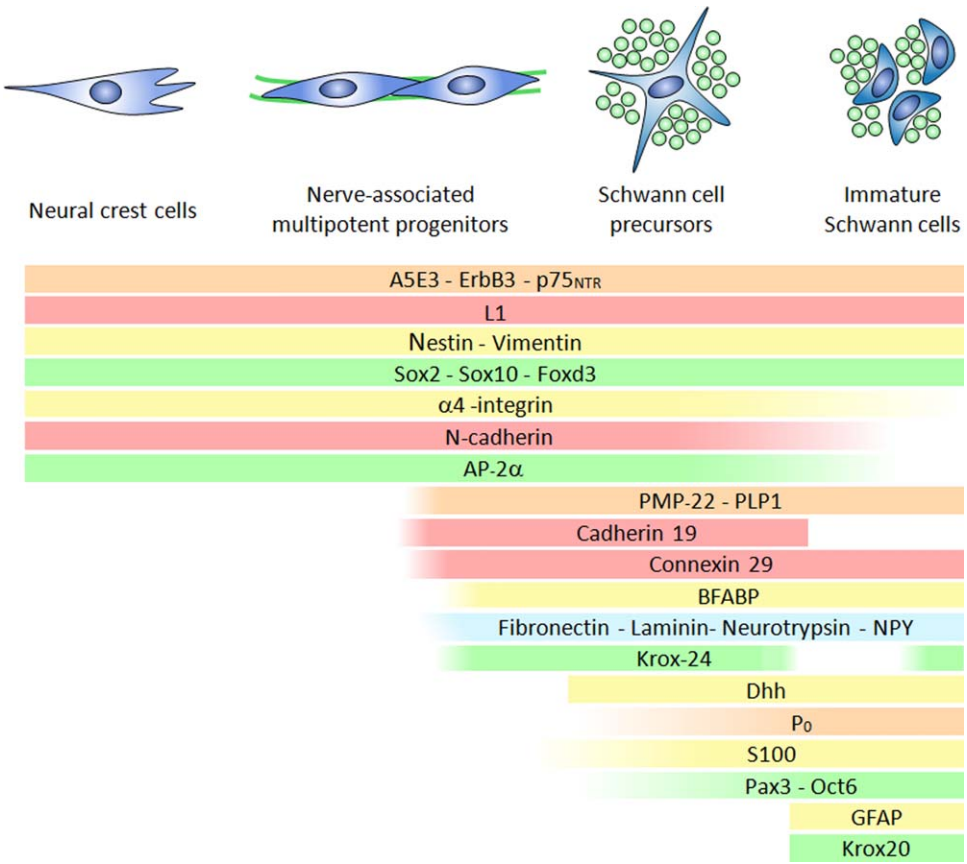

FIGURE 1 Early markers in Schwann cell lineage. Of note: the specific phenotype of early Schwann cell precursors (named as nerve-associated multipotent progenitors) has largely not been characterized with regards to most of SCP markers. Light orange: cell surface molecules. Light red: adhesion molecules. Light yellow: cytoplasmic. Light green: transcriptional factors. Light blue: extracellular matrix/released molecules

their migratory behavior as compared with SCPs (Wanner et al., 2006a). Moreover, N-cadherin downregulation in immature SCs seems to allow for the appearance of the endoneural space between glial cells and for extensive interactions with the underlying connective tissue (Wanner et al., 2006a). In addition, SCPs show nuclear localization of the transcriptional factors Id4 and REB (Stewart et al., 1997). These cells were also seen to express neuropeptide-Y (NPY), which might be involved in axonal outgrowth and/or in SCPs motile behavior through autocrine/paracrine mechanisms (Ubink & Hokfelt, 2000). Low levels of some markers were found in SCPs which were upregulated in SCs, such as: the POU domain protein Oct-6 (Tst-1, SCIP, and Pou3f1; with a peak in early postnatal life; Blanchard et al., 1996); protein zero (P_0; which is downregulated postnatally in the non-myelinating Schwann cell lineage) (Blanchard et al., 1996; Lee et al., 1997), and paired-box 3 (Pax3; Blanchard et al., 1996). In addition, rat SCPs express very low levels of S100 (Mirsky & Jessen, 1999; Mirsky et al., 2008), while mouse late SCPs are positive for this marker both *in vivo* and *in vitro* (Aquino et al., 2006; Furlan et al., 2017). SCPs lack from glial fibrillary acidic protein (GFAP) expression (Aquino et al., 2006; Jessen et al., 1990) and Krox20 (Blanchard et al., 1996; Topilko et al., 1997) and O4 (Dong et al., 1999) which are first found in immature SCs.

Oct6 was shown to be active in the Schwann cell lineage after Pax3 but before Krox-20 (Kuhlbrodt, Herbarth, Sock, Hermans-Borgmeyer, & Wegner, 1998). Sox10 seems to lack from autonomous transcriptional activities in glial cells; instead, Sox10 would function in late SCPs/immature SCs as accessory proteins for Pax3, Oct-6, and Krox20, resulting in the synergistic activation of their target genes promoters, thus suggesting different roles for those transcriptional factors in the glial differentiation program (Kuhlbrodt et al., 1998). The chromatin remodelers HDAC1/2 induce the expression of Pax3 in NCCs (Jacob et al., 2014). In turn, Pax3 was found to maintain high levels of Sox10 and to induce the expression of BFABP and P_0 in the SC lineage (Jacob et al., 2014). Expression of ErbB3 was also found to be regulated by Sox10 (Britsch et al.. 2001) and therefore one of Sox10 functions would be to provide glia responsiveness to NRGs (Britsch et al., 2001; Prasad et al., 2011). NRGs induce an increase in cytoplasmic calcium in the Schwann cell lineage which activates calcineurin and its downstream NFATc3 and c4 transcriptional factors (Kao et al., 2009). In addition, in the same article calcineurin/NFAT axis was shown to be required for NRG signaling and the NFAT complex was found to synergistically interact with Sox10 to activate Krox20 and P_0.

1.2 | Intermediate stages from NCCs to immature SCs

Dong et al. (1999) reported different responses to insulin-like growth factor 1 (IGF-1) in mouse peripheral glia progenitors thus suggesting

distinct subpopulations *in vivo*. They found that at E14 nearly all nerve cells and at E15 about half of them survive if medium is supplemented with IGF-1 but die without it, suggesting that they have not developed autocrine survival loops yet. The authors also suggest that, while at E14 about half of nerve cells would still be SCPs, at E15 basically all SCPs might have differentiated into immature SCs or into an IGF-I responsive intermediate stage. Transitional phenotypes could also be expected in between NCCs and SCPs in mouse E12 and in rat E14 nerves, with characteristics of NCCs but more biased to a glia progenitor phenotype (Morrison et al., 2000; Morrison, White, Zock, & Anderson, 1999). In fact, as it was previously highlighted (Adameyko & Lallemend, 2010), early PLP1^{+} Dhh^{-} SCPs but not late PLP1^{+} Dhh^{+} SCPs were shown to give rise to melanocytes in the hair follicle, which suggests that diverse subpopulations of SCPs are to be characterized in developing peripheral nerves with different multipotent and/or plastic properties.

1.3 | SCPs origins

In mammals, SCPs are known to be derived from migratory NCCs and from some NCCs which stop migrating at prospective dorsal and ventral root entry zone levels and become clustered, forming a structure named boundary cap. Multipotent boundary cap neural crest cells (bNCCs) were thought to give rise to SCPs of dorsal and ventral spinal cord roots, satellite glia cells and few nociceptive neurons during embryonic development (Maro et al., 2004). Nevertheless, by analyzing *Prss56*$^{Cre/+}$;*R26*^{tdTom} embryos, Gresset et al. (2015) showed that bNCCs contribute with SCPs which migrate through the dorsal and ventral ramus nerves to reach the skin and originate multipotent terminal Schwann cells (Aquino, 2017). More recently, boundary cap neural crest-derived cells (bNCDCs) were also shown to contribute with cells of sympathetic ganglia and the adrenal medulla (Furlan et al., 2017). In birds, zebrafish, and mammals, some CNS-derived glia which exit the ventral neural tube in parallel with motor-neuron axons give rise to perineurial glia cells (Clark et al., 2014; Kucenas et al., 2008; Lunn, Scourfield, Keynes, & Stern, 1987). No proper lineage tracing analyses were yet performed to address whether or not some SCPs could derive from the ventral neural tube. Furthermore, differences in properties among SCPs and SCs of diverse origins are largely unknown.

2 | FUNCTIONS OF SCHWANN CELL PRECURSORS IN HEALTH

Some of SCPs functions were previously reviewed (Jessen & Mirsky, 2005), including their trophic support to axons. Interestingly, different research groups showed that in mice lacking from SCPs and immature SCs (for instance Sox10, NRG1-βIII, ErbB2, or ErbB3 mutant animals), around 80% of DRG neurons and motorneurons die in between E13 and E18 (see review by Mirsky & Jessen, 1999). In such cases, neurons were able to previously extent their axons following more or less their expected trajectory. This phenotype was suggested to result from the absence of glia-derived growth factors. However, it can also be caused by lack of nutritional factors and/or other kinds of metabolic support provided by SCPs/immature SCs, an issue that remains unexplored.

2.1 | Nerve fasciculation and target innervation

In addition, in such studies SCPs and immature SCs were also found to be required for normal fasciculation of peripheral nerves (Mirsky & Jessen, 1999). At nerve fronts and close to axonal target tissues, lamellipodia and filopodia protrusions of E14 rat SCPs are seen extensively associated through adherens junctions (Wanner et al., 2006b), which is consistent with the expression of N-cadherin in these cells (Wanner et al., 2006a). SCPs were found covering axonal growth cones, and both migrate concomitantly (Wanner et al., 2006b). Moreover, N-cadherin which is more highly expressed in SCPs at nerve front areas might also play growth promoter activities (Wanner et al., 2006a). From nerves origin at the CNS boundary and up to their growing fronts, SCPs form a biological network that limits and maintains bundles tightly associated and reduces their exposure to the extracellular environment of surrounding mesenchyme (Wanner et al., 2006b). At the same time, nerve compaction facilitates migration of growth cones in groups and it restricts openings of growth cones toward distal areas, thus causing polarization of axonal guidance molecules access (Wanner et al., 2006b). Interestingly, loss of semaphorin 3A-neuropilin-1 (Sema3A-Npn-1) signaling, an axis mediating repulsive axonal behavior, in mouse was found to result in the depletion from SCPs, a feature likely linked to cranial sensory and somatic motor axon defasciculation (Huettl & Huber, 2011). Furthermore, SCPs constitute 80% of the nerve growth front surface thus reducing axonal contact with growth inhibitory molecules on their close environment (Wanner et al., 2006b). In addition, SCPs located on the outer side of the nerve facing the mesenchyme but not those at the nerve growth front, also secrete some inhibitory molecules such as tenascin C which they deposit close to axonal surface (Wanner et al., 2006a; Wanner et al., 2006b). From these particular studies it can be concluded that axonal growth cones seem to use SCPs as scaffolds and chaperons during final stages of limb innervation (Wanner et al., 2006b), a feature which might be linked to defects in the innervation of distal limb areas observed in mice devoid of peripheral glia. Finally, Desert hedgehog (Dhh) secreted by SCPs and immature SCs were found to control nerve connective tissue sheaths formation (Kucenas et al., 2008; Parmantier et al., 1999).

2.2 | Arterial branching patterning and differentiation

Within the developing mouse limb skin, SCPs were found to control the branching pattern and the subsequent differentiation of arterial vessels (Li et al., 2013). At E13.5, SCPs express Cxcl12 whereas its receptor Cxcr4 was found in capillaries nearby nerve trajectories. By E15.5, immature Schwann cells are still Cxcl12^{+} and small-caliber arteries associated with nerves keep expressing Cxcr4. Consistent with a role for SCPs in the branching pattern and in differentiation of blood vessels, *SemaA*$^{-/-}$ mice arteries are found aligned following the disorganized trajectory of nerves, and Cxcl12$^{-/-}$ as well as Cxcr4$^{-/-}$ animals show defects in vessel-nerve alignment. Such defects cause the

impairment in arterial differentiation and in smooth muscle coverage, a feature related to lack of nerve-derived VEGF-A. As it was suggested (Li et al., 2013), the hypoxic environment would likely induce the expression of Cxcl12 and VEGF-A in nerves which in turn promote neovascularization. Whether or not secretion of NPY by SCPs is involved in angiogenesis remains to be addressed (Kitlinska, 2007; Ubink & Hokfelt, 2000).

2.3 | Morphogenetic functions with regards to the neural tube

In ventral roots, boundary cap cells and bNCD-SCPs were found to be crucial in maintaining the position of motorneurons in the spinal cord, avoiding their exit from the neural tube (Vermeren et al., 2003), a feature also likely involving repulsive signaling mechanisms.

2.4 | Multipotent properties of Schwann Cell Precursors

Solid scientific data support that peripheral glia progenitors in mammals are multipotent progenitors with outstanding plastic properties (Aquino, 2017).

2.4.1 | Melanocytes

Early studies made in 1977 suggested that some bipotent cells, able to produce Schwann cells and melanocytes, are found in early postnatal chick DRG and peripheral nerves (Nichols & Weston, 1977). Approximately 10 years later, Hess et al. (1988) showed that the drug 12-O-tetradecanoylphorbol acetate (TPA) is able to induce the differentiation of some nerve cells into melanocytes by increasing protein kinase C (PKC) activity levels. They also suggested that such nerve cells would likely be SCPs since they express S100 and other characteristic cell-surface markers. Five years later, Sherman et al. (1993) published that TPA increases bFGF expression in nerve supportive cells, which is a required mechanism for their transdifferentiation into melanocytes. In 2009, Adameyko et al. (2009) provided *in vivo* conclusive evidences of that SCPs from embryonic growing nerves are a source of melanocytes in mouse and chicken. In this study, through *in ovo* electroporation, ablations of different NCC migratory pathways and sectioning of embryonic spinal nerves in chick, they found that limb melanoblasts are nerved-derived and that SCPs express the melanoblast marker Microphthalmia-associated transcription factor (Mitf) when they lose axonal contact. The authors have also performed lineage tracing analyses using $PLP1^{Cre}$;$R26R^{YFP}$mice. Such studies allowed them to conclude that a large number of melanocytes in hair follicles and interfollicular dermis (Van Raamsdonk & Deo, 2013), which represent nearly all populations of pigment cells in the trunk skin of adult mouse (Quevedo & Fleischmann, 1980), are of SCP origin. Furthermore, they also showed that myelinating mature Schwann cells retain the capacity to differentiate into melanocytes after injury, and that IGF-I and platelet-derived growth factor (PDGF) can act in opposing manner to NRGs allowing generation of melanocytes. Interestingly, nerves cells in zebrafish have been shown to be a source of adult melanophores, as it was recently reviewed (Petersen & Adameyko, 2017). The fact that Dhh^{+} late SCPs are not able to originate melanoblasts during normal development (Van Raamsdonk & Deo, 2013) would further support differences in the developmental potential of SCPs subpopulations.

2.4.2 | Endoneural fibroblasts

Within peripheral nerves, Dhh^{+} SCPs/immature SCs were shown to originate endoneural fibroblasts, a process which take place by the time of SCP-immature Schwann cell transition (Jessen & Mirsky, 2005; Joseph et al., 2004). Joseph et al. (2004) also showed that incubation of E14.5 rat sciatic nerve cells with a combination of bone morphogenetic protein-4 (BMP-4), NRG1 and Delta-Fc (which activates Notch signaling) results in the greatest proportion of colonies originating both glia and smooth muscle cells (52%), or glia or smooth muscle cells separately. As speculated by the authors, these factors promote the differentiation of neural crest stem cells into Schwann cells and endoneurial fibroblasts.

2.4.3 | Parasympathetic neurons

In 2014, two simultaneously published studies from independent scientific groups showed that SCPs are the source of parasympathetic neurons (Dyachuk et al., 2014; Espinosa-Medina et al., 2014). By lineage tracing with $Wnt1^{Cre}$ and $Phox2b^{Cre}$ mice, Espinosa-Medina et al. (2014) found that between E10 and E13.5, according the each region, cranial nerve $Sox10^{+}$ cells start expressing the transcriptional factor Phox2b, migrate along nerves and reach areas of ganglion formation. $Phox2b^{+}$ cells were found to co-express markers of neural crest cells (Foxd3, Sox2 and p75) as well as SCPs (ErbB3, Cadherin19 and PLP1), but not of neurons. One or two days later, Sox10 expression was downregulated in $Phox2b^{+}$ cells adopting a neuronal phenotype at the emerging ganglia, while other cells previously co-expressing Sox10 and Phox2b downregulated Phox2b and gave rise to Schwann cells. Interestingly, cells originating parasympathetic neurons were found to never express Neurogenin 2 (Espinosa-Medina et al., 2014). By using $Sox10^{CreERT2}$;$R26R^{YFP}$ and $PLP1^{CreERT2}$;$R26R^{Confetti}$ (injected with tamoxifen-TAM- at E11.5 or E12.5 and collected at E17.5), Dyachuk et al. (2014) traced the contribution of $Sox10^{+}$ $PLP1^{+}$ SCPs to cranial, heart, and pelvic parasympathetic ganglia. Moreover, they found that Ascl1 expression, which is essential to produce parasympathetic neurons, appear in $Sox10^{+}$ nerve cells. Consistent with an origin of parasympathetic ganglia from Schwann cell precursors, $ErbB3^{-/-}$ mice (lacking from SCPs) do not form such structures. Moreover, in the absence of Ascl1 expression all cranial nerve cells differentiated into Schwann cells. It is worth noting that while some traced $Phox2b^{+}$ cells could become Schwann cells (Espinosa-Medina et al., 2014), Ascl1 genetically-traced cells were only able to originate neurons (Dyachuk et al., 2014). Even though signals involved in parasympathetic gangliogenesis are largely unknown, it was recently found that the emergence of the ganglia associated with submandibular glands depend on Wnt signals derived from keratin 5^{+} progenitors of gland ducts, which antagonize FGF signaling (Knosp et al., 2015).

2.4.4 | Enteric neurons

By using different mouse strains for cellular lineage tracing (for instance: Dhh^{Cre};$Gfr\alpha1^{fl\text{-}GFP}$, Dhh^{Cre};$Ret^{fl\text{-}CFP/+}$ and Dhh^{Cre};$Ret^{fl\text{-}CFP/+}$), SCPs were also found to be a source of enteric neurons, contributing

with <5% of submucosal neurons of the small intestine and ~20% of enteric neurons in the large intestine (Uesaka, Nagashimada, & Enomoto, 2015). Thus, many axial levels of NCCs/NCDCs (including vagal, trunk, and sacral ones) are now known to contribute to the enteric nervous system. Considering that cells of both parasympathetic and enteric neuron lineages express Phox2b (Green, Uy, & Bronner, 2017), a marker of visceral neurons (Nomaksteinsky et al., 2013), it remains to be analyzed whether or not other kind of visceral neurons also shared a similar origin. This can be also the case of the late-born intrinsic airway neurons (Brouns, Van Genechten, Scheuermann, Timmermans, & Adriaensen, 2002). Interestingly, a recent study showed evidences supporting that enteric neurons in lamprey can be originated from SCPs (Green et al., 2017). It is therein suggested that, during evolution and in early jawless vertebrates, SCPs might have originated enteric neurons much before NCCs migratory behavior acquisition.

2.4.5 | Spleen glia

Very recently, a SCP like-origin for astrocyte-like glial cells was shown in the spleen (Barlow-Anacker, Fu, Erickson, Bertocchini, & Gosain, 2017). Before such study, immune defects were previously seen in the spleen of NCC-conditional Endothelin receptor B knockout (*EdnrB*$^{-/-}$) mice. Consistently, the authors found smaller spleens in those animals; nevertheless, a change in their size was observed from postnatal day (P)18 but not before and the number of NCCs colonizing the spleen remained unchanged during the early postnatal period. The first NCDCs were found to enter the spleen by E16.5, and by P0 they have colonized this tissue. Prior to entering the spleen, NCDCs were in contact with axons and close to blood vessels, and expressed the SCP-marker BLBP. Later on and within the spleen, they were observed not to originate pericytes or neurons but S100β^{+} Sox10^{-} astrocyte-like glial cells. Moreover, similar features were also found for NCDCs in chick and in non-human primates although markers used for their phenotype characterization differed. Finally, a reduced expression in Sphingosine-1-Phosphate Receptor 1 (S1P1), a protein expressed by B-lymphocytes which is required for their relocation to the marginal zone (MZ), was found in *EdnrB*$^{-/-}$ mice. Since S1P1 ligand is produced by NCDCs, this signaling pathway might be linked to the reduction of MZ size seen by the authors in the conditional mutant mice.

2.4.6 | Dental pulp mesenchymal stromal cells

In 2014, another paper published by Igor Adameyko's group in which they performed lineage tracing with *PLP1*^{CreERT2} and *Sox10*^{CreERT2} mice showed that SCPs are the source of some dental pulp mesenchymal stromal cells (DP-MSCs; Kaukua et al., 2014). In both strains, when recombination was induced by TAM at E12.5 and animals were collected at E15.5–E17.5, YFP^{+} cells were found in surrounding nerves as well as inside of incisors, in a stream of cells oriented toward and in the odontoblast layer. In the adult, SCPs were shown to likely originate Thy1 (CD90)$^{+}$ DP-MSCs, able to give rise to both dental pulp cells and odontoblasts. By analyzing *PLP1*^{CreERT2};*R26R*^{Confetti} embryos, the authors showed clear evidences of clonal contribution of SCPs to pulp cells and odontoblasts within the same streams, being the latter originated from earlier nerve-detached cells which were the first in getting displaced distally. In the adult, when incisors were denervated 24 hr after TAM injection, 10 days later almost no YFP^{+} cells were found in those areas. Finally, to test whether SCP-derived odontoblast cells could produce regenerative dentine, they have inflicted a localized damage to a tooth and one month later found many traced cells in the regenerated area including odontoblast-like alizarin-red-positive cells adjacent to matrix fragments.

Also in 2014, by fate mapping with *Wnt1*^{Cre2} mice, Isern et al. (2014) showed that NCDCs also contribute with bone marrow MSCs likely through the innervation process. Indeed, they found that the CD90^{+} MSCs pool was reduced two-fold in *Erbb3*$^{-/-}$ limb bone marrow; moreover, a five-fold reduction was observed in the number of hematopoietic progenitors in the same condition. Interestingly, no changes in the number of bone marrow hematopoietic progenitors were found in *Dhh*^{Cre};*Erbb3*$^{fl/fl}$ mice. This may suggest that hematopoietic stem cell (HSC) niche-forming MSCs would likely originate from neural crest cells or from early Dhh^{-} SCPs.

2.4.7 | Adrenal medulla chromaffin cells

In 2017, by using different *in vivo* approaches, Igor Adameyko's group showed evidences in support of that the majority of catecholaminergic cells of the adrenal medulla are SCP-derived (Furlan et al., 2017). By injecting TAM at E11.5 in *Sox10*^{CreERT2};*R26R*^{YFP} and *PLP1*^{CreERT2};*R26R*^{YFP} mice, they found that most chromaffin cells are derived from SCPs of the preganglionic nerve while TH^{+} sympathetic neurons were not. Interestingly, when TAM was applied at E12.5 fewer chromaffin cells were traced, and at E15.5 SC lineage cells did not contributed any longer with them. Ablation of SCPs (by crossing *Sox10*^{CreERT2} with *R26R*^{DTA} mice) or of preganglionic nerves (by crossing *HB9*^{Cre} with *Isl2*^{DTA} mice) resulted in a reduction in chromaffin cells (reaching up to 78%) while numbers of sympathetic ganglia neurons remained unaffected. Further studies allowed the authors to uncover that sympathetic neurons are born earlier and originate from migratory NCCs. Finally, by single cell RNA sequencing and using *Wnt1*^{Cre};*R26R*^{Tomato} mice, Furlan and collaborators were able to discover SCP-chromaffin intermediate phenotypes, named by them as bridge cells, and to characterize their expression profiles. Changes in the expression levels of specific transcriptional factors and signaling molecules in SCPs, chromaffin and bridge cells are therein provided although it remains to be elucidated which external factors drive such differentiation process.

3 | FUNCTIONS OF SCHWANN CELL PRECURSORS IN REGENERATION AND DISEASE

As recently reviewed, multipotent and/or plastic properties of SCPs would likely allow tissue regenerative mechanisms (Aquino, 2017) and might be involved in disease progression.

3.1 | Adult skin repair and digit tip regeneration

Nerve innervation was shown to be required for tissue regeneration in different animal models (Kaucka & Adameyko, 2014). For instance, in newts Schwann cells migrate to injured limbs and secrete factors triggering mesenchymal cell proliferation, key events required for proper

limb regeneration. In mammals, even though dorsal skin hair follicle $Sox2^+$ $Nestin^+$ $p75^+$ $S100\beta^+$ nerve-terminal associated cells with properties of SCPs (Aquino, 2017; Johnston et al., 2016) contribute with wound bed, most of cells which mediate skin tissue repair are derived from cutaneous nerves and upregulate Sox2 after injury (Johnston et al., 2013). Interestingly by applying TAM in 9 months-old $Sox2^{fl/fl}$;$R26^{CreERT2/+}$ mice, the authors found that depleting from Sox2 expression in these neural crest precursor-like cells turned them dysfunctional and resulted in an aberrant skin repair.

While the involvement of NCDCs recruitment through systemic circulation from the bone marrow in the wound healing process remains to be addressed; more recently, requirement of Schwann cells from injured nerves has also been recently shown in adult mammals (Johnston et al., 2016). Moreover, SCPs were found to play a key role in the regeneration of the digit tip when it is removed distally to the nail in adult mice. The blastema formed after injury was seen to comprise precursors of multiple lineages including mesenchymal, epidermal and neural crest. When the digit tip of $Sox2^{CreERT2/+}$;$R26^{LSL\text{-}TdT}$ mice was amputated after sciatic nerve resection, blastema formation was depleted from SCPs and this resulted in aberrant scaring and deficit in wound healing and regeneration, thus involving SCPs in mammals multiple-tissue regeneration. Upon injury, Schwann cells dedifferentiate and SCPs migrate to the site of blastema formation, wherein they secrete growth factors, such as oncostatin M (OSM) and platelet-derived growth factor isoform AA (PDGF-AA), which promote mesenchymal stem cells and other precursors to proliferate allowing tissue regeneration. Both OSM and PDGF-AA were sufficient to rescue the deficits in regeneration caused by loss of SCPs. During the regenerative process, axons would then re-grow into the newly formed tissue and SCPs differentiate again into Schwann cells.

3.2 | Regeneration in the adult intestine

To explore contribution of glia to adult neurogenesis in enteric ganglia, Laranjeira et al. (2011) used another strategy for lineage tracing in mice. They generated transgenic mice expressing a TAM-inducible form of Cre recombinase (iCreERT2) under the control of *Sox10* promoter (*Sox10::iCreERT2*). With this aim, a fragment of the *Sox10* gene in a 170-kb phage artificial chromosome (PAC) was replaced by a $Sox10^{iCreERT2}$ sequence. They generated different $Sox10^{iCreERT2}$;$R26R^{eYFP}$ transgenic lines. One of these lines, named SER26, was used in injury models to address contribution of glia to enteric ganglia regeneration in the adult (> postnatal day 84). For this purpose, the authors injected animals with TAM and later on they applied the cationic detergent benzalkonium chloride (BAC), known to locally ablate the myenteric plexus, to a small serosal surface of the intestine. As expected, 3 days later enteric ganglia were ablated from the injured area. One month later, the affected area was invaded by glia and axonal projections. However, when this region was analyzed 70–90 days after BAC treatment, on the area bordering the injury zone around 9% of enteric neurons were found to express eYFP. This fraction gradually decreased at increasing distances from the affected area. From this result we can conclude that SCP-derived cells (SCPDCs) might be involved in plastic regenerative mechanisms to restore enteric ganglia function. In another study, Joseph et al. failed to detect significant enteric glia-derived neurogenesis in adult $GFAP^{Cre}$ or $GFAP^{CreERT2}$ mice, in different injury models including BAC. Nevertheless, it could be argue against that SCPs do not express GFAP and that SCPs were shown to contribute postnatally with enteric neurons (see above). Lastly, it still remains unclear to which extent in the adult the neurogenic cells are any kind of vagal NCD enteric nervous system precursors and/or SCPs, since both cell types express Sox10.

3.3 | Tumorigenesis

SCPs were implicated in the origin of several kinds of tumors (see also review by Kaucka & Adameyko, 2014).

Neurofibromatosis Type 1 is a heritable genetic disease in which the neurofibromin1 (NF1) gene, which controls cell proliferation, is deleted in cells of the Schwann cell linage. This was shown to result in the development of multiple benign tumors of peripheral nerves (Le et al., 2011). It is worth noting that the onset of this disease requires either biallelic mutations of NF1 in the SCPs or immature Schwann cells, or the overexpression of glial growth factor β3, one of the NRG isoforms (Wu, Liu, Williams, & Ratner, 2017). There are two types of neurofibromas: dermal (exclusively found in the skin, and likely originated in bNCD-SCPs or terminal Schwann cells) and plexiform (which can form along the peripheral nerve, originated in SCPs or immature Schwann cells; Le et al., 2011; Wu et al., 2017). Mouse genetic models ($PLP1^{CreERT2}$;$NF1^{flox/-}$, Dhh^{Cre};$NF1^{flox/flox}$, P_0^{Cre};$NF1^{flox/-}$, and $Krox20^{Cre}$;$NF1^{flox/-}$) in which the NF1 gene was depleted in SCPs or immature Schwann cells, originate plexiform neurofibromas in the adult (Le et al., 2011; Wu et al., 2017). Nevertheless, depletion of NF1 in the adult, using for instance $PLP1^{CreERT2}$;$NF1^{flox/-}$ mice, only rarely develop neurofibroma formations (Le et al., 2011). The tyrosine kinase receptor EGFR, expressed in SCPs, has also been implicated in the plexiform neurofibroma formation (Wu et al., 2017). Overexpression of EGFR would promote cell proliferation, migration, angiogenesis and adhesion, processes likely involved in tumor initiation.

Other tumors involving SCPs were found to show both melanocytic and neural features. Since melanocytes and Schwann cells can be originated from SCPs, such association between melanocytes and Schwann cells usually complicates the diagnosis of tumors expressing both melanocytic and Schwann cell markers. This is not unexpected since, in another context, mature Schwann cells were found to regain competence to originate pigment cells after nerve injury *in vivo* (Adameyko et al., 2009). Schwann cell based-tumors, for instance, may also express melanocytic markers: for example, melanotic schwannomas are positive for melanoma markers such as tyrosinase and HMB-45 and even contain melanosomes in different stages of maturation while maintaining Schwann cells features (Van Raamsdonk & Deo, 2013). A similar case, although on the opposite side, is found in desmoplastic melanomas which are considered to arise from melanocytes, based on their melanocytic features; however, they are often found to express SCPs markers, such as Sox10, p75, N-CAM and S100, and some of them even show mutations in the SC-related NF1 gene (Van

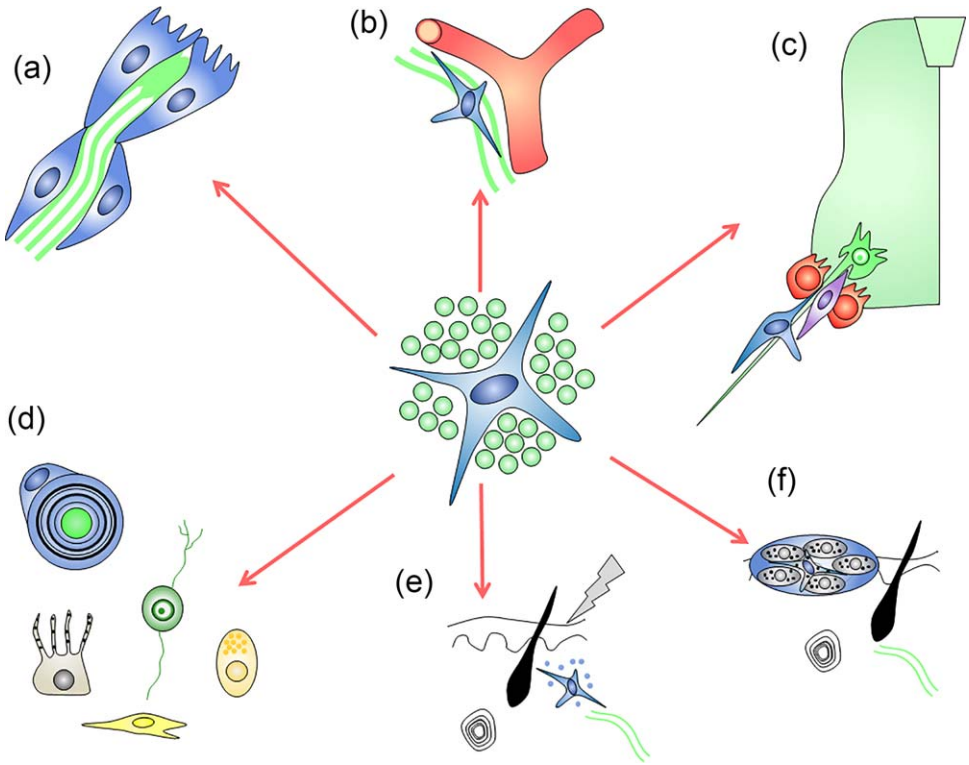

FIGURE 2 Schwann cell precursors functions in health, regeneration and disease. Some of the main roles of SCPs are illustrated. (a) Nerve fasciculation and axonal elongation. (b) Arterial branching, patterning, and differentiation. (c) Morphogenesis of the ventral neural tube and formation of the perineurium. (d) Multipotency. (e) Tissue regeneration. (f) Tumorigenesis

Raamsdonk & Deo, 2013). Interestingly, dissection of subcutaneous melanoma tissue followed by RNA extraction from some melanoma mouse models showed upregulation in markers associated with the Schwann cell lineage such as Mbp, retinaldehyde binding protein (Rlbp; expressed in SCPs) and nestin (Handoko et al., 2013). Moreover, it was also shown in transgenic zebrafish that dominant negative forms of two autophagy proteins, Atg4b and Atg5, under the control of the melanocyte master gene mitfa (*mitfa:atg4b*^{C74A} *and mitfa:atg5*^{K130R}), develop malignant peripheral nerve sheath tumors, neuroendocrine tumors and small-cell tumors (Lee et al., 2016). Since those tumors were found to express Sox10 the authors reasonably concluded that they are SCPs-derived and that in their model autophagy inhibition likely resulted in oncogenesis.

All these taken into account, a better understanding of the connection between melanocytes and Schwann cells during development is required in order to explain their shifts in phenotype observed during the development of certain cancers.

4 | SUMMARY

Some of the main aspects herein discussed are summarized in Figures 1–3. SCPs are known from some time ago to play a significant role in nerve fasciculation, target innervation and neuronal survival. Migratory NCCs were described to originate the first-born SCPs. In addition, in the process of axonal elongation and target innervation, some bNCD Sox10^{+} PLP1^{+} Dhh^{-} SCPs were recently described to migrate in contact with axons toward the skin and other peripheral tissues, contributing to multipotent terminal glia cells found even in the adult. Only early Sox10^{+} PLP1^{+} Dhh^{-} SCPs could contribute with skin melanocytes and eventually dental pulp and bone marrow mesenchymal stromal cells whereas Dhh^{+} SCPs are able to originate endoneurial fibroblast and enteric neurons and eventually parasympathetic neurons, splenic glia and chromaffin cells. Some other SCPs functions are known to correspond to Dhh^{+} SCPs such as: nerve connective tissue sheath formation; distal digit, skin and enteric nervous system regeneration; vasculogenesis, and tumorigenesis.

5 | FINAL REMARKS

SCPs previously thought to merely be short-term intermediate cells in the SC lineage, are now considered to be able to migrate through nerves and contribute with multipotent terminal Schwann cells in late embryonic development; moreover, they can even persist up to adulthood. Furthermore, these cells keep some stem-like cell properties and are a postnatal source of enteric neurons, immune-regulating glia of the spleen, skin cells, and pulp and odontoblast cells of the teeth. They are likely involved in hair cycle, and in multiple-tissue regeneration such as distal digit repair and skin wound healing, even in mammals. In addition, under tissue remodeling (for instance, after injury or in tumorigenic processes) mature Schwann cells and/or other SCP derivatives get most likely reprogrammed and acquire multipotent properties characteristic of SCPs.

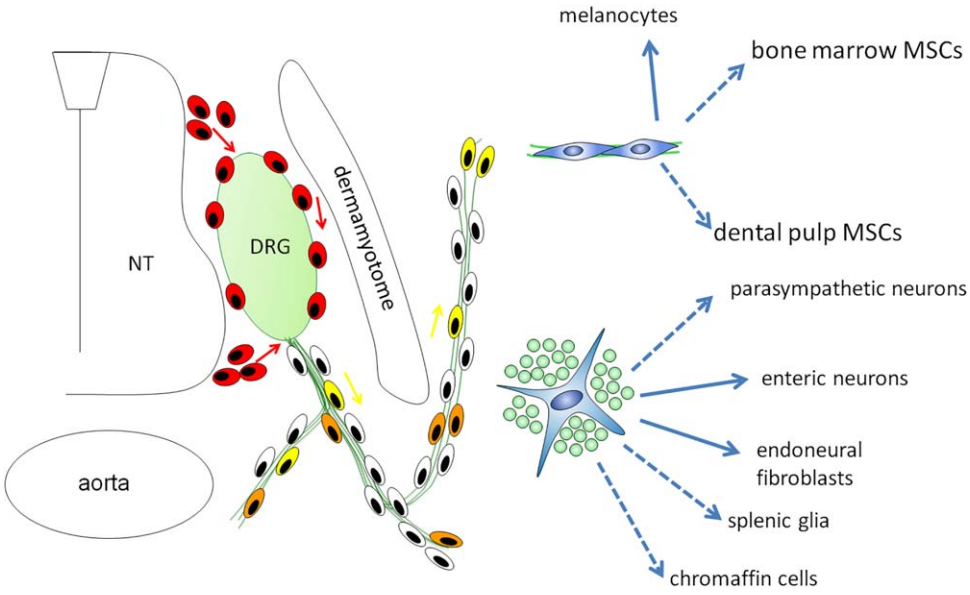

FIGURE 3 Schwann cell precursors origins and multipotency. Schematic figure showing different origins of SCPs from NCCs and boundary cap neural crest cells (red). Some late born Sox10^{+} PLP1^{+} Dhh^{-} SCPs (yellow) migrate in contact with axons toward peripheral organs. Multipotent properties of SCPs are also depicted. Certain SCPs derivatives can originate only from Dhh^{-} cells. Red and yellow arrows: orientation of specific cell type migration. Dashed arrows: hypothetical features. NT: neural tube. DRG: dorsal root ganglion

All through this article, many unsolved aspects in SCPs biology are proposed. Although major milestones in SCPs knowledge were achieved, it still remains largely fragmentary and caveats accumulate in parallel to our progress. Among others, fundamental issues that remain unclear include: to which extent SCPs subpopulations may differ and which are the properties of niches harboring them. New studies are required to uncover the mechanisms driving SCPs differentiation to most of their diverse lineages, and signaling axes therein involved. Thanks to genetic lineage tracing and to single cell RNA sequencing technologies we can expect that this research field would move forward faster and possible new shifts will take place in some of our current developmental biology paradigms. Nevertheless, it is important to be cautious with for instance which mouse lines to use, and to confirm data with different validated strains (see review by Heffner et al., 2012). For instance and regarding NC derivatives, it is important to take into account that a very broadly used *Wnt1*^{Cre} mouse strain has some ectopic activation of the promoter at least in certain brain areas (Lewis, Vasudevan, O'neill, Soriano, & Bush, 2013).

In spite of that, it is surprising the broad plasticity of SCPs and/or of some of their derivatives considering that they might contribute with cells typical of the three germ layers. With this regard, conclusive evidences of endoderm-like derivatives from SCPDCs were not published yet. Furthermore, such plasticity seems to remain up to adulthood in certain anatomical regions and/or might be induced in the context of tissue remodeling likely through *in vivo* cell reprogramming events. Perhaps the maintenance of the expression of early blastula genes in SCPs, such as Foxd3 and Myc might explain such notable plastic/multipotent properties (Aquino, 2017; Buitrago-Delgado, Nordin, Rao, Geary, & LaBonne, 2015; Widera et al., 2011).

Recent findings of SCPs involvement in angiogenesis and in tissue regeneration allow as hypothesizing that these cells might significantly contribute to different kinds of tumors as well as in the regeneration of other organs and tissues. With respect to eventual SCPs major contribution to certain cancers, recent evidences showing a SCPs origin of chromaffin cells and of transitional SCPs-chromaffin cell phenotypes would likely involve SCPDCs in neuroblastoma and pheochromocytoma development (Furlan et al., 2017; Szabo et al., 2012).

Moreover, SPCDCs might also be involved in the schwannosis and other events taking place after traumatic spinal cord injuries (Agudo et al., 2008; Norenberg, Smith, & Marcillo, 2004). In addition, it is not known if after injury cells with SCPs properties can also originate from NG2^{+} glia of the CNS (also known as oligodendrocyte precursor cells), which were shown to produce SCs (Zawadzka et al., 2010) and other kinds of cranial neural crest-derived glia (such as aldynoglia cells; Nieto-Sampedro, 2002).

As it was suggested by others (Petersen & Adameyko, 2017) and since early SCPs likely differ from those expressing Dhh and S100, it could be reasonable naming them with more appropriate terms such as nerve-associated multipotent progenitors (NAMPs) or nerve-associated multipotent neural crest-derived cells (NAM-NCDCs). Finally, it remains to be elucidated if adult bone marrow SCPDCs might get mobilized after injury and if they can contribute with parenchyma cells of affected tissues (Kucia et al., 2008; Labat, Milhaud, Pouchelet, & Boireau, 2000). We know now much about SCPs derivatives in health; it is time to focus on their contribution to disease and to other models of tissue remodeling and regeneration which might open new ways for therapeutic strategies and for tissue repair/replacement.

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