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Genetic Events and Signaling Mechanisms Underlying Schwann Cell Fate in Development and Cancer

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In this review, we describe Schwann cell development from embryonic neural crest cells to terminally differentiated myelinated and nonmyelinated mature Schwann cells. We focus on the genetic drivers and signaling mechanisms mediating decisions to proliferate versus differentiate during Schwann cell development, highlighting pathways that overlap with Schwann cell development and are dysregulated in tumorigenesis. We conclude by considering how our knowledge of the events underlying Schwann cell development and mouse models of schwannoma, neurofibroma, and malignant peripheral nerve sheath tumor can inform novel therapeutic strategies for patients with cancers derived from Schwann cell lineages.

KEY WORDS: Malignant peripheral nerve sheath tumor, Neural crest, Neurofibroma, NF1, NF2, Schwannoma, Schwann cell

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The embryonic neural crest is an evolutionarily conserved multipotent cell population that gives rise to a diversity of cell types, including numerous components of the peripheral nervous system (PNS), such as Schwann cells. Anatomically, the neural crest is divided into cranial, vagal, trunk, and sacral components along the anterior-posterior axis, and each segment is regulated via a complex gene regulatory network that dictates neural crest specification, migration, proliferation, and differentiation.[1] The Schwann cell lineage is no different, as these various cellular outcomes must be balanced throughout the developmental process (Figure 1). Following delamination from the dorsal neural tube, trunk neural crest cells migrate along ventral and dorsolateral pathways, and classic lineage tracing experiments demonstrate that the Schwann cell lineage primarily arises from ventrally migrating trunk neural crest cells.[2] This migratory process is highly coordinated across both cell autonomous transcriptional programs and noncell autonomous signaling events.[3] Consistent with the diverse migratory destinations of Schwann cell progenitors, Schwann cell-derived tumors present anatomically throughout the body.

FROM NEURAL CREST TO SCHWANN CELL PRECURSOR: TAKING THE FIRST STEPS TOWARD A GLIAL FATE REQUIRES SOX10 INDUCTION AND NRG1 RESPONSIVENESS

The subsequent transition between migratory trunk neural crest and Schwann cell precursors (SCPs) (Figure 1), the first intermediate population in fate commitment down the Schwann cell lineage, does not appear to constitute a specific spatiotemporal stage but more likely exists within a differentiation continuum. Nonetheless,

ABBREVIATIONS: GFAP, glial fibrillary acidic protein; **HDAC,** histone deacetylase complexe; **iSC,** immature Schwann cell; **MAPK,** mitogen activation protein kinase; **MPNST,** malignant peripheral nerve sheath tumor; ***mpz*** **,** myelin protein zero; **MRI,** magnetic resonance imaging; **NF1,** neurofibromatosis type 1; **NF2,** neurofibromatosis type 2; **PI3K,** phosphoinositide 3-kinase; **PNS,** peripheral nervous system; **PRC2,** polycomb repressive complex 2; **Ras-GAP,** ras GTPase-activating protein; **RNA,** ribonucleic acid; **SCP,** Schwann cell precursor; **VEGF,** vascular endothelial growth factor

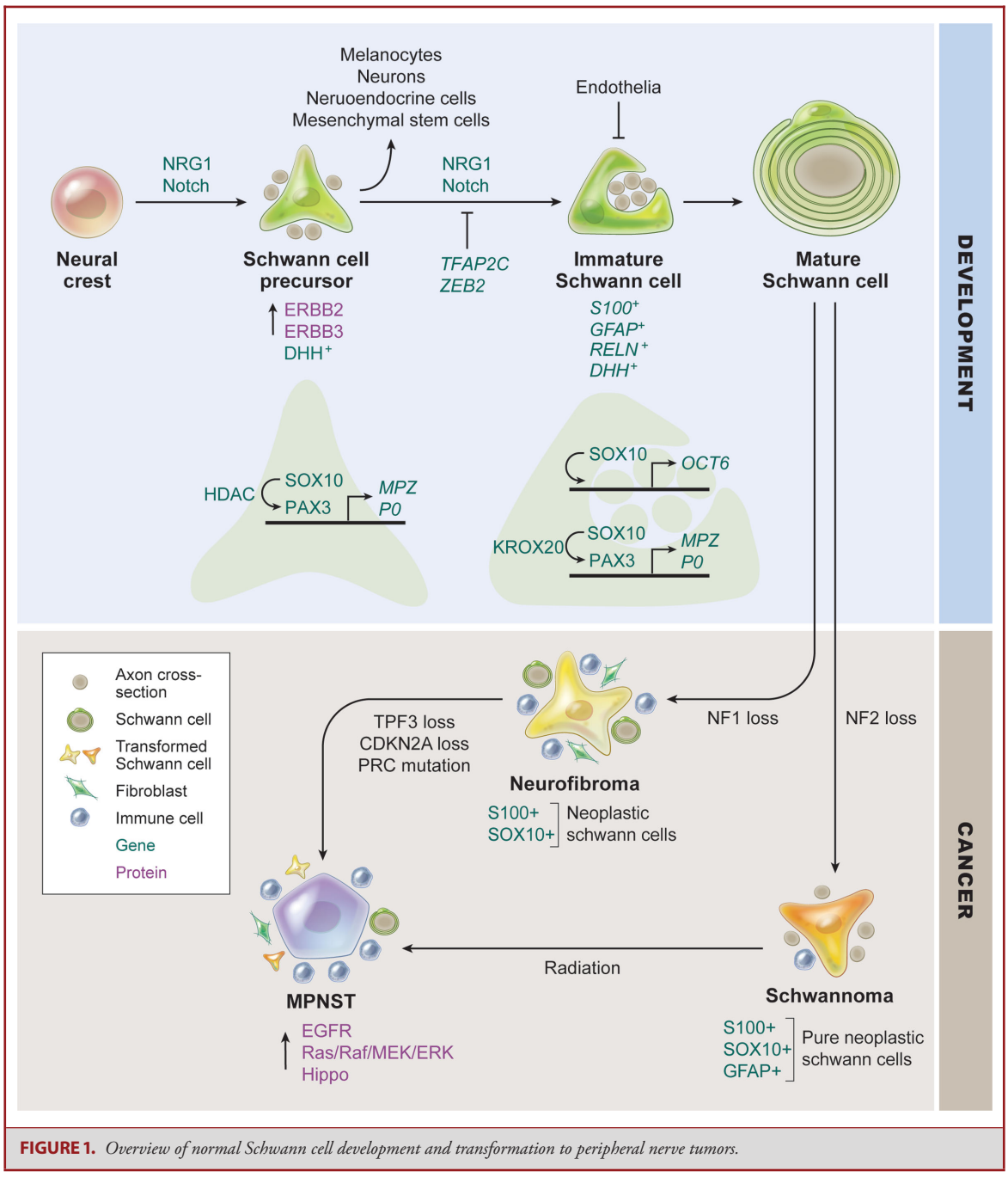

FIGURE 1. *Overview of normal Schwann cell development and transformation to peripheral nerve tumors.*

efforts to identify the key transcriptional programs and noncell autonomous signals mediating the balance between migration, proliferation, and differentiation have revealed a number of factors important for cellular decision-making. Among these, the transcription factor SOX10 is necessary for Schwann cell and melanocytic differentiation[4,5] and serves as a master regulator of neural crest multipotency by repressing neuronal lineages.[6] In addition, Sox10 cooperates with histone deacetylase complexes (HDACs) to activate *Pax3*, leading to expression of the Schwann marker myelin protein zero (*mpz*) and P0 protein, consistent with commitment to a glial fate.[7,8] With regard to noncell autonomous signals, SCPs are dependent on NRG1 (glial growth factor)[9,10] and its partner receptor tyrosine kinases ErbB2 and ErbB3[11] for cell proliferation and Schwann commitment, as well

as Notch signaling to promote glial differentiation.[12] With regard to crosstalk between cell autonomous and noncell autonomous determinants of cell identity, Sox10 further regulates expression of ErbB3 in Schwann cells in order to maintain responsiveness to NRG1.[4] Despite the aforementioned mechanisms biasing SCPs toward a glial fate, SCPs remain multipotent[13] and can give rise to numerous other neural crest derivatives, including melanocytes,[14] neurons,[15] neuroendocrine cells in the adrenal medulla,[16] and dental mesenchymal stem cells.[17] Thus, SCPs comprise an intermediate progenitor in the neural crest hierarchy exhibiting early commitment to the glial lineage, yet retaining broad developmental potential (Figure 1).

SCHWANN CELL MATURATION REFLECTS ACTIVATION OF CRITICAL TRANSCRIPTIONAL NETWORKS TO NARROW DEVELOPMENTAL POTENTIAL AND DRIVE TERMINAL DIFFERENTIATION TO IMMATURE AND MATURE SCHWANN CELLS

As the embryo develops, SCPs reach their migratory destination and begin to organize around developing axons, continuing to survive in an axon-dependent manner due to neuronal secretion of NRG1.[18] Intercalated with developing axons, SCPs begin the transition to immature Schwann cells (iSCs), the direct progenitor population for mature Schwann cells (Figure 1).[19,20] A number of shared genes and factors play an important role in both SCP commitment and iSC transition, confounding the study of these 2 processes in isolation. Indeed, Sox10 modulates a positive feedforward loop to promote iSC differentiation by directly activating *Oct6* expression through binding to a Schwann cell-specific enhancer, which leads to Oct6-mediated recruitment of HDAC genes.[21,22] In addition, Sox10 and Krox20 cooperatively drive expression of key myelin genes, such as myelin basic protein and *mpz*.[23,24] From a noncell autonomous perspective, NRG1 is sufficient to drive iSC formation from SCPs,[11] and Notch signaling via its transcriptional activator RBP-J is critical for mediating the transition from SCPs to iSCs. In contrast, endothelin signaling[25] and the transcription factors *Tfap2a*[26] and *Zeb2*[27,28] delay progression to iSCs and thus maintain the developmental potential of SCPs. Functionally, iSCs exhibit a significantly narrowed developmental potential compared to SCPs, as iSCs primarily give rise to myelinated and nonmyelinated Schwann cells. Accordingly, iSCs induce key Schwann commitment markers such as *S100* and glial fibrillary acidic protein (*GFAP*),[29] gain the ability to survive without mitogenic input from nearby axons, and develop a basal lamina associated with loss N-cadherin.[30] The transition to mature Schwann cells is ultimately driven by interactions with axons through radial sorting and paracrine signaling that serves to compartmentalize myelinating Schwann cells with large caliber axons, and nonmyelinating Schwann cells with small caliber axons (Figure 1).[20] Radial sorting coincides with exit from the cell cycle and terminal differentiation into mature Schwann cells, completing the developmental trajectory of the Schwann cell lineage, and the decision to form a myelinating or nonmyelinating Schwann cell is primarily driven by axonal secretion of NRG1 in noncell autonomous manner.[31,32] Accordingly, disruption of radial sorting impairs terminal Schwann differentiation, and numerous signaling pathways have been implicated in this process, including NRG1/ErbB signaling, mitogen activation protein kinase (MAPK), and phosphoinositide 3-kinase (PI3K) activation, Notch signaling, and transcription factor activity, including Sox10, Oct6, Egr2, and NF-kB.[33,34] In sum, the Schwann cell lineage arises through an ordered progression from neural crest to differentiated Schwann cell requiring integration of both cell autonomous and noncell autonomous signaling mechanisms.

SCHWANN CELL-DERIVED TUMORS SHARE MOLECULAR SIGNATURES AND SIGNALING DEPENDENCIES WITH KEY DEVELOPMENTAL STAGES IN SCHWANN CELL DEVELOPMENT

Given the broad developmental potential of Schwann cells, it is perhaps unsurprising that many tumors are derived from this lineage. Canonically, schwannomas, neurofibromas, and malignant peripheral nerve sheath tumors (MPNSTs) arise from Schwann cells (Figure 1), and recent evidence suggests certain melanomas[14] and sympathoadrenal tumors such as pheochromocytoma, neuroblastoma, and paraganglioma[16] can also arise from the Schwann cell lineage.

SCHWANNOMAS ARE NF2-ASSOCIATED TUMORS MARKED BY RETENTION OF SCHWANN CELL LINEAGE MARKERS AND DYSREGULATED MAP KINASE SIGNALING WITH MINIMAL TUMOR HETEROGENEITY

Schwannomas are the most common cancer of PNS.[35] Patients with schwannomas typically present with neurological symptoms secondary to impingement of nearby neurological structures, and workup generally comprises neurological examination and radiological evaluation with magnetic resonance imaging (MRI) (Figure 2), which may reveal the classic finding of bilateral vestibular schwannomas in patients with neurofibromatosis type 2 (NF2) (Figure 2A-2A′). Molecularly, these tumors are primarily associated with loss of the tumor suppressor *NF2* and rare gene fusions driving MAPK activation,[36,37] consistent with the role of receptor tyrosine kinase signaling in Schwann cell development (Table 1). Of note, schwannomatosis, defined as the presence of multiple schwannomas in a single patient, appears to involve a multi-hit genetic mechanism, including *SMARCB1* and *LZTR1* loss, in addition to *NF2* loss.[38] Microscopically, schwannomas are almost entirely composed of homogeneous

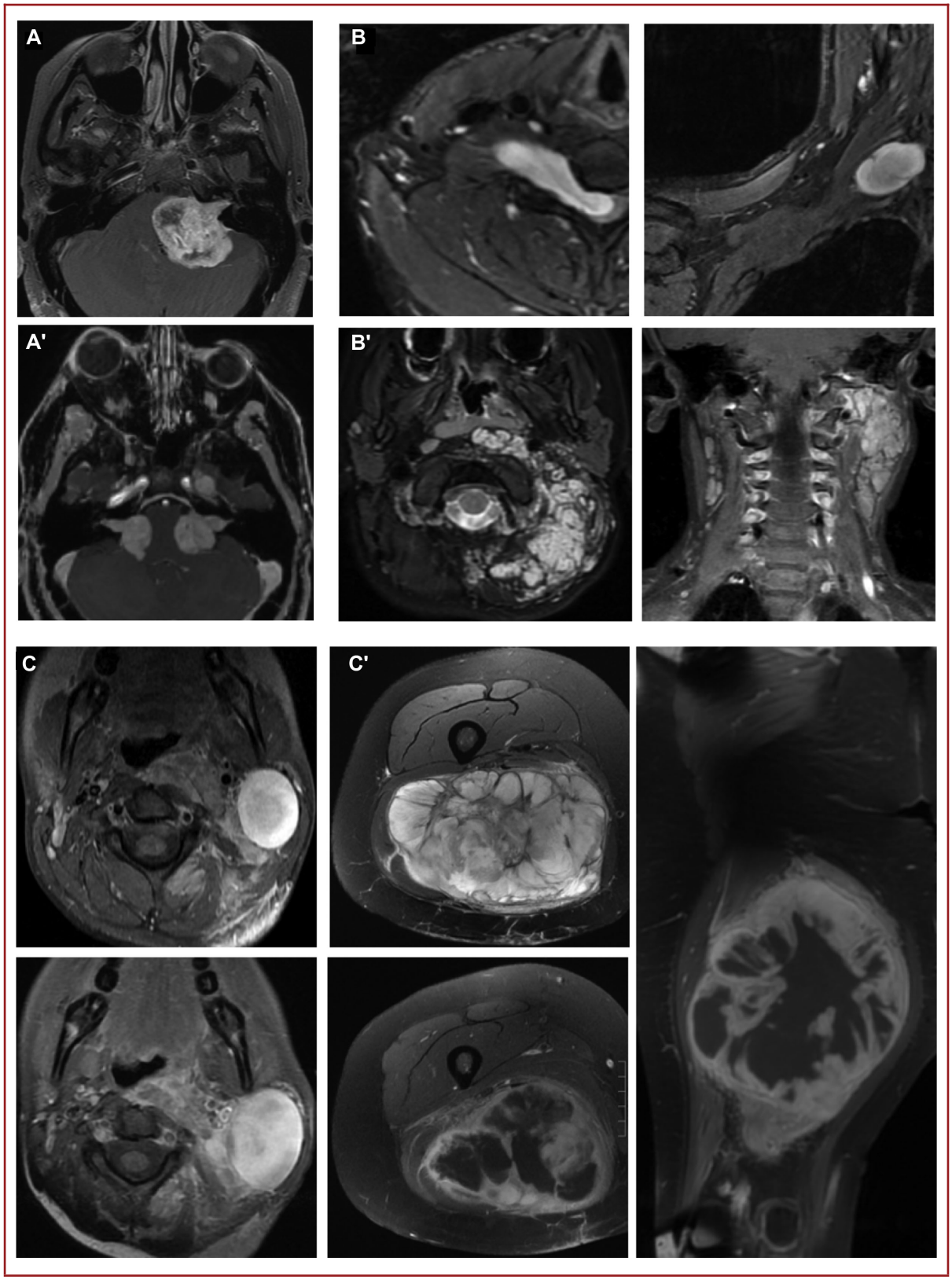
A
B
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FIGURE 2. *MRI appearance of Schwann cell-derived peripheral nerve tumors.* **A**, *Enhancing left cerebellopontine angle mass extending into the internal auditory canal along the course of the vestibulocochlear nerve (cranial nerve VIII) with resultant mass effect upon the adjacent pons and cerebellum consistent with a vestibular schwannoma.* **A′**, *Bilateral vestibular schwannomas are pathognomonic of NF2.* **B**, *T2 hyperintense ovoid lesion extending along the course of the right C7 nerve root consistent with a deep intraneural neurofibroma.* **B′**, *Left cervical mass with intense enhancement and multicompartmental extension from the posterior neck and into the prevertebral soft tissues consistent with a plexiform neurofibroma in the setting of NF1.* **C**, *Rapid interval growth (upper image at baseline, lower image 12 mo later) of an intensely enhancing nodule within a left cervical plexiform neurofibroma in a patient with NF1. Plexiform neurofibromas are at risk of malignant transformation to MPNSTs, particularly in the setting of rapid growth.* **C′**, *Large heterogeneous, enhancing, T2 hyperintense right thigh mass with internal degeneration intimately associated with the sciatic nerve. Size and irregular margins along the posterior thigh muscles are consistent with an MPNST.*

TABLE 1. Key Studies Regarding Genomic Investigation of Human Schwannoma, Neurofibromas, and MPNSTs

Study	Method	Key finding
Schwannoma		
Agnihotri et al[36] *Nature Genetics*, 2016	Whole exome (n = 26)	The majority of tumors (n = 20) harbored *NF2* mutations with additional low-frequency variants in many other genes
	Targeted sequencing (n = 99)	Exon sequencing of mutations identified from Whole Exome Sequencing (WES) showed recurrent *NF2* mutation (n = 76)
	Methylation array (n = 125)	Two epigenomic groups were identified corresponding to vestibular versus spinal schwannomas
	Ribonucleic acid sequencing (n = 41)	Rare *SH3PXD2A-HTRA1* fusion (n = 5) observed with tumorigenic and promitogenic functions
Håvik et al[37] *Journal of Neurosurgery*, 2018	Whole exome (n = 46)	The majority of tumors (n = 35) harbored *NF2* mutations while the remaining exhibited alterations in genes linked to *NF2*
Neurofibroma and MPNST		
Lee et al[79] *Nature Genetics*, 2014	MPNST whole exome (n = 15)	The majority of tumors harbored recurrent *NF1*, *EED*, *SUZ12*, *CDKN2A*, and *TP53* mutations with only n = 1 sample showing no alterations in any of these genes
	MPNST ribonucleic acid sequencing (n = 15)	Tumors segregated on PCA by PRC2 mutational status with enrichment of a homeobox gene expression signature in PRC2 mutant MPNSTs
	MPNST targeted sequencing (n = 37)	Consistent with WES data, the majority of tumors harbored recurrent NF1, EED, SUZ12, CDKN2A, and TP53 mutations with only n = 2 samples showing no alterations in any of these genes
Zhang et al[80] *Nature Genetics*, 2014	MPNST whole genome/whole exome (n = 8)	The majority of tumors demonstrate inactivating *NF1* or *SUZ12* mutations (5/8) as well as *EED* (n = 1) and *EPC1* (n = 1) mutations
	MPNST targeted sequencing (n = 42)	Redemontrated recurrent mutations in *SUZ12* (n = 11) while further confirming these mutations result in abrogation of SUZ12 expression
	Neurofibroma targeted sequencing (n = 11)	No inactivating *SUZ12* mutations were identified in neurofibromas
Nielsen et al[81] *Am Journal of Pathology*, 1999	MPNST IHC and *CDKN2A* sequencing (n = 11)	Recurrent CDKN2A loss observed in the majority of MPNSTs (n = 10)
	Neurofibroma IHC and CDKN2A sequencing (n = 7)	Intact CDKN2A observed in all non-MPNST lesions

neoplastic Schwann cells with spindle-shaped nuclei demonstrating classic biphasic architecture with nuclear palisading (Figure 3). Histologic variants include cellular schwannomas (monophasic with compact spindle cells), melanotic schwannomas (expressing melanin pigment), epithelioid schwannomas (rounded cells arranged in single cells and clusters), or plexiform schwannomas (occurring superficially with a nodular growth pattern).[39] By immunohistochemistry, schwannomas typically express S100[40] and SOX10[41] proteins (Figure 3A-A′) consistent with a homogenously transformed population of Schwann origin, and a subset exhibits GFAP positivity,[42] mimicking the marker expression patterns observed during normal Schwann cell differentiation. In mice, NF2 misactivation results in a greater range of phenotypes with unclear overlap to human NF2 patients, the latter of which predominantly develop nervous system tumors such as schwannomas, meningiomas, ependymomas, and, rarely, astrocytomas (Table 2).[43] NF2 null mice do not complete gastrulation,[44] and in contrast to human patients, NF2 heterozygotes

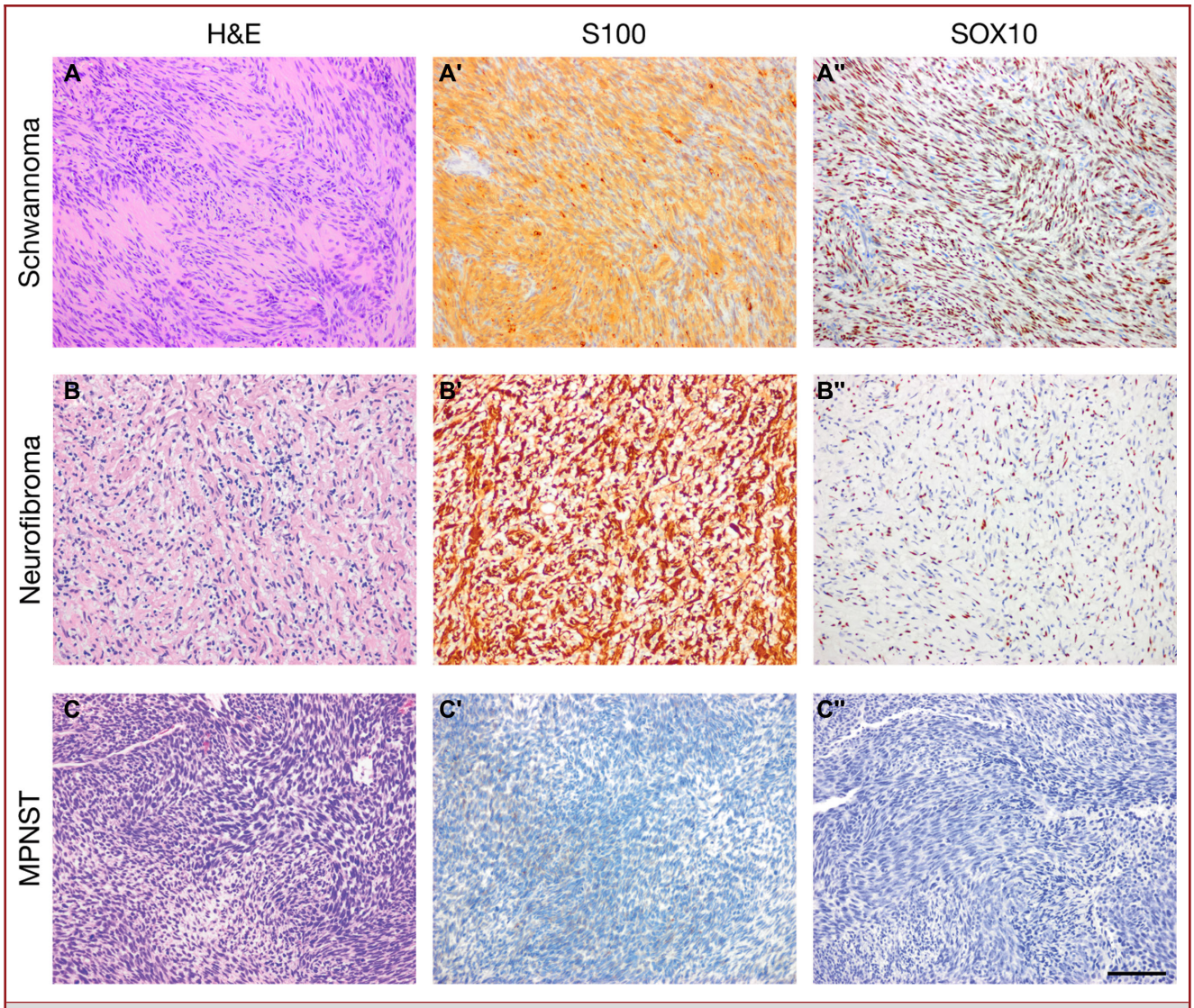

FIGURE 3. *Histopathologic appearance of Schwann cell-derived peripheral nerve tumors. Representative hematoxylin and eosin (H/E) staining* **A-C** *as well as S100* **A′**, **B′**, **C′** *and SOX10* **A″**, **B″**, **C″** *immunohistochemistry for* **A**, *schwannoma,* **B**, *neurofibroma, and* **C**, *MPNST.*

develop osteosarcomas, fibrosarcomas, and hepatocellular carcinomas that demonstrate high metastatic proclivity and cooperativity with *Tp53* loss.[45] In contrast, conditional genetics has led to the development of mouse models with greater similarity to human NF2 loss. Introduction of pathogenic NF2 variants specifically in the myelinated Schwann cell lineage leads to schwannoma formation,[46] and conditional NF2 deletion with *P0Cre*, an SCP marker that directs target gene expression in myelinating Schwann cells, results in the development of schwannomas in mice.[47] More recently, conditional NF2 mutant mice generated with a *Periostin-Cre* were shown to develop vestibular schwannomas and hearing impairment similar to human NF2 patients with bilateral schwannomas. With regard to clinical management, schwannomas demonstrate excellent tumor control following surgery or radiation therapy,[48,49] although morbidity from these treatments remains a significant concern.[50-56] In sum, schwannomas are NF2-associated lesions composed of a homogeneous S100- and SOX10-positive Schwann cell population that are managed primarily with local treatment and have limited metastatic potential.

TABLE 2. Foundational Genetic Analysis of Mouse Mutants Harboring Mutations in Recurrently Mutated Genes Across Human Schwann Cell-derived Tumors

Genotype	Study	Key finding
NF2		
Nf2$^{-/-}$	McClatchey et al[44] *Genes & Development*, 1997	Homozygous *Nf2* mutants fail to complete gastrulation due to an extraembryonic defect
Nf2$^{+/-}$; *Tp53*$^{+/-}$	McClatchey et al[45] *Genes & Development*, 1998	Heterozygous *Nf2* mutants develop many distinct tumors (osteosarcoma, lymphoma, lung adenocarcinoma, hepatocellular carcinoma, and fibrosarcoma) with a high metastasis rate in cooperation with P53 loss
P0Cre; Nf2$^{fl/fl}$	Giovannini et al[46] *Genes & Development*, 2000	Homozygous *Nf2* conditional mutations under control of the Schwann cell specific *P0Cre* leads to numerous human NF2 sequelae, including schwannoma formation
NF1		
Nf1$^{-/-}$	Jacks et al[65] *Nature Genetics*, 1994	Homozygous *Nf1* mutants display embryonic lethality at mid gestation while heterozygotes demonstrate increased propensity for pheochromocytoma and myeloid leukemia development
Nf1$^{-/-}$	Brannan et al[66] *Genes & Development*, 1994	Homozygous *Nf1* mutants display embryonic lethality at E14.5 due to cardiac defects with sympathetic ganglia hyperplasia
Nf1$^{+/-}$; *Tp53*$^{+/-}$	Vogel et al[82] *Science*, 1999	Double heterozygous *Nf1* and *Tp53* mice demonstrate fully penetrant soft tissue sarcoma formation that exhibit loss of heterozygosity and express neural crest markers
Nf1$^{+/-}$; *Tp53*$^{+/-}$	Cichowski et al[83] *Science*, 1999	Compound loss of both *Nf1* and *Tp53* lead to MPNST development while homozygous *Nf1* loss alone primarily results in neurofibroma formation
DhhCre; Nf1$^{fl/fl}$	Wu et al[71] *Cancer Cell*, 2007	Homozygous *Nf1* conditional mutants under control of the Schwann lineage specific *DhhCre* driving deletion at E12.5 leads to both plexiform and dermal neurofibroma formation, suggesting spatiotemporal pattern of *Nf1* loss during development is critical
Nf1$^{+/-}$; *Tp53*$^{+/-}$; *Suz12*$^{+/-}$	De Raedt et al[92] *Nature*, 2014	*Suz12* loss in addition to *Nf1* and *Tp53* loss results in increased tumor formation across multiple sites due to potentiation of Ras-driven gene expression by *Suz12* loss
Lats1$^{-/-}$; *Lats2*$^{-/-}$	Wu et al[93] *Cancer Cell*, 2018	Hippo signaling pathway activation by homozygous loss of *Lats1* and *Lats2* lead to MPNST formation, which is abrogated by concurrent inactivation of Hippo pathway activators *Taz* and *Yap*

NEUROFIBROMAS ARE NF1-ASSOCIATED TUMORS COMPRISED OF NUMEROUS CELL TYPES YET EXHIBIT A DUAL SCHWANN CELL ORIGIN

While the neoplastic population in schwannomas appears homogeneous, neurofibromas exhibit significant cellular heterogeneity.[57] In addition to neoplastic Schwann cells, neurofibromas are comprised of non-neoplastic Schwann cells, fibroblasts, perineurial cells, axons, and immune cells such as mast cells, macrophages, T cells, and other antigen-presenting cells (Figure 3B) while maintain expression of Schwann markers such as S100 and SOX10 (Figure 3B′-3B′).[58-60] In mice, neurofibroma tumor heterogeneity is critical for oncogenesis, as conditional mutagenesis demonstrates that loss of neurofibromatosis type 1 (NF1) in the Schwann cell lineage is sufficient for neurofibroma formation, and haploinsufficiency of *Nf1* in non-Schwann lineages further enhances tumorigenesis.[61] Loss of NF1,[62] a ras GTPase-activating protein (Ras-GAP) that functions as a negative regulator of key intracellular signaling pathways such as Ras/Raf/MEK/ERK and PI3K,[63] is the critical genetic event as often observed in patients with syndromic NF1.[64] Developmentally, mice lacking *Nf1* demonstrate numerous deficits in neural crest-derived tissues and increased propensity for tumor formation.[65,66] Clinically, it is further important to distinguish superficial dermal neurofibromas (small nodular tumors of the skin and subcutaneous tissue arising from small superficial nerves that present with pain and bleeding but not neurological symptoms) from deep intraneural neurofibromas (nerve root-associated lesions causing symptoms from mass effect, including radicular pain or local neurological deficits) (Figure 2B), with plexiform neurofibromas (Figure 2B′) constituting a distinct entity characterized by multinodular continuous masses affecting large nerves and generally considered to be pathognomonic for syndromic NF1. Consistent with this classification, dermal and plexiform neurofibromas exhibit distinct methylation profiles,[67] and these subgroups further arise from distinct embryologic populations with dermal neurofibromas originating in dermal

skin-derived precursors,[68] while plexiform neurofibromas derive from SCPs and iSCs within a narrow developmental window.[69] This dual origin of dermal and plexiform neurofibromas may explain, in part, the divergent clinical behavior of these tumors despite their similar appearance on histopathology. Curiously, dermal neurofibromas arising from skin-derived precursors appear to exhibit hormonal dependence on estrogen and progesterone, and indeed, recent work suggests NF1 functions as an estrogen receptor corepressor.[70] More generally, conditional mutagenesis in mice has shown that *Nf1* loss in the embryonic glial progenitor population leads to both dermal and plexiform neurofibroma population, consistent with the notion that adult Schwann derivatives in the skin and nerves share a common developmental origin.[71] The clinical management of neurofibromas is primarily to improve patient morbidity, manage patient-reported symptoms, and obviate local complications due to mass effect, as the risk of metastatic spread is very low. Thus, neurofibromas constitute a second group of benign Schwann cell-derived lesions arising that share key genetic and signaling mechanisms across development and cancer.

MPNSTS DEMONSTRATE LOSS OF SCHWANN LINEAGE MARKER EXPRESSION, SEQUENTIAL GENETIC PERTURBATIONS, AND INCREASED INFLAMMATORY INFILTRATION

Although schwannomas and neurofibromas are generally well-managed with surveillance and local therapy, these lesions are at risk for transformation to MPNSTs from neurofibromas in NF1 patients or, rarely, from schwannomas in schwannomatosis or NF2 patients.[72] Accordingly, lesions that demonstrate adverse clinical or radiologic features (Figure 2C-2C′) concerning for progression warrant a more aggressive treatment paradigm.[73] In contrast to neurofibromas and schwannomas, patients with MPNSTs have high risk of metastatic progression and poor overall outcomes,[74] and multimodal therapy consisting of surgery, radiation, and systemic therapy is generally the standard of care, although definitive efficacy trials are lacking. Histologically, MPNSTs present as spindle cell neoplasms with high mitotic rate and gross necrosis (Figure 3C) that can be difficult to distinguish from other aggressive sarcomatous malignancies.[75] While immunohistochemistry may be positive for markers such as S100[76] or SOX10,[77] immunoreactivity for these neural crest lineage markers is often lost in MPNSTs (Figure 3C′-C′), adding to the diagnostic challenge these tumors pose. With regard to the molecular mechanisms underlying MPNST tumorigenesis,[78] precursor lesions require multiple hits in addition to *NF1* loss in order to transform into MPNSTs. In that regard, deoxyribonucleic acid sequencing of MPNSTs in human patients has identified recurrent mutations in *SUZ12* and *EED,* which are components of the polycomb repressive complex 2 (PRC2) family of epigenetic regulators, as well as tumor suppressor loss such as *TP53* mutation and *CDKN2A* deletion.[79-81] Mouse experiments have further demonstrated the importance of combinatorial loss of NF1 and *Tp53*,[82,83] as well as additional *Ink4a/Arf* loss, in MPNST pathogenesis.[84] Moreover, zebrafish lacking *Tp53* also develop MPNSTs,[85] reflecting the conserved important of tumor suppressor loss in MPNST pathogenesis. Consistent with the role of NF1 in this process, receptor tyrosine kinase pathways[86,87] and downstream regulators such as Raf/MEK/ERK[88] and PI3K signaling[89] are implicated in MPNST formation. Indeed, Raf and MEK inhibitors have shown efficacy in Vitro and in mouse models of MPNST,[90,91] although clinical trials in humans based on dysregulated pathways in mice are inconclusive, as targeted inhibitors of receptor tyrosine kinase pathways, including Raf, MEK, PI3K (and its mammalian target of rapamycin), epidermal growth factor, and vascular endothelial growth factor (VEGF), show unclear benefit in MPNST.[73] Intriguingly, the role of NF1 as a Ras-GAP regulating Ras/Raf/MEK/ERK and observed mutations in PRC2 components such as SUZ12 may converge to drive Ras-mediated transcription and render such tumors sensitive to bromodomain inhibitors.[92] In addition to receptor tyrosine kinase signaling and PRC2 components, Hippo signaling also appears to be important for MPNST progression via crosstalk with platelet-derived growth factor signaling,[93] which may again reflect convergence on Ras-mediated signal transduction mechanisms. Finally, although neoplastic Schwann cells are the cell of origin for MPNSTs, NF1 loss in the Schwann population alone is necessary but not sufficient for transformation to MPNST.[61] Thus, noncell autonomous mechanisms are critical for Schwann cell tumor transformation from a clinically indolent to aggressive neoplasm. Indeed, *NF1* deficient Schwann cells mediate a robust inflammatory response through numerous mechanisms, including recruitment of mast cells via the receptor tyrosine kinase *Kit*,[94] increased NF1 heterozygous mast cell proliferation through the Rho-GTPase Rac2,[95] and activation of a CXCR4-CXCL12 axis to drive cell proliferation.[96] These observations have led to the supposition that Schwann cell injury and neurofibroma transformation are similar biologic processes, and consistent with this hypothesis, nerve crush injury in NF1 mutant mice leads to neurofibroma formation.[97] Taken together, these studies reveal the cellular heterogeneity and signaling complexity underlying MPNST formation, requiring coordination and corruption of multiple signaling pathways through both cell autonomous and noncell autonomous mechanisms.

The molecular mechanisms underlying Schwann cell development and transformation have informed the selection of targeted agents to treat patients Schwann cell-derived tumors. As alluded to above, the treatment paradigm for schwannomas and neurofibromas primarily comprises local approaches such as surgery and/or radiation therapy. However, for large, rapidly progressive tumors particularly in syndromic cases associated with NF1 or NF2, more aggressive systemic therapy may be warranted to reduce morbidity. In that regard, inhibition of receptor tyrosine kinases or their downstream effectors such as Ras/Raf/MEK/ERK have demonstrated clinical efficacy. For example, the use of bevacizumab, a VEGF inhibitor,

for NF2 associated vestibular schwannoma improves hearing loss and inhibits tumor progression.[98,99] More recently, the MEK inhibitor selumetinib demonstrated clinical efficacy for inoperable plexiform neurofibromas in NF1 patients,[100] offering the first potential systemic therapy option to improve morbidity in these patients. Finally, given the need for multimodality treatment and overall poor prognosis for MPNST patients, numerous targeted agents are currently being tested in the clinical trial setting, including inhibitors of MEK (selumetinib), PI3K (sirolimus and everolimus), and BET inhibitors (CPI-0610).[101] These efforts illustrate the importance of defining critical developmental pathways underlying tumorigenesis from the Schwann cell lineage in order to rationally select agents to improve outcomes for our patients.

CONCLUSION

The Schwann cell lineage is a remarkable population that undergoes a complex developmental trajectory requiring coordination of cell autonomous and noncell autonomous inputs to undergo differentiation, migration, and proliferation. In many ways, this process happens in reverse in human patients who develop Schwann cell-derived tumors, as evidenced by progressive loss of Sox10, S100, and GFAP positivity during the transformation from benign to malignant cancers (Figure 1). Furthermore, as observed in human patients and interrogated in mouse genetic models, NF1 or NF2 loss in Schwann cells is necessary but not sufficient for transformation, as additional genetic hits and noncell autonomous contributions play a critical role in tumorigenesis.

With respect to the broader parallels between Schwann cell development and tumorigenesis, there are a number of questions that remain to be investigated. First, it will be important to define the effect of observed genetic aberrations in how noncell autonomous signals are interpreted by Schwann cells, and whether the genotype or transcriptome of Schwann cells fully dictates their cellular outcome. Second, single cell analyses will be critical to better understand the degree of cell type heterogeneity within these tumors, and how patterns of mutation co-occurrence are distributed across these populations to influence cellular phenotypes. Third, it will be important to test how the sequential order of mutations observed in human patients affects Schwann cell transformation. Finally, in addition to the canonical Schwann cell fates outlined above, cellular descendants of the early Schwann cell lineage can give rise to nonglial cell types, highlighting the remarkable plasticity of this population. Understanding the mechanisms underlying this process will provide insight into how related tumors, such as melanoma, take on aggressive features. Such analyses will pave the way for a deeper understanding of the mechanisms underlying transformation and metastasis in all neural crest lineages, which will ultimately improve outcomes for patients who develop these tumors.

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REFERENCES

1. Martik ML, Bronner ME. Regulatory logic underlying diversification of the neural crest. *Trends Genet*. 2017;33(10):715-727.
2. Le Douarin NM, Teillet MAM. Experimental analysis of the migration and differentiation of neuroblasts of the autonomic nervous system and of neurectodermal mesenchymal derivatives, using a biological cell marking technique. *Dev Biol*. 1974;41(1):162-184.
3. Theveneau E, Mayor R. Neural crest delamination and migration: from epithelium-to-mesenchyme transition to collective cell migration. *Dev Biol*. 2012;366(1):34-54.
4. Britsch S, Goerich DE, Riethmacher D, et al. The transcription factor SOX10 is a key regulator of peripheral glial development. *Genes Dev*. 2001;15(1):66-78.
5. Kuhlbrodt K, Herbarth B, Sock E, Hermans-Borgmeyer I, Wegner M. Sox10, a novel transcriptional modulator in glial cells. *J Neurosci*. 1998;18(1):237-250.
6. Kim J, Lo L, Dormand E, Anderson DJ. SOX10 maintains multipotency and inhibits neuronal differentiation of neural crest stem cells. *Neuron*. 2003;38(1):17-31.
7. Bhattacharyya A, Frank E, Ratner N, Brackenbury R. P0 is an early marker of the Schwann cell lineage in chickens. *Neuron*. 1991;7(5):831-844.
8. Jacob C, Christen CN, Pereira JA, et al. HDAC1 and HDAC2 control the transcriptional program of myelination and the survival of Schwann cells. *Nat Neurosci*. 2011;14(4):429-436.
9. Birchmeier C, Nave KA. Neuregulin-1, a key axonal signal that drives Schwann cell growth and differentiation. *Glia*. 2008;56(14):1491-1497.
10. Shah NM, Marchionni MA, Isaacs I, Stroobant P, Anderson DJ. Glial growth factor restricts mammalian neural crest stem cells to a glial fate. *Cell*. 1994;77(3):349-360.
11. Newbern J, Birchmeier C. Nrg1/ErbB signaling networks in Schwann cell development and myelination. *Semin Cell Dev Biol*. 2010;21(9):922-928.
12. Yoon K, Gaiano N. Notch signaling in the mammalian central nervous system: insights from mouse mutants. *Nat Neurosci*. 2005;8(6):709-715.
13. Furlan A, Adameyko I. Schwann cell precursor: a neural crest cell in disguise? *Dev Biol*. 2018;444(February):1-11.
14. Adameyko I, Lallemend F, Aquino JB, et al. Schwann cell precursors from nerve innervation are a cellular origin of melanocytes in skin. *Cell*. 2009;139(2):366-379.
15. Uesaka T, Nagashimada M, Enomoto H. Neuronal differentiation in Schwann cell lineage underlies postnatal neurogenesis in the enteric nervous system. *J Neurosci*. 2015;35(27):9879-9888.
16. Furlan A, Dyachuk V, Kastriti ME, et al. Multipotent peripheral glial cells generate neuroendocrine cells of the adrenal medulla. *Science*. 2017;357(6346):eaal3753.
17. Kaukua N, Shahidi MK, Konstantinidou C, et al. Glial origin of mesenchymal stem cells in a tooth model system. *Nature*. 2014;513(7519):551-554.
18. Dong Z, Brennan A, Liu N, et al. Neu differentiation factor is a neuron-glia signal and regulates survival, proliferation, and maturation of rat Schwann cell precursors. *Neuron*. 1995;15(3):585-596.
19. Jessen KR, Mirsky R. Schwann cell precursors; multipotent glial cells in embryonic nerves. *Front Mol Neurosci*. 2019;12:69.
20. Monk KR, Feltri ML, Taveggia C. New insights on Schwann cell development. *Glia*. 2015;63(8):1376-1393.
21. Jaegle M, Mandemakers W, Broos L, et al. The POU factor Oct-6 and Schwann cell differentiation. *Science*. 1996;273(5274):507-510.
22. Weider M, Küspert M, Bischof M, et al. Chromatin-remodeling factor brg1 is required for Schwann cell differentiation and myelination. *Dev Cell*. 2012;23(1):193-201.

23. Ghislain J, Charnay P. Control of myelination in Schwann cells: a *Krox20* cis-regulatory element integrates Oct6, Brn2 and Sox10 activities. *EMBO Rep*. 2006;7(1):52-58.
24. Topilko P, Schneider-Maunoury S, Levi G, et al. Krox-20 controls myelination in the peripheral nervous system. *Nature*. 1994;371(6500):796-799.
25. Brennan A, Dean CH, Zhang AL, Cass DT, Mirsky R, Jessen KR. Endothelins control the timing of Schwann cell generation in vitro and in vivo. *Dev Biol*. 2000;227(2):545-557.
26. Stewart HJS, Brennan A, Rahman M, et al. Developmental regulation and overexpression of the transcription factor AP-2, a potential regulator of the timing of Schwann cell generation. *Eur J Neurosci*. 2001;14(2):363-372.
27. Wu LMN, Wang J, Conidi A, et al. Zeb2 recruits HDAC-NuRD to inhibit Notch and controls Schwann cell differentiation and remyelination. *Nat Neurosci*. 2016;19(8):1060-1072.
28. Quintes S, Brinkmann BG, Ebert M, et al. Zeb2 is essential for Schwann cell differentiation, myelination and nerve repair. *Nat Neurosci*. 2016;19(8):1050-1059.
29. Buchstaller J, Sommer L, Bodmer M, Hoffmann R, Suter U, Mantei N. Efficient isolation and gene expression profiling of small numbers of neural crest stem cells and developing Schwann cells. *J Neurosci*. 2004;24(10):2357-2365.
30. Wanner IB, Guerra NK, Mahoney J, et al. Role of N-cadherin in Schwann cell precursors of growing nerves. *Glia*. 2006;54(5):439-459.
31. Michailov GV, Sereda MW, Brinkmann BG, et al. Axonal neuregulin-1 regulates myelin sheath thickness. *Science*. 2004;304(5671):700-703.
32. Mei L, Xiong WC. Neuregulin 1 in neural development, synaptic plasticity and schizophrenia. *Nat Rev Neurosci*. 2008;9(6):437-452.
33. Pereira JA, Lebrun-Julien F, Suter U. Molecular mechanisms regulating myelination in the peripheral nervous system. *Trends Neurosci*. 2012;35(2):123-134.
34. Jessen KR, Mirsky R. The origin and development of glial cells in peripheral nerves. *Nat Rev Neurosci*. 2005;6(9):671-682.
35. Ostrom QT, Cioffi G, Gittleman H, et al. CBTRUS statistical report: primary brain and other central nervous system tumors diagnosed in the United States in 2012-2016. *Neuro Oncol*. 2019;21(Supplement_5):v1-v100.
36. Agnihotri S, Jalali S, Wilson MR, et al. The genomic landscape of schwannoma. *Nat Genet*. 2016;48(11):1339-1348.
37. Håvik AL, Bruland O, Myrseth E, et al. Genetic landscape of sporadic vestibular schwannoma. *J Neurosurg*. 2018;128(3):911-922.
38. Kehrer-Sawatzki H, Farschtschi S, Mautner VF, Cooper DN. The molecular pathogenesis of schwannomatosis, a paradigm for the co-involvement of multiple tumour suppressor genes in tumorigenesis. *Hum Genet*. 2017;136(2):129-148.
39. Louis DN, Perry A, Reifenberger G, et al. The 2016 World Health Organization classification of tumors of the central nervous system: a summary. *Acta Neuropathol*. 2016;131(6):803-820.
40. Weiss SW, Langloss JM, Enzinger FM. Value of S-100 protein in the diagnosis of soft tissue tumors with particular reference to benign and malignant Schwann cell tumors. *Lab Invest*. 1983;49(3):299-308.
41. Nonaka D, Chiriboga L, Rubin BP. SOX10: a pan-schwannian and melanocytic marker. *Am J Surg Pathol*. 2008;32(9):1291-1298.
42. Kawahara E, Oda Y, Ooi A, Katsuda S, Nakanishi I, Umeda S. Expression of glial fibrillary acidic protein (GFAP) in peripheral nerve sheath tumors. *Am J Surg Pathol*. 1988;12(2):115-120.
43. Asthagiri AR, Parry DM, Butman JA, et al. Neurofibromatosis type 2. *Lancet North Am Ed*. 2009;373(9679):1974-1986.
44. McClatchey AI, Saotome I, Ramesh V, Gusella JF, Jacks T. The Nf2 tumor suppressor gene product is essential for extraembryonic development immediately prior to gastrulation. *Genes Dev*. 1997;11(10):1253-1265.
45. McClatchey AI, Saotome I, Mercer K, et al. Mice heterozygous for a mutation at the Nf2 tumor suppressor locus develop a range of highly metastatic tumors. *Genes Dev*. 1998;12(8):1121-1133.
46. Giovannini M, Robanus-Maandag E, Niwa-Kawakita M, et al. Schwann cell hyperplasia and tumors in transgenic mice expressing a naturally occurring mutant NF2 protein. *Genes Dev*. 1999;13(8):978-986.
47. Giovannini M, Robanus-Maandag E, Van Der Valk M, et al. Conditional biallelic Nf2 mutation in the mouse promotes manifestations of human neurofibromatosis type 2. *Genes Dev*. 2000;14(13):1617-1630.
48. Lunsford LD, Niranjan A, Flickinger JC, Maitz A, Kondziolka D. Radiosurgery of vestibular schwannomas: summary of experience in 829 cases. *J Neurosurg*. 2005;102(Special_Supplement):195-199.
49. Kondziolka D, Lunsford LD, McLaughlin MR, Flickinger JC. Long-term outcomes after radiosurgery for acoustic neuromas. *N Engl J Med*. 1998;339(20):1426-1433.
50. Delanian S, Lefaix JL, Pradat PF. Radiation-induced neuropathy in cancer survivors. *Radiother Oncol*. 2012;105(3):273-282.
51. Monfared A, Corrales CE, Theodosopoulos PV. Facial nerve outcome and tumor control rate as a function of degree of resection in treatment of large acoustic neuromas. *Neurosurgery*. 2016;79(2):194-203.
52. Safaee MM, Lyon R, Barbaro NM, et al. Neurological outcomes and surgical complications in 221 spinal nerve sheath tumors. *Spine*. 2017;26(1):103-111.
53. Bartek J, Förander P, Thurin E, et al. Short-term surgical outcome for vestibular schwannoma in Sweden: a nation-wide registry study. *Front Neurol*. 2019;10(Jan):43.
54. Gurgel RK, Dogru S, Amdur RL, Monfared A. Facial nerve outcomes after surgery for large vestibular schwannomas: Do surgical approach and extent of resection matter? *Neurosurg Focus*. 2012;33(3):E16.
55. Kim SM, Seo SW, Lee JY, Sung KS. Surgical outcome of schwannomas arising from major peripheral nerves in the lower limb. *Int Orthop*. 2012;36(8):1721-1725.
56. Guthikonda B, Theodosopoulos PV, Van Loveren H, Tew JM, Pensak ML. Evolution in the assessment and management of trigeminal schwannoma. *Laryngoscope*. 2008;118(2):195-203.
57. Louis DN, Perry A, Reifenberger G, et al. The 2016 World Health Organization classification of tumors of the central nervous system: a summary. *Acta Neuropathol*. 2016;131(6):803-820
58. Miettinen MM, Antonescu CR, Fletcher CDM, et al. Histopathologic evaluation of atypical neurofibromatous tumors and their transformation into malignant peripheral nerve sheath tumor in patients with neurofibromatosis 1—a consensus overview. *Hum Pathol*. 2017;67:1-10.
59. Fletcher JS, Pundavela J, Ratner N. After Nf1 loss in Schwann cells, inflammation drives neurofibroma formation. *Neuro-Oncology Adv*. 2020;2(Supplement_1):i23-i32.
60. Perry A, Roth KA, Banerjee R, Fuller CE, Gutmann DH. NF1 deletions in S-100 protein-positive and negative cells of sporadic and neurofibromatosis 1 (NF1)-associated plexiform neurofibromas and malignant peripheral nerve sheath tumors. *Am J Pathol*. 2001;159(1):57-61.
61. Zhu Y, Ghosh P, Charnay P, Burns DK, Parada LF. Neurofibromas in NF1: Schwann cell origin and role of tumor environment. *Science*. 2002;296(5569):920-922.
62. Pemov A, Li H, Patidar R, et al. The primacy of NF1 loss as the driver of tumorigenesis in neurofibromatosis type 1-associated plexiform neurofibromas. *Oncogene*. 2017;36(22):3168-3177.
63. Simanshu DK, Nissley DV. RAS proteins and their regulators in human disease. *Cell*. 2017;170(1):17-33.
64. Gutmann DH, Ferner RE, Listernick RH, Korf BR, Wolters PL, Johnson KJ. Neurofibromatosis type 1. *Nat Rev Dis Prim*. 2017;3(1):1-17.
65. Jacks T, Shih TS, Schmitt EM, Bronson RT, Bernards A, Weinberg RA. Tumour predisposition in mice heterozygous for a targeted mutation in nf1. *Nat Genet*. 1994;7(3):353-361.
66. Brannan CI, Perkins AS, Vogel KS, et al. Targeted disruption of the neurofibromatosis type-1 gene leads to developmental abnormalities in heart and various neural crest-derived tissues. *Genes Dev*. 1994;8(9):1019-1029.
67. Röhrich M, Koelsche C, Schrimpf D, et al. Methylation-based classification of benign and malignant peripheral nerve sheath tumors. *Acta Neuropathol*. 2016;131(6):877-887.
68. Le LQ, Shipman T, Burns DK, Parada LF. Cell of origin and microenvironment contribution for NF1-associated dermal neurofibromas. *Cell Stem Cell*. 2009;4(5):453-463.
69. Le LQ, Liu C, Shipman T, Chen Z, Suter U, Parada LF. Susceptible stages in Schwann cells for NF1-associated plexiform neurofibroma development. *Cancer Res*. 2011;71(13):4686-4695.
70. Zheng ZY, Anurag M, Lei JT, et al. Neurofibromin is an estrogen receptor-α transcriptional co-repressor in breast cancer. *Cancer Cell*. 2020;37(3):387-402.e7.
71. Wu J, Williams JP, Rizvi TA, et al. Plexiform and dermal neurofibromas and pigmentation are caused by Nf1 loss in desert hedgehog-expressing cells. *Cancer Cell*. 2008;13(2):105-116.

72. Evans DGR, Huson SM, Birch JM. Malignant peripheral nerve sheath tumours in inherited disease. *Clin Sarcoma Res*. 2012;2(1):17.
73. Farid M, Demicco EG, Garcia R, et al. Malignant peripheral nerve sheath tumors. *Oncologist*. 2014;19(2):193-201.
74. Stucky C-CH, Johnson KN, Gray RJ, et al. Malignant peripheral nerve sheath tumors (MPNST): the Mayo Clinic experience. *Ann Surg Oncol*. 2012;19(3):878-885.
75. Rodriguez FJ, Folpe AL, Giannini C, Perry A. Pathology of peripheral nerve sheath tumors: diagnostic overview and update on selected diagnostic problems. *Acta Neuropathol*. 2012;123(3):295-319.
76. Karamchandani JR, Nielsen TO, Van De Rijn M, West RB. SOX10 and S100 in the diagnosis of soft-tissue neoplasms. *Appl Immunohistochem Mol Morphol*. 2012;20(5):445-450.
77. Kang Y, Pekmezci M, Folpe AL, Ersen A, Horvai AE. Diagnostic utility of SOX10 to distinguish malignant peripheral nerve sheath tumor from synovial sarcoma, including intraneural synovial sarcoma. *Mod Pathol*. 2014;27(1):55-61.
78. Carroll SL. The challenge of cancer genomics in rare nervous system neoplasms. *Am J Pathol*. 2016;186(3):464-477.
79. Lee W, Teckie S, Wiesner T, et al. PRC2 is recurrently inactivated through EED or SUZ12 loss in malignant peripheral nerve sheath tumors. *Nat Genet*. 2014;46(11):1227-1232.
80. Zhang M, Wang Y, Jones S, et al. Somatic mutations of SUZ12 in malignant peripheral nerve sheath tumors. *Nat Genet*. 2014;46(11):1170-1172.
81. Nielsen GP, Stemmer-Rachamimov AO, Ino Y, Moøller MB, Rosenberg AE, Louis DN. Malignant transformation of neurofibromas in neurofibromatosis 1 is associated with CDKN2A/p16 inactivation. *Am J Pathol*. 1999;155(6):1879-1884.
82. Vogel KS, Klesse LJ, Velasco-Miguel S, Meyers K, Rushing EJ, Parada LF. Mouse tumor model for neurofibromatosis type 1. *Science*. 1999;286(5447):2176-2179.
83. Cichowski K, Shih TS, Schmitt E, et al. Mouse models of tumor development in neurofibromatosis type 1. *Science*. 1999;286(5447):2172-2176.
84. Joseph NM, Mosher JT, Buchstaller J, et al. The loss of Nf1 transiently promotes self-renewal but not tumorigenesis by neural crest stem cells. *Cancer Cell*. 2008;13(2):129-140.
85. Phane Berghmans S, Murphey RD, Wienholds E, et al. Tp53 mutant zebrafish develop malignant peripheral nerve sheath tumors. *Proc Natl Acad Sci USA*. 2005;102(2):407-412.
86. Perrone F, Da Riva L, Orsenigo M, et al. PDGFRA, PDGFRB, EGFR, and downstream signaling activation in malignant peripheral nerve sheath tumor. *Neuro Oncol*. 2009;11(6):725-736.
87. Ling BC, Wu J, Miller SJ, et al. Role for the epidermal growth factor receptor in neurofibromatosis-related peripheral nerve tumorigenesis. *Cancer Cell*. 2005;7(1):65-75.
88. Hirbe AC, Pekmezci M, Dahiya S, et al. BRAFV600E mutation in sporadic and neurofibromatosis type 1-related malignant peripheral nerve sheath tumors. *Neuro-oncol*. 2014;16(3):466-467.
89. Gregorian C, Nakashima J, Dry SM, et al. PTEN dosage is essential for neurofibroma development and malignant transformation. *Proc Natl Acad Sci*. 2009;106(46):19479-19484.
90. Jessen WJ, Miller SJ, Jousma E, et al. MEK inhibition exhibits efficacy in human and mouse neurofibromatosis tumors. *J Clin Invest*. 2013;123(1):340-347.
91. Peacock JD, Pridgeon MG, Tovar EA, et al. Genomic status of MET potentiates sensitivity to MET and MEK inhibition in NF1-related malignant peripheral nerve sheath tumors. *Cancer Res*. 2018;78(13):3672-3687.
92. De Raedt T, Beert E, Pasmant E, et al. PRC2 loss amplifies Ras-driven transcription and confers sensitivity to BRD4-based therapies. *Nature*. 2014;514(7521):247-251.
93. Wu LMN, Deng Y, Wang J, et al. Programming of Schwann cells by Lats1/2-TAZ/YAP signaling drives malignant peripheral nerve sheath tumorigenesis. *Cancer Cell*. 2018;33(2):292-308.e7.
94. Feng-Chun Y, Ingram DA, Chen S, et al. Neurofibromin-deficient Schwann cells secrete a potent migratory stimulus for Nf1+/− mast cells. *J Clin Invest*. 2003;112(12):1851-1861.
95. Ingram DA, Hiatt K, King AJ, et al. Hyperactivation of p21ras and the hematopoietic-specific rho GTPase, rac2, cooperate to alter the proliferation of neurofibromin-deficient mast cells in vivo and in vitro. *J Exp Med*. 2001;194(1):57-70.
96. Mo W, Chen J, Patel A, et al. CXCR4/CXCL12 mediate autocrine cell- cycle progression in NF1-associated malignant peripheral nerve sheath tumors. *Cell*. 2013;152(5):1077-1090.
97. Ribeiro S, Napoli I, White IJ, et al. Injury signals cooperate with Nf1 loss to relieve the tumor-suppressive environment of adult peripheral nerve. *Cell Rep*. 2013;5(1):126-136.
98. Lu VM, Ravindran K, Graffeo CS, et al. Efficacy and safety of bevacizumab for vestibular schwannoma in neurofibromatosis type 2: a systematic review and meta-analysis of treatment outcomes. *J Neurooncol*. 2019;144(2):239-248.
99. Plotkin SR, Stemmer-Rachamimov AO, Barker FG, et al. Hearing improvement after bevacizumab in patients with neurofibromatosis type 2. *N Engl J Med*. 2009;361(4):358-367.
100. Gross AM, Wolters PL, Dombi E, et al. Selumetinib in children with inoperable plexiform neurofibromas. *N Engl J Med*. 2020;382(15):1430-1442.
101. Natalie Wu LM, Lu QR. Therapeutic targets for malignant peripheral nerve sheath tumors. *Future Neurol*. 2019;14(1):1430-1442.

COMMENTS

Similar to Mirsky and Jessen's recent review of the neurobiology of regenerating Schwann cells,[1] I feel that this manuscript will become a highly-cited reference moving forward. The first figure alone is gorgeous. To summate, the authors have provided an in-depth yet accessible review that details the molecular events of both Schwann cell development and fate determination, in addition to what is currently known regarding the genetic events that surround tumors of Schwann cell origin.

Of particular value, the authors analyze both the human and experimental animal literature regarding the latter topic, including potential therapeutics. We get an optimistic impression that the advent of conditional genetics in mouse models has led to a greater understanding of the biology of these tumors, allowing testing of new therapeutic strategies based in molecular medicine. The authors nicely summarise these findings in several tables that are a concise introduction to the key literature of this field.

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1. Jessen K, Mirsky R. The repair Schwann cell and its function in regenerating nerves. *J Physiol*. 2016;594(13):3521-3531.

This papers is an excellent and current review of the Schwann cell, with an emphasis on developmental aspects, and maldevelopment which heralds oncogenesis potential.

Many tumors recapitulate their developmental programs during progression, and peripheral nerve tumors are of no exception. In the era of precision medicine, understanding the molecular pathways leading to Schwann cell differentiation, as summarized nicely in this review article, and equally important, de-differentiation will certainly provide the starting point for novel therapies.

As the authors point out, the fate and diversity of peripheral nerve tumors from relatively benign schwannoma and neurofibroma to malignant peripheral nerve sheath tumor is likely the combinatorial outcomes from cell and non-cell autonomous events. These include gene mutations (NF1 vs NF2), different stages along the Schwann cell lineage and interactions with neighboring cells in the microenvironment. In fact, the review highlights the notion that the Schwann cell is not a homogenous population but instead a pool of heterogeneous cells with specialized functions. One example is the newly discovered capacity of Schwann cells in skin that enable nociceptive function, with the ability

to initiate and transmit pain signal to adjacent axons and nerve bundles.[1] The heterogeneity is, however at the moment, masked by the lack of rigorous markers for individual subtypes.

With increasing ability to examine cell genotype and phenotype at high molecular and genomic resolution, we may one day achieve personalized medicine for different types of nerve tumors.

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1. Abdo H, Calvo-Enrique L, Lopez JM, et al. Specialized cutaneous Schwann cells initiate pain sensation. *Science*. 2019;365(6454):695-699.