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Emerging mechanism and therapeutic potential of neurofibromatosis type 1-related nerve system tumor: Advancing insights into tumor development

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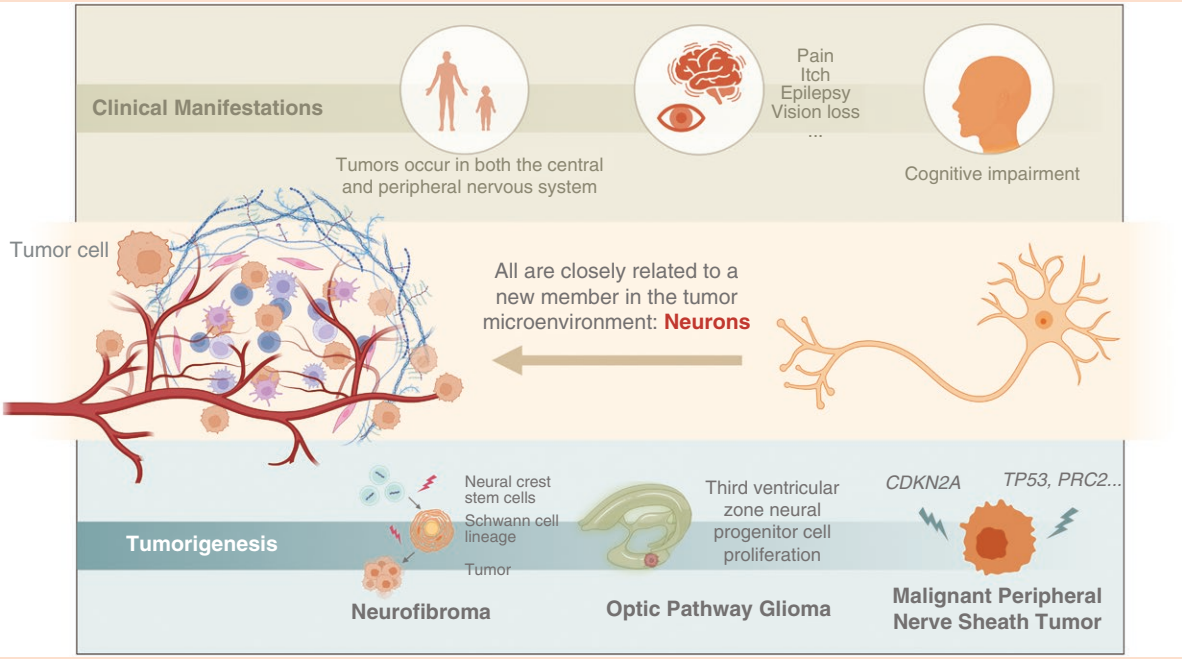
Abstract

Neurofibromatosis Type 1 (NF1) is a genetic disorder resulting from mutations in the *NF1* gene, which increases susceptibility to various nervous system tumors, including plexiform neurofibromas, malignant peripheral nerve sheath tumors, and optic pathway gliomas. Recent research has shown that these tumors are intricately connected to the complex, dynamic interactions within neurons, culminating in neuronal signaling that fosters tumor growth. These interactions offer crucial insights into the molecular mechanisms underpinning tumor development, as well as broader implications for therapeutic strategies. This review summarizes the mechanisms through which mutations in the *NF1* gene within neural tissues trigger tumorigenesis, while examining the role of the neuron—via factors such as visual experience, neurotransmitter, tumor microenvironment, and psychological influences—in both promoting tumor progression and being affected by the tumors themselves. By investigating the dynamic relationship between NF1-associated nervous system tumor cells and neurons, we aim to shed light on novel biological pathways and disease processes, emphasizing the potential of interdisciplinary approaches that combine neurobiology, oncology, and pharmacology to enhance treatment strategies and even inhibit the tumorigenesis.

Key Points

- Neurofibromatosis type 1 is a tumor-predisposing syndrome affecting multiple nervous system tumors and causing various neurological dysfunctions.
- Neurofibromatosis type 1 is closely linked to neuronal activity, influencing neuronal excitability and contributing to tumor growth that is dependent on neuronal activity.
- The tumor types associated with NF1 are diverse; we hope that research in cancer neuroscience can expand from gliomas to other peripheral nervous system tumors.

Graphical Abstract



Neurofibromatosis Type 1 (NF1) is an autosomal dominant disease caused by inherited or de novo germline mutations in the *NF1* gene, with an estimated global occurrence of about 1 in every 3164 individuals.[1] Its clinical features are diverse, affecting multiple organ systems such as the skin, nervous system, and skeletal structures[2] (Figure 1). A defining feature of NF1 is nervous system tumorigenesis, leading to the development of plexiform neurofibromas (PNF), malignant peripheral nerve sheath tumors (MPNST), and optic pathway gliomas (OPG).[2] These tumors, which develop from Schwann cells (SC) lineage, rely significantly on the tumor microenvironment (TME) for their growth and progression.[3] Recent studies highlight the nervous system's role as an active element within the TME, not only supporting tumor cells but also shaping fundamental aspects of tumor biology. These insights emphasize the need to explore neuro-mediated molecular pathways in NF1-related tumorigenesis.

Recent advances in cancer neuroscience have significantly enhanced our understanding of the complex relationships between tumor development and neural activity. Neural signals, essential for maintaining normal physiological functions, are increasingly recognized as critical drivers in the initiation and progression of tumors.[4–7] In NF1, for instance, studies reveal that various nervous system tumors engage in intricate, dynamic interactions with neural tissues. This bidirectional cross talk is marked by neural signals that stimulate tumor growth, while, conversely, the tumors adaptively modify the nervous system to create a more favorable environment for their expansion. Such interactions underscore the dual role of the nervous system as both a modulator and a target of tumor-induced changes, supporting tumor maintenance and progression.[8]

Understanding the nervous system's role in tumor progression in NF1 is essential for identifying new therapeutic targets. The complex challenges presented by NF1 and its tumorigenic processes require an interdisciplinary approach, combining neuroscience, oncology, and molecular biology. By studying neuro-oncological mechanisms, researchers can develop treatments that go beyond mere tumor inhibition, aiming instead to modulate neural activity for better therapeutic outcomes. This broader perspective opens promising avenues for addressing the needs of NF1 patients, ultimately leading to improvements in both quality of life (QOL) and tumor burden for those affected by the disease.

NF1: A Tumor Predisposition Syndrome of the Nervous System

Clinical research consistently indicates that individuals with NF1 face a significantly higher risk of tumor development, especially in the nervous system, compared to the general population.[9] Tumors of the peripheral nervous system (PNS) are a distinctive feature of NF1, with cutaneous neurofibromas (CNF) and PNF—also known as benign peripheral nerve sheath tumors—being the most frequently observed.[10] Notably, there is a substantially increased risk of central nervous system (CNS) tumors in NF1 patients, particularly those over the age of 10, who are 100 times more likely to develop such tumors than individuals of the same age in the general population.[11] These CNS tumors predominantly consist of low-grade gliomas (LGG), such as OPG, although more aggressive malignancies, including high-grade gliomas (HGG) like glioblastomas

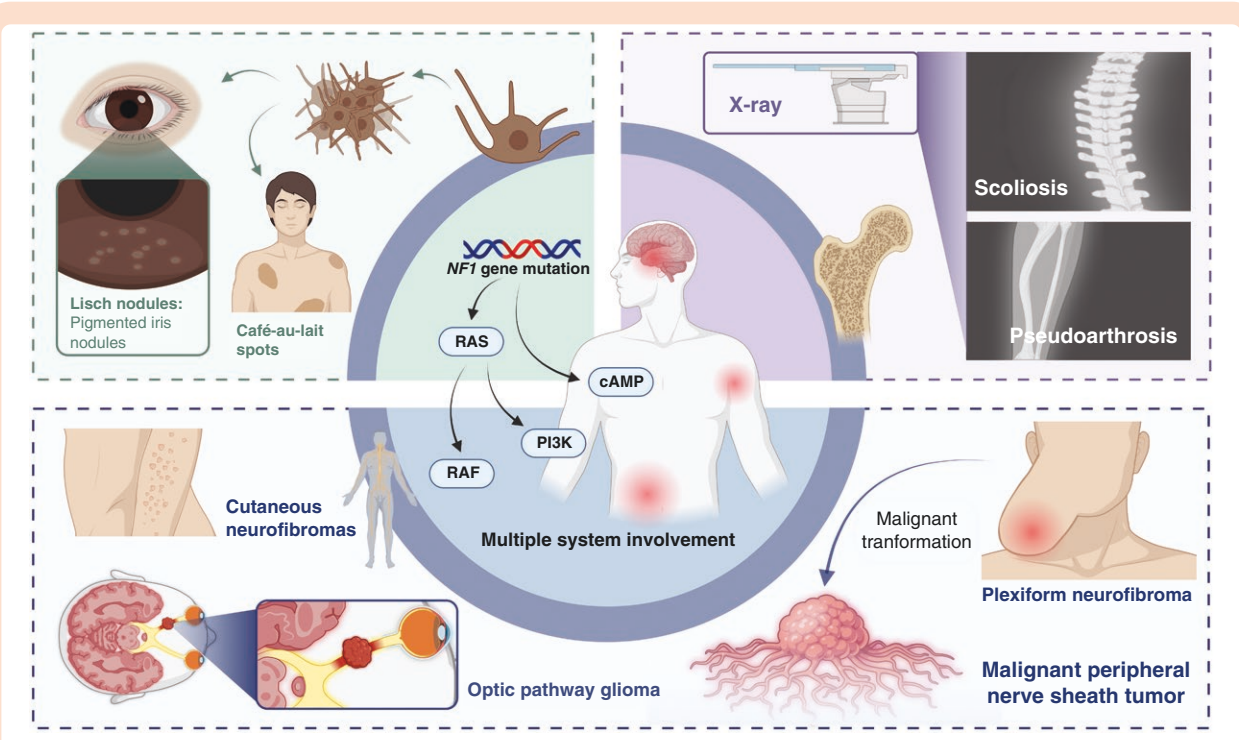


Figure 1. Multisystem involvement in NF1. Created with BioRender.com.

(GBM), may also occur.[12] While some tumors, like PNF, can be present at birth, others, such as CNF, tend to exhibit rapid growth during adolescence.[13] Additionally, certain tumors may undergo malignant transformation and metastasis, as seen in MPNST and HGG, contributing to a significant disease burden and potentially life-threatening complications. For clarity, Table 1 summarizes the CNS and PNS tumors commonly associated with NF1.

PNF

Neurofibromas are the most common tumors found in individuals with NF1.[14] While CNF affect nearly all NF1 patients, they are typically localized to the dermis and often present as polypoid skin lesions.[10] PNF are more complex and arise from larger internal nerve plexuses, such as the brachial or lumbosacral plexus, affecting multiple nerve fascicles. These tumors are most frequently located around deep spinal nerves and are the most common neural tumors in NF1, occurring in 30% to 50% of those affected.[15–17] Many PNF are diagnosed before the age of 5,[18] suggesting their congenital nature, and their development can present as a whole-body pattern.[19] Typically, these tumors enlarge with age, becoming clinically noticeable during childhood or adolescence, and in some cases, they may grow to substantial sizes,[15] leading to severe complications. These include compression of adjacent organs, severe neurological deficits, limb paralysis, sensory loss, and localized neuropathic pain caused by the compression of critical nerves and nerve roots.[20]

Complete surgical resection of PNF presents substantial challenges due to their involvement with critical nerve structures and their invasive growth patterns, which frequently lead to significant neurological impairment,[16] and partial resection may result in recurrence. To address these challenges, the U.S. Food and Drug Administration approved the MEK inhibitor (MEKi), Selumetinib, in 2020 for treating symptomatic and/or progressive, inoperable PNF in children with NF1 aged three years and older. This approval marks a major step forward in therapeutic options for managing PNF when surgery is not a viable option.[21,22] In addition to tumor shrinkage, clinical trials have shown that MEKi also result in pain relief and improvements in cognitive impairment, suggesting a potential role of the MEK pathway in neurological manifestations.[21,23] Although Selumetinib is currently the only approved treatment for this indication in children, there is evidence suggesting that other MEKi (Binimetinib, Trametinib, and Mirdametinib) may have similar effects.[24] A phase II trial investigating Binimetinib showed a comparable partial response rate (14/19, 74%)[25] to that of Selumetinib (35/50, 70%).[26] We look forward to more prospective evidence supporting the use of other MEKi in pediatric PNF or selumetinib in adult PNF.

MPNST

Although PNF are typically benign, they carry an estimated 15.8% risk of malignant transformation into MPNST.[27] MPNST most frequently occurring between the ages of 20 and 40,[28] with a probability of only 0.5% in children.[29] These tumors often arise in the limbs, pelvis, or trunk, typically at the junction of major nerve roots and bundles, and present as rapidly enlarging masses accompanied by localized pain

Table 1. Overview of Key Characteristics and Treatment Approaches for NF1-Tumors

Tumor	Incidence in NF1[a] individuals	System affected	Molecular mechanisms	Clinical features	Malignancy
PNF[b]	30%-50%	PNS[c]	LOH[d] in *NF1*$^{+/-}$ SCPs[e]	Severe neurological deficits, paralysis, sensory loss, and pain due to nerve compression.	Moderate to high
MPNST[f]	15.8%	PNS	Mutations in *TP53*, *PTEN* loss, *EGFR* overexpression, loss of *CDKN2A*, and *PRC2* dysfunction on an *NF1*$^{-/-}$ background	Rapidly enlarging masses, pain, neurological deficits, high recurrence, and metastasis risk.	High
OPG[g]	20%	CNS[h]	AKT/mTOR pathway activation, reduced AC/cAMP function	May cause proptosis, visual loss, field defects, strabismus, and optic nerve atrophy.	Low
HGGs[i]	0.28%-5%	CNS	Mutations in the *ATRX*, *TP53*, and *CDKN2A* genes, as well as mutations in genes involved in the PI3K pathway	Progressive neurological decline, headaches, seizures, cognitive dysfunction.	High

[a]Neurofibromatosis type 1.
[b]Plexiform neurofibromas.
[c]Peripheral nervous system.
[d]Loss of heterozygosity.
[e]Schwann cell precursors.
[f]Malignant peripheral nerve sheath tumors.
[g]Optic pathway gliomas.
[h]Central nervous system.
[i]High-grade gliomas.

and neurological deficits.[30] While PNF and MPNST may share some overlapping neurological symptoms, MPNST is particularly alarming due to their aggressive progression. The 5-year survival rate for individuals with MPNST is less than 50%, with a median overall survival (mOS) of just 48 months after diagnosis. Notably, the prognosis for NF1-MPNST is poorer compared to sporadic cases, which have a 5-year survival rate ranging from 60% to 65%.[31] This difference in survival outcomes may be partly attributed to the difficulty in distinguishing between PNF and MPNST through imaging modalities such as MRI, delaying early diagnosis and intervention. Furthermore, NF1-MPNST exhibit a higher propensity for recurrence, with 38% to 45% of patients with NF1 ultimately succumbing to the disease, primarily due to the high rates of recurrence and distant metastasis.[32]

The current standard of management for both sporadic and NF1-MPNST is surgical treatment with wide local excisional margins. There is no established consensus on the efficacy of adjuvant chemotherapy—such as ifosfamide and anthracyclines—or radiotherapy in the management of NF1-MPNST.[33–35] This uncertainty arises from the limited impact of these treatments and the potential risk of promoting malignant transformation in nearby benign tumors, as well as the drug toxicity.[36–38] Due to the lack of identified driving events for NF1-MPNST pathogenesis, there is no clear objective response to targeted therapies.[39] Single-agent MEKi may not prevent the progression of PNF to MPNST,[40,41] and there is also a lack of evidence regarding its efficacy in treating MPNST. Current efforts are primarily focused on combination inhibition of multiple signaling pathways, with MEKi also being part of these efforts (NCT05253131, NCT06735820, NCT03433183).

LGG

LGG are the most common CNS tumors linked to NF1, affecting around 20% of children with NF1. Histopathologically, they are typically classified as World Health Organization grade I gliomas, with pilocytic astrocytomas being the most common subtype.[42] The symptoms of NF1-LGG are largely dependent on the tumor's location, with the optic pathway being the most commonly affected area,[43] followed by the brainstem.[44]

NF1-OPG typically appear before age 8, with an average onset of 4.5 years,[45,46] manifest much earlier than sporadic OPG and tend to involve both optic nerves bilaterally.[47] Their progress leads to serious visual complications such as unilateral proptosis, reduced visual acuity, visual field defects, strabismus, relative afferent pupillary defects, and either optic disc edema/papilledema or optic atrophy.[48] Regular monitoring through annual eye examinations by experienced ophthalmologists is critical for detecting early signs of progression and preventing irreversible vision loss. When LGG occur in the brainstem, most patients with brainstem gliomas (BSG) remain asymptomatic. However, symptoms such as headaches, nausea, cranial neuropathies (eg, dysarthria), and ataxia may also manifest.[44] Other non-OPG can also occur in regions such as the basal ganglia and cerebellum.[49]

Due to the fact that many NF1-LGG remain asymptomatic or even spontaneously regress,[50] surveillance and observation are generally the primary strategies after initial diagnosis. When progress, surgical resection is typically not a viable option due to the deep and critical locations of some NF1-LGG, with the exception of cases where hydrocephalus can be managed by cerebrospinal fluid diversion to alleviate symptoms.[51] Radiation therapy is rarely used for

NF1-LGG due to concerns regarding the risks of malignant transformation, endocrine dysfunction, and possible cognitive impairments.[52] As a result, chemotherapy remains the primary treatment approach for NF1-LGG, with commonly used agents including carboplatin, vincristine.[53,54] Although chemotherapy has demonstrated effectiveness in slowing tumor progression and preserving vision in certain cases, up to 30% of children with NF1-OPG still experience vision impairment posttreatment.[55] Many prospective trials have indicated that inhibitors of mTOR[56,57] and MEKi[58] may improve progression-free survival in patients with NF1-LGG. Ongoing phase 3 clinical trials aim to comprehensively compare the tumor response, visual function, and QOL outcomes between targeted therapies and current standard treatments (NCT04576117, NCT03871257, NCT04166409), which may ultimately redefine the care standards for NF1-LGG patients. However, further research is needed to address questions regarding the duration of MEKi treatment and the sustainability of the response.[24]

HGG

HGG occur in approximately 0.28% to 5% of children with NF1. Histologically, these tumors are commonly classified as anaplastic astrocytomas and GBM, with a higher incidence in the thalamic region.[12] Unlike PNF, LGG rarely transform into HGG,[59] except following radiation therapy. Studies have indicated that the relative risk of developing secondary malignant tumors is 3.04 times higher in NF1 patients who have undergone radiation therapy compared to those who have not.[11,12,60] These tumors are distinguished by their aggressive nature and rapid growth, typically resulting in a poor prognosis. Affected patients often present with progressive neurological decline, manifesting as headaches, seizures, and cognitive dysfunction. Research led by Brett J. Theeler suggests that adult NF1 patients with HGG may benefit from treatment regimens incorporating bevacizumab, which could potentially improve survival outcomes.[61] Currently, a Phase 1 study is recruiting to evaluate the toxicity and early efficacy of combined treatment with MEKi (Trametinib) for the treatment of NF1-LGG and NF1-HGG (NCT06712875).

In conclusion, NF1-nervous system tumors—including PNF, MPNST, and gliomas—exhibit distinct patterns of onset and progression across different groups.

The Cell of Origin and Development of NF1-Tumors

From a macroscopic perspective, the aforementioned NF1-tumors share the common characteristic of originating in either the central or PNS and causing a variety of neurological symptoms. At the molecular level, these tumors also exhibit similarities, as their formation, progression, and malignant transformation are closely linked to abnormalities in neural tissue and the surrounding microenvironment. The main factors driving this process are the inactivation of the *NF1* gene and the disruption of multiple signaling pathways. Additionally, multiple genetic mutations and disruptions of key regulatory pathways further contribute to tumor initiation and progression.

The *NF1* gene, located on chromosome 17q11, encodes neurofibromin, a large GTPase-activating protein essential for regulating cell growth. Neurofibromin promotes the intrinsic GTPase activity of small G proteins, including members of the Ras superfamily (eg, HRAS, KRAS, NRAS, and RRAS). By converting the active Ras-GTP form into its inactive Ras-GDP state, neurofibromin downregulates the RAS/MAPK signaling pathway, thereby inhibiting tumor formation. Although neurofibromin is widely expressed across various organs, it is particularly abundant in the brain, spinal cord, and PNS, highlighting the critical role of the normal *NF1* gene in maintaining the stability and proper functioning of the nervous system. In individuals with NF1, mutations in the *NF1* gene lead to a loss of neurofibromin function, resulting in abnormal activation of the RAS/MAPK signaling pathway. Activated Ras binds to RAF kinases, triggering the RAS/RAF/MEK/ERK signaling cascade, which drives excessive cellular proliferation and underlies the formation of various tumors in NF1 patients.[62–64]

Cell of Origin and TME in PNF Development

The use of Krox20-Cre murine models has revealed that PNF originates from the *Nf1*$^{-/-}$ SC lineage.[3] However, considering the congenital nature of PNF, which is typically detected at birth or in early infancy, it is hypothesized that these tumors do not arise from mature SC, but rather from an early SC lineage. This hypothesis was substantiated by Chen et al., who, after administering tamoxifen to *PlpCre-ERT;Nf1*$^{flox/-}$*;R26R-LacZ* mice for 7 months starting at E9.5, demonstrated that embryonic Schwann cell precursor originating from spinal nerve roots are the cellular origin of PNF. The predominant cell population was identified as PLP+ cells, with Krox20+ and Dhh+ cells also present within this group.[65] These cells undergo loss of heterozygosity in the nerve root, subsequently migrating to the dorsal root ganglia and peripheral nerves to form PNF.[64,66] These findings have been leveraged in numerous studies to model PNF development in vivo and to uncover other molecular modifier like RAC1,[67] CDKN2A,[68] and PTPRS,[69] providing valuable insights for the preclinical evaluation of emerging targeted and combination therapies for NF1-PNF.[70,71]

PNF is a unique and complex tumor that consists of neoplastic SC and various other local supporting elements of nerve fibers, including fibroblasts, immune cells, endothelial cells, and extracellular matrix (ECM) components such as collagen, fibronectin, laminin, and hyaluronic acid. Deciphering the role of the TME is crucial for elucidating the pathogenesis of PNF. Notably, it was originally discovered that the onset and growth potential of *Nf1*$^{-/-}$ neurofibromas are suppressed when the TME retains both functional *Nf1* alleles.[3] For example, *NF1*$^{-/-}$ SC release stem cell factor, which binds to c-KIT receptors on mast cells, stimulating their recruitment and proliferation. In response, mast cells secrete transforming growth factor β (TGF-β), which promotes abnormal ECM deposition by fibroblasts in PNF. This results in extensive ECM remodeling, notably an increase in collagen—a hallmark of PNF.[72,73] Recent studies have shown that the activation of the STING pathway leads to an

increase in CXCL10, which subsequently recruits CXCR3-expressing dendritic cells, particularly cDC1, and CD8+ T cells into the PNF-TME. These immune cells play a crucial role in the initiation and maintenance of PNF.[74]

Mutated NF1 Gene in Conjunction with Other Factors Contributing to MPNST

NF1-MPNST primarily arise from PNF through the accumulation of additional somatic mutations. This malignant transformation advances through an intermediate precancerous stage, termed atypical neurofibromas with uncertain biological potential (ANNUBP), recently marked by *CDKN2A/B* homozygous inactivation.[75] The transition from benign to malignant states is driven by key genetic and epigenetic changes, such as the loss of tumor suppressor genes like *TP53*, *PTEN*, and *CDKN2A*/*Ink4a*, alongside the overexpression of oncogenes including *EGFR*, *ZEB1*, and *ALDH1A1*.[76–82]

A key molecular player implicated in MPNST pathogenesis is the epigenetic regulator polycomb repressive complex 2 (PRC2), which comprises core components including enhancer zeste homolog 2, suppressor of zest 12 (SUZ12), and embryonic ectoderm development (EED). These components coordinate chromatin remodeling and gene expression. However, in up to 70% of NF1-MPNST, somatic mutations in *EED* and/or *SUZ12* have been identified, resulting in PRC2 inactivation.[83] The loss of PRC2 function enhances Ras-driven transcriptional activity, which accelerates tumor growth and metastasis. This involves the upregulation of matrix remodeling enzymes, collagen-dependent invasion, and ultimately leads to fibrosis, metastasis, and poor survival outcomes for patients with MPNST.[84] Pathologically, the loss of PRC2, resulting in the global loss of the histone H3 lysine 27 trimethylation (H3K27me3) epigenetic mark, serves as a driver of malignancy and represents a valuable diagnostic marker.[85]

The TME also undergoes significant alterations during the malignant transformation of PNF into MPNST.[86] As the tumor advances, there is a notable increase in fibroblasts and pro-tumorigenic (M2) macrophages, both of which contribute to the tumor's invasiveness and metastatic potential.[87,88] It is also noteworthy that Nestin$^+$ cells were initially considered a marker for tumor stem cells in MPNST. However, recent studies have revealed that Nestin is expressed in both mature SC and SCPs, indicating that Nestin is not the sole marker for tumor stem cells in MPNST. Furthermore, this study identified for the first time a Nestin$^-$ mesenchymal stem-like cell subpopulation, which exhibits stronger stemness than Nestin$^+$ cells and shows prominent epithelial-mesenchymal transition characteristics, playing a critical role in MPNST progression by enhancing the migratory capacity and drug resistance of tumor cells.[69,89] These findings highlight the complexity and challenges of studying the origins of MPNST cells.

NF1 Gene Loss in the CNS Leading to Glioma Formation

In the CNS, loss of the *NF1* gene results in hyperactivation of Ras effector pathways, disrupting the cellular equilibrium within the third ventricular zone.[90] This disruption prevents neural progenitor cells (NPCs) from undergoing normal differentiation, instead keeping them in an undifferentiated, proliferative state. Over time, these NPCs transform into optic glioma stem cells (o-GSC), ultimately leading to the formation of OPG.[91,92] *NF1* gene-deficient CNS glial cells, primarily astrocytes, undergo molecular pathological processes similar to those observed in *NF1* gene-deficient SC. Specifically, the absence of neurofibromin results in RAS hyperactivation, which drives unchecked cell proliferation. In neurofibromin-deficient astrocytic tumors, both the MEK/ERK and AKT-mediated mTOR pathways are activated.[93] Within this framework, the PI3K/AKT pathway is pivotal in promoting the proliferation of o-GSC, whereas the MEK/ERK pathway governs the multipotent differentiation of progenitor cells.[94] Furthermore, neurofibromin loss leads to reduced adenylate cyclase (AC) activity, lowering intracellular cyclic adenosine monophosphate (cAMP) levels, which in turn enhances cell survival in response to chemotactic signals and promotes proliferation.[95,96] Interestingly, although unrelated to tumor formation, this downregulation of the AC/cAMP pathway can inhibit the growth of *NF1*$^{+/-}$ retinal ganglion cells (RGC) through atypical protein kinase C-zeta (PKC ζ), contributing to vision loss in NF1 patients.[97,98]

When *NF1* gene loss occurs alongside mutations in other key genes, it can drive the formation of HGG. Molecular analysis of NF1-HGG has revealed genomic alterations similar to those found in sporadic HGG, including mutations in the *ATRX*, *TP53*, and *CDKN2A* genes, as well as mutations in genes involved in the PI3K pathway.[99] Further multiplatform molecular analyses have also identified several less common genetic drivers potentially associated with malignancy, including mutations in *PIK3CA* or *PIK3R1*, *PTEN* mutations, *PDGFRA* amplification, *MYCN* amplification, *PPM1D* mutations, and *SETD2* mutations.[100] Notably, *IDH* and *histone H3* mutations, commonly observed in sporadic cases, are less prevalent in NF1-HGG.[101]

NF1 Gene Mutation in Neuronal Development and Its Implications for Tumor Progression

The loss of neurofibromin has profound effects on neuronal development, particularly in key processes such as axonogenesis and synaptogenesis. This is specifically characterized by excessive synaptic growth and increased synaptic transmission.[102] This may be attributed to reduced levels of cAMP, which disrupts the PKA-dependent Rho/ROCK/MLC pathway, as well as impaired interactions with key proteins like collapsin response mediator protein-2 (CRMP-2) and focal adhesion kinase.[36,103,104] Wang et al. demonstrated that neurofibromin and valosin-containing protein interact and work together to regulate dendritic spine density.[105] These neuronal abnormalities not only affect the neurons themselves but also have a broader impact on surrounding glial cells. For instance, Zhu et al. (2001) demonstrated that *NF1* gene-deficient neurons can induce cortical developmental abnormalities and reactive astrogliosis through a noncell-autonomous mechanism, highlighting a potential role for neurons in regulating neural tissue proliferation.[106] More recent studies have revealed that the *NF1* gene-deficient nervous system

facilitates the progression of NF1-tumors. This is likely mediated by increased neuronal excitability and the abnormal secretion of neurotransmitters and growth factors, a phenomenon referred to as neural system-NF1 tumor cross talk.

Neuron-NF1 Tumor Cross Talk

The understanding of tumorigenesis and progression in NF1-tumors reveals that their growth within the nervous system is not merely the result of cell-autonomous changes but is significantly modulated by the TME. Traditionally, the TME consists of various components, including immune cells, blood vessels, fibroblasts, signaling molecules, and the ECM, which interact dynamically with the tumor. Tumors maintain a reciprocal and evolving relationship with their surrounding microenvironment.[107] In recent years, research has increasingly highlighted the pivotal role of the neurons in the progression of various tumorigenic diseases. Studies on solid tumors such as those in the pancreas, breast, and prostate have shown that neuronal activity not only promotes tumor initiation but also facilitates tumor growth and metastasis.[108,109]

Cancer cells can interact with neurons and recruit them into the TME to influence neuro-tumor interactions. This process is regulated by a variety of factors, including nerve growth factor, brain-derived neurotrophic factor (BDNF), glial cell line-derived neurotrophic factor (GDNF), matrix metalloproteinases (MMPs), neurotransmitters, semaphorins, netrins, axon guidance molecules like ROBO and Slit proteins, and microRNAs that regulate cellular differentiation.[110] Incorporating neural elements, such as neurons and neural signaling, into the concept of the TME has revealed increasingly complex functional cross talk between the nervous system and tumor cells. This intricate interplay creates a microenvironment where neuronal activity not only supports but also actively drives tumor progression. In NF1-tumors, which originate from neural cell lineages, neuronal activity is a critical factor in their development and progression (Figure 2).

Cancer Neuroscience of NF1-Glioma

Due to the significant molecular heterogeneity of gliomas and the complex interactions between neurons and glial cells, glioma research has become a key window for exploring cancer neuroscience within the NF1 field. Neurons play a crucial role in influencing the initiation and growth of gliomas (Table 2).

Visual experience.—After comparing the optic nerve volume and proliferation rates between the unstimulated and light-stimulated groups of mice, Pan, Yuan et al. discovered that optic nerve activity can enhance the growth of Nf1-OPG. They further explored the initiation of OPG using mice with NF1-OPG phenotypes: reducing optic nerve activity by decreasing visual stimulation (such as by keeping the mice in a dark environment) can prevent tumor formation. In contrast, all control mice exposed to normal visual stimuli developed tumors.[111] This effect is driven by neuronal activity inducing the release of neuroligin-3 (NLGN3) from surrounding neurons and oligodendrocyte precursor cells (OPCs).[112] NLGN3 is cleaved into its extracellular form by the protease ADAM10, which then binds to receptors on tumor cells, activating the PI3K-mTOR signaling pathway and promoting tumor proliferation (Figure 2).[112,113] The presence of NLGN3 in the TME also induces the glioma cells to express and release NLGN3, which in turn drives oncogenic signaling through both autocrine and paracrine pathways.[113]

In addition to directly promoting tumor growth, elevated NLGN3 levels enhance synaptic connections between neurons and glioma cells,[114] effectively incorporating glioma cells into neural circuits. The increased excitability of *NF1*$^{+/-}$ RGC further amplifies this process during visual exposure.[115] These interactions may establish a positive feedback loop that further increases ADAM10 activity, thereby accelerating glioma progression.

Similar to LGG, optogenetic stimulation of cortical projection neurons has been shown to drive the growth of patient-derived HGG xenografts within the stimulated neural circuit.[112]

The involvement of immune cells.—In NF1-OPG, a complex interplay exists between neurons, immune cells, and tumor cells. One key component of this interaction is the chemokine CCL5, which is secreted by microglia and macrophages and plays a role in promoting tumor growth. Importantly, CCL5 secretion is regulated by the neuronal activity. RGC within the TME secrete midkine, which facilitates the recruitment and activation of CD8$^+$ lymphocytes. These lymphocytes infiltrate the tumor and secrete the chemokine CCL4, which subsequently induces the expression of CCL5 in microglia/macrophages. This signaling cascade drives tumor cell proliferation and inhibits apoptosis, ultimately supporting tumor maintenance and progression (Figure 2).[116] Interestingly, the expression of retinal midkine RNA and protein was influenced by neuronal excitability not reduction in visual experience, indicating the presence of an alternative mechanism for the activity-dependent production of midkine in neurons. Paradoxically, CD8$^+$ T cells, which typically serve as antitumor inflammatory agents, in this context maintain proliferative signals and contribute to immune evasion by tumor cells.

Neurotrophic factors.—Dopamine (DA), an essential neurotransmitter, also has complex roles in the context of NF1. The interaction between *NF1*$^{+/-}$ neurons and *NF1*$^{-/-}$ glial cells contributes to decreased DA levels in the striatum, potentially linked to NF1-associated attention deficits.[98] While DA itself has not been directly associated with tumor growth, the overexpression of dopamine receptor D2 (DRD2) in HGG is strongly correlated with poor clinical outcomes.[117] Both selective and nonselective DA receptor blockers, including DRD2 antagonists such as haloperidol and ONC201,[118,119] as well as DRD4 antagonists,[120] have demonstrated efficacy in inhibiting tumor cell growth.

BDNF and its receptor NTRK are also involved in promoting the survival of various cancers, such as ovarian cancer and multiple myeloma,[121,122] and NF1-tumors are no

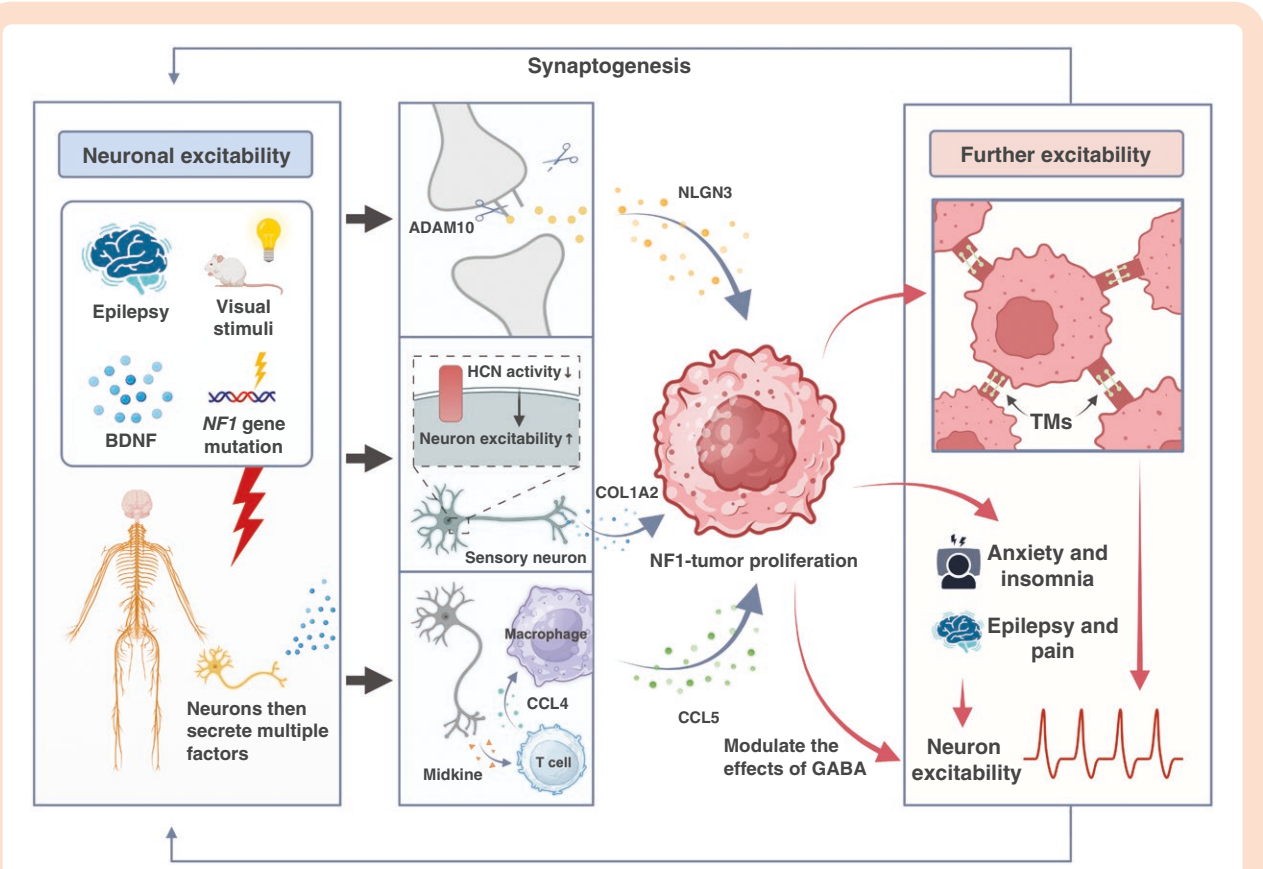


Figure 2. Neuronal activity facilitates the progression of NF1-tumors through several mechanisms, while proliferating tumors simultaneously hijack neural processes to support their own growth, establishing a self-perpetuating positive feedback loop. Targeted strategies aim to interrupt this loop, offering potential dual benefits: inhibiting tumor growth while alleviating associated symptoms. Created with BioRender.com.

exception. In the healthy brain, BDNF regulates synaptic plasticity and strength—functions that also play a role in neuron-glioma interactions. Through signaling via its receptor tropomyosin receptor kinase B (TrkB), BDNF influences the number of synapses formed between neurons and glioma cells. Specifically, secreted BDNF activates TrkB receptors on glioma cells, subsequently triggering calcium/calmodulin-dependent protein kinase II (CAMKII), which promotes the trafficking of AMPA receptors to the glioma cell membrane. AMPA receptors, a type of ionotropic glutamate receptor, amplify glutamate-induced inward currents, increasing the excitability of malignant cells—a process potentially linked to the development of epilepsy in glioma patients.[123] Additionally, paracrine glutamate release through the cystine/glutamate antiporter system has been shown to enhance neuronal hyperexcitability and drive glioma growth in adult GBM models.[124] In summary, BDNF is crucial in fostering neuronal hyperexcitability and promoting glioma growth (Table 2).

Beyond BDNF, glucose-regulated protein 78 (GRP78) has been identified as a mitogen in glioma cells, with its expression linked to neuronal activity and increased tumor proliferation.[125] Similarly, thrombospondin-1, a synaptogenic factor secreted by glial cells, strengthens the functional neuronal connections with glioma cells—a process associated with decreased survival rates in GBM patients.[126]

Glioma hijacking of neurons via tumor microtubes to drive self-progression.—Similar to certain gliomas, which develop neurite-like extensions and form functional synapses with neurons to enhance proliferation, invasion, and resistance to conventional therapies,[114,127] NF1-associated glioma cells can also form specialized membrane structures called tumor microtubes (TMs), which are composed of myosin and microtubules and contain proteins such as growth-associated protein 43 (GAP43)[128] and tweety-homolog 1 (TTYH1)[129] at their tips (Figure 2). These TMs facilitate the propagation of calcium (Ca^{2+}) waves between gap junction-connected tumor cells, effectively integrating cancer cells into a highly interconnected and functional network. The "connectivity" of this network serves as a strong prognostic biomarker for TMs, with higher connectivity observed in tumors harboring *NF1* mutations, indicating the potential importance of studying TMs in NF1-tumors. This network enhances the tumor's resistance to treatments, as interconnected glioma cells exhibit collective behavior that protects them from therapeutic interventions.[114,127]

Interestingly, glioma cells not fully integrated into this network can drive further invasion of tumor cells, potentially leading to the expansion of GBM. Similar to immature neurons and OPCs, which receive synaptic inputs, the dynamics and genesis of TMs increase following neuronal stimulation.[130] Furthermore, in both pediatric and adult

Table 2. Molecular Mechanisms Underlying Tumor Growth in NF1-Tumors

Tumor type	Key molecular Factors	Mechanism
Glioma	BDNF[a]	BDNF is released in a manner dependent on neuronal activity, where it binds to the TrkB[b] receptor, subsequently enhancing glioma growth.[122]
	NLGN3[c], ADAM10[d]	NLGN3 is secreted by nearby non-glioma neurons and subsequently cleaved by the protease ADAM10 in a manner that depends on neuronal activity. The resulting soluble form of NLGN3 then facilitates glioma growth through a pathway reliant on PI3K-mTOR signaling.[111]
	CCL5	Neurons secrete midkine, which stimulates $CD8^+$ lymphocytes to secrete CCL4, inducing the expression of CCL5 in microglia.[116]
	AMPAR[e]	1. Glutamatergic synapses between neurons and glioma cells regulate invasion mediated by TMs.[f114,127] 2. Glioma cells release glutamate into surrounding tissues, promoting glutamate-responsive growth via $Ca2^+$-permeable AMPA receptors.[114,127]
	GABA[g]	Gliomas can induce changes in neuronal chloride transporters, converting the action of GABA from inhibitory to excitatory.[160]
	TMs	Promotes communication with surrounding cells via gap junctions mediated by GAP43[h], allowing the propagation of calcium waves.[128]
Neurofibromas	COL1A2[i]	Upon sensory nerve stimulation, increased secretion of COL1A2 can promote the mitosis of *NF1* gene-deficient SCs[j].[115]
MPNSTs[k]	ADRB2[l]	Activation of the ADRB2-YAP/TAZ axis can regulate cancer stem cells, driving development of MPNSTs.[139]

[a]Brain-derived neurotrophic factor.
[b]Tropomyosin receptor kinase B.
[c]Neuroligin-3.
[d]A disintegrin and metalloprotease-10.
[e]α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor.
[f]Tumor microtubes.
[g]Gamma-aminobutyric acid.
[h]Growth-associated protein 43.
[i]Collagen 1a2.
[j]Schwann cells.
[k]Malignant peripheral nerve sheath tumors.
[l]Adrenergic receptor β2.

HGG, a specific subset of tumor cells has been discovered that function similarly to "pacemaker" neurons found in the developing brain. These cells autonomously produce rhythmic depolarization currents, serving as central "hubs" within the tumor network. Through gap junctions, they drive depolarization and calcium transients, thus promoting glioma growth and progression by coordinating tumor expansion throughout the network.[131]

Approaching Neurofibroma

Studies have shown that sensory neurons isolated from *Nf1*$^{+/-}$ mice generate action potentials at more than twice the frequency of their wild-type counterparts.[132] Additionally, dorsal root ganglion neurons with *Nf1* gene mutations, which extend sensory axons into neurofibromas, exhibit higher firing rates of action potentials compared to wild-type controls.[115] This may be due to neurofibromin's binding to and regulation of hyperpolarization-activated cyclic nucleotide-gated (HCN) channels, which directly influence neuronal excitability.[133,134] Epilepsy, affecting 4%-13% of NF1 patients, is linked to this increased neuronal excitability and is primarily associated with neuronal dysplasia, tumor-induced nerve compression, and structural brain abnormalities such as cortical nodules, white matter lesions, and mesial temporal sclerosis, though the precise mechanisms remain unclear.[135] This process contributes to the formation of a glioma-neuron positive feedback loop and is closely associated with PNS tumors. Despite the limited research on this topic, existing studies focus on how tumor-associated *Nf1*-mutant sensory neurons upregulate RAS-GTP to promote collagen type 1a2 (COL1A2) production in an activity-dependent manner, which, in turn, stimulates the proliferation of *Nf1*-null SC and drives the growth of PNF (Figure 2).[115] Furthermore, recent studies in a mouse model have demonstrated that the purinoreceptor P2RY14, expressed in SC, plays a role in stimulating neurofibroma formation via cAMP signaling.[136] These represent a significant advancement in cancer neuroscience, particularly in the study of NF1-related PNS tumors.

The growth of PNF is heavily dependent on a rich blood supply, and *NF1*$^{+/-}$ endothelial cells and inflammatory cells have been shown to promote angiogenesis.[137] In studies of prostate cancer, adrenergic signaling has been found to shift cellular metabolism towards aerobic glycolysis, thereby promoting angiogenesis. Interestingly,

targeted inhibition of the β2-adrenergic receptor in prostate cancer cells has been shown to enhance oxidative phosphorylation, suppressing tumor angiogenesis.[138] Additionally, β-blockers have been found to modulate the immune response, potentially improving the efficacy of cytotoxic therapies. While the impact of adrenergic signaling on PNF has not been thoroughly studied, it has been shown to upregulate the stemness of sporadic MPNST cells through the stimulation of the β2-adrenergic receptor (ADRB2)-YAP/TAZ axis, which is associated with a poorer prognosis (Table 2).[139] This raises the possibility that combination therapy with β-blockers could enhance the effectiveness of PNF treatment, an avenue worth further exploration. Additionally, BDNF plays a crucial role in the ERK signaling pathway within NF1-MPNST, promoting tumor growth. This suggests that further development of inhibitors targeting the BDNF/TrkB signaling pathway holds significant therapeutic potential for the treatment of NF1-MPNST.[140]

Mental State Impacts Cancer Resistance

Among patients with NF1, the most commonly reported concerns across all age groups include pain, appearance and disfigurement, participation in social activities, and stigma associated with the disorder.[141] These emotional and psychological challenges, stemming directly from the impact of the NF1 genetic condition, can persist throughout the lifespan and severely affect mental health. Research indicates that 55% of children with NF1 are at risk of developing depression, while 15% are at risk of anxiety disorders. This is particularly concerning because psychological distress and tumor progression may reinforce each other: repeated exposure to emotional stress may reduce the functionality of natural killer cells, which play a critical role in controlling tumor growth.[142] This vicious cycle may be linked to chronic stress from anxiety and depression, which dysregulates the hypothalamic–pituitary–adrenal axis and the stress-glucocorticoid-Tsc22d3 pathway. Such dysregulation leads to elevated glucocorticoid levels and upregulation of Tsc22d3, complicating tumor dynamics. This not only inhibits DNA repair and weakens the immune system's ability to target cancer cells but also reverses the anticancer effects of immune therapies.[143,144]

Additionally, depressive moods often correlate with insomnia, but studies have demonstrated that the loss of neurofibromin itself can disrupt circadian rhythms in both locomotor activity in Drosophila and sleep patterns in mice.[145,146] In individuals with NF1, this condition presents as an increased prevalence—around 50%—of particular sleep disorders, such as sleepwalking, night terrors, challenges with sleep onset and maintenance, excessive sweating, and disruptions in arousal and sleep-wake transitions.[147,148] Disrupted circadian rhythms present a significant challenge to daily functioning, but what is even more concerning, as Anja Harder proposed at the 2024 CTF Conference, is that these disturbances may promote tumor development. Disrupted circadian rhythms can alter the rhythmic expression of clock genes and enhance the rhythmic expression of oncogenes in NF1-MPNST, further contributing to tumor growth. This creates another positive feedback loop, suggesting the need to consider the biopsychosocial interactions between tumors and the body, beyond purely physiological mechanisms.[149]

Conclusion and Future Directions

Currently, there is no fully satisfactory treatment for NF1-tumors. Patients often face high surgical risks, frequent tumor recurrence, severe side effects from therapies, and prohibitive costs.[150] In recent years, cancer neuroscience has emerged as a rapidly growing interdisciplinary field, emphasizing the complex, bidirectional interactions between the nervous system and tumor progression. Major breakthroughs in NF1 research have brought this condition to the forefront of this dynamic area of oncology, shedding light on the intricate ways in which nervous system activity influences tumor development and growth.[8] These advancements offer a critical new direction for further exploration of the phenotypes and functions of NF1 tumor cells and their TME counterparts, with the potential to drive new drug discoveries or clinical trials aimed at therapeutic and care interventions for NF1-tumors.

Targeting Neuron-Tumor Cell Interactions as a Potential Therapeutic Strategy for NF1-Tumors

Among the various tumors associated with NF1, neuronal excitability plays a critical role, as demonstrated in Figure 2, by contributing to both clinical symptoms, such as epilepsy, and driving malignant processes like synaptogenesis, tumor proliferation, and cellular differentiation. By targeting neuronal excitability, we could disrupt this harmful feedback loop, providing dual benefits: alleviating symptoms and inhibiting tumor progression.

Drugs such as lamotrigine and tetrodotoxin (TTX), which inhibit sodium ion influx, have been shown to reduce the production of tumor-promoting factors like COL1A2 and chemokines CCL4/CCL5 in *NF1* gene-mutant mouse models.[115] This suggests the potential for these therapies to limit neurofibroma growth, although clinical validation is still required. Furthermore, addressing symptoms such as pain and itching could also serve as a means of reducing neural stimulation, thereby potentially inhibiting neurofibroma growth. This approach is supported by studies in basal cell carcinoma[151] and pancreatic cancer,[108] indicating promising possibilities.

One of the most promising therapeutic targets in NF1-OPG is the ADAM10-NLGN3 axis, which plays a central role in tumor formation and maintenance. Preclinical studies in NF1-mutant mouse models have shown that inhibiting ADAM10 can eliminate OPG formation by reducing NLGN3 shedding, highlighting the potential of targeting this axis for therapeutic intervention in pediatric NF1-gliomas. Several ADAM10 inhibitors, including INCB7839, GI254023X, and XL-784, are currently under investigation and may hold promise as treatments for these tumors.[113,152,153] Moreover, as light exposure influences neuronal activity, light avoidance strategies might also be

considered to reduce sensory neuron input, potentially slowing tumor progression—a concept that has been validated in mouse models.[111] The direct use of lamotrigine to inhibit neuronal activity could serve as a potential preventive or chemotherapeutic agent for children with NF1-OPG.[154]

Treatments such as calcium chelators, inhibitors of the cAMP response element-binding protein (CREB), NTRK2 (TrkB) inhibitors, and AMPA receptor antagonists have shown efficacy in various glioma models, and their potential in treating NF1-gliomas and neurofibromas warrants further investigation.[114,123,127,130,155–157] Additionally, Current research is focused on developing taxanes with better CNS penetration or small molecule inhibitors that target GAP43, a key protein involved in the growth of TMs.[158] A clinical trial (MecMeth/NOA-24; EudraCT 2021-000708-39) is currently investigating whether inhibiting TM-dependent intercellular communication within GBM through the use of meclofenamate, a gap junction inhibitor, can enhance the effectiveness of temozolomide chemotherapy.[159] This approach may also hold potential for NF1-OPG by disrupting their tumor cell networks and making them more susceptible to treatment.

Exploring the Interactions *b*etween Neurons and Various Components of the TME

Recognizing the role of CCL4/CCL5 in promoting the growth of NF1-LGG highlights the significant impact of interactions between immune cells, tumor cells, and neurons within the TME on tumor progression. However, immune cells represent only one part of the TME in NF1-tumors. With the increasing application of multi-omics technologies, such as metabolomics and proteomics, it may be possible to uncover the potential connections between fibroblasts, mast cells, endothelial cells, and neurons, thereby identifying novel strategies for indirectly inhibiting tumor growth.

Shifting Focus to the PNS and Comprehensive Research on NF1

In this review, we have examined the latest literature on the neural involvement in NF1-related tumorigenesis (Table 2). As with many studies in cancer neuroscience that focus primarily on the CNS, much of the progress in NF1 research has centered on gliomas. However, neurofibromas, which are the hallmark of NF1 and the most common concern for patients, remain underexplored. Future research should prioritize understanding the neural factors driving neurofibroma development and progression, as well as developing targeted therapies to address these challenges. Such advancements hold the potential to significantly improve treatment outcomes and QOL for individuals with NF1.

Keywords:

cancer neuroscience | nervous system | neurofibromatosis type 1 | tumor

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No new data were generated or analyzed in support of this research.

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