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REVIEW

Neurofibromatosis Type 1-Associated Optic Pathway Gliomas: Current Challenges and Future Prospects

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Abstract: Optic pathway glioma (OPG) occurs in as many as one-fifth of individuals with the neurofibromatosis type 1 (NF1) cancer predisposition syndrome. Generally considered low-grade and slow growing, many children with NF1-OPGs remain asymptomatic. However, due to their location within the optic pathway, ~20-30% of those harboring NF1-OPGs will experience symptoms, including progressive vision loss, proptosis, diplopia, and precocious puberty. While treatment with conventional chemotherapy is largely effective at attenuating tumor growth, it is not clear whether there is much long-term recovery of visual function. Additionally, because these tumors predominantly affect young children, there are unique challenges to NF1-OPG diagnosis, monitoring, and longitudinal management. Over the past two decades, the employment of authenticated genetically engineered *Nf1*-OPG mouse models have provided key insights into the function of the *NF1* protein, neurofibromin, as well as the molecular and cellular pathways that contribute to optic gliomagenesis. Findings from these studies have resulted in the identification of new molecular targets whose inhibition blocks murine *Nf1*-OPG growth in preclinical studies. Some of these promising compounds have now entered into early clinical trials. Future research focused on defining the determinants that underlie optic glioma initiation, expansion, and tumor-induced optic nerve injury will pave the way to personalized risk assessment strategies, improved tumor monitoring, and optimized treatment plans for children with NF1-OPG.

Keywords: neurofibromatosis type 1, optic glioma, vision loss, genetically engineered mouse models

Introduction

Neurofibromatosis type 1 (NF1) is a rare cancer predisposition syndrome, affecting approximately 1 in 3000 live births worldwide.[1] As an autosomal dominant condition, NF1 is caused by germline inactivating mutations of the *NF1* tumor suppressor gene. However, many of the clinical features of NF1, such as tumor formation, require loss of the remaining functional *NF1* allele, a process called copy neutral loss of heterozygosity.[2,3] While NF1 is completely penetrant, affected individuals, even those with the same germline *NF1* gene mutation, manifest with a wide range of clinical manifestations. In keeping with this variable expressivity, individuals with NF1 usually have café-au-lait macules, skinfold freckling, Lisch nodules, and peripheral nerve sheath tumors (cutaneous neurofibromas), but may also develop brain tumors (gliomas), plexiform neurofibromas, and bony lesions.[4] The majority of children with NF1 also exhibit cognitive dysfunction, including impairments in visuospatial function, executive function, language ability, and motor skills, as well as attention-deficit/hyperactivity disorder (ADHD), learning disabilities, autism, sleep disorders, anxiety, and depression.[5–10] In addition, adults with NF1 are at increased risk for tumors, including malignant peripheral nerve sheath tumors, malignant gliomas, glomus tumors, pheochromocytoma, and breast cancer.[11–13]

Optic pathway gliomas (OPG) are classified as World Health Organization grade 1 (pilocytic) astrocytomas.[14] Approximately 15–20% of young children with NF1 will develop a pilocytic astrocytoma along the optic pathway, typically detected before 7 years of age.[15–20] Although NF1-OPGs are usually considered slow-growing brain tumors, 20-30% of

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affected children will experience clinical or visual symptoms, such as vision loss or precocious puberty, and require therapeutic intervention.[17,19]

Due to their location, surgery is rarely performed because of the risk of iatrogenic neurological, ophthalmological, and endocrinological damage.[21–25] Radiation therapy is usually contraindicated due to the high risk of secondary malignancy, neurovascular abnormalities (moyamoya), and cognitive impairment in children with a cancer predisposition syndrome.[26–28] Currently, the first line therapy for symptomatic OPGs entails the use of chemotherapy agents (eg, vincristine and carboplatin), which are more effective at controlling tumor growth than halting or reversing visual loss.[19,29] As such, only 30% of children will experience an improvement in vision after treatment, and as many as 30% will continue to exhibit visual decline despite treatment.[19] Vision loss from NF1-OPG can be severe and permanent, which can significantly and negatively impact quality of life.[30] Moreover, ~30% children with NF1-OPG will fail first-line therapy and require additional treatment.[31] For these reasons, new therapeutic options are urgently needed for this at-risk population, especially those directed at restoring vision loss. In this review, we will describe the recent advances in our understanding of optic glioma initiation and progression, as well as promising therapeutic targets identified through preclinical drug discovery in *Nf1*-OPG small animal models.

Clinical Presentation

The majority of individuals with NF1 affected by OPG are young children, less than 7 years of age,[15,32] with a mean age at OPG diagnosis of 4.5 years.[17,33] A small fraction of children with NF1-OPG are diagnosed in adolescence or later years.[34–37] The exact incidence of late-onset OPG is difficult to ascertain, as some of the children may have had existing OPGs that went undiagnosed until they develop symptoms in adolescence.[35] It is worth noting that NF1-OPGs have several unique features relative to their sporadic counterparts, such as younger ages of onset, higher likelihood of bilateral involvement, more indolent clinical courses, and overall better prognoses.[38,39]

NF1-OPGs can arise within any segment of the visual pathway (Figure 1). Although the majority (>75%) occur in the anterior visual pathway (prechiasmatic optic nerves and optic chiasm), NF1-OPGs can also arise in the posterior visual pathway (optic tracts and optic radiations).[15,40,41] In one large retrospective study of 149 children with NF1-OPG, 64.4% of tumors were located in the prechiasmatic optic nerves, 28.2% in the optic chiasm, and 7.4% in the optic tracts and radiations (post-chiasmatic regions).[42] As tumor location partly dictates clinical symptoms and signs, the Dodge classification scheme was developed in the 1950s to parse OPGs anatomically into stage 1 (optic nerve), stage 2 (chiasmal), or stage 3 (nearby structures) tumors.[43] A modified Dodge classification was later proposed by the PLAN working group to further subdivide the anatomical localization of OPGs and more accurately characterize the tumor, track their impact on visual and endocrinologic function, and assist in treatment decision making.[41] In general, while tumors arising anywhere along the visual pathway have the potential to cause vision loss, those involving the optic nerves can also lead to strabismus, amblyopia, and proptosis of the affected eye.[35,44] In contrast, NF1-OPGs affecting the optic

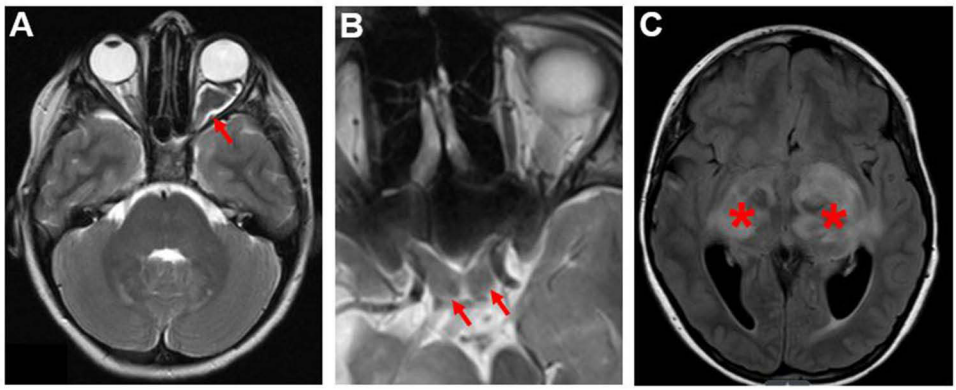

Figure 1 NF1-OPGs in children. (**A**) A pre-chiasmatic OPG (red arrow) involving the left optic nerve. The optic nerve is enlarged and tortuous compared to the normal optic nerve on the right. (**B**) An OPG involving the optic chiasm. Red arrows point to the enlarged chiasm. (**C**) An OPG involving the bilateral optic radiations (red asterisks). The images are axial T2-weighted MRI scans.

chiasm often cause bi-temporal vision loss or endocrinologic abnormalities, such as precocious puberty due to hypothalamic involvement. Besides vision loss, strabismus, exophthalmos, and amblyopia are the most frequently documented ophthalmological symptoms/signs of NF1-OPG.[37] Endocrinologic disorders are also common in children with NF1-OPG, especially those with hypothalamic involvement, and can range from precocious puberty, growth hormone hypersecretion or deficiency, diabetes insipidus, diencephalic syndrome, obesity with insulin resistance, and hypogonadism.[44–47]

Risk Factors for Vision Loss in NF1-OPG

Over the past decade, efforts have focused on the identification of risk factors for developing NF1-OPGs and associated visual impairment. While some studies of individuals with NF1-OPG report no clear genotype-phenotype correlation,[48,49] other studies have suggested that the location of the germline *NF1* gene mutation could be one risk factor for OPG development.[50–53] These studies found that mutations in the 5′ end of the *NF1* gene were associated with OPG development. Strikingly, other mutations are associated with a lack of OPG development, including the Arg1809 missense and Met991 in-frame deletion mutations.[54–57] In contrast, individuals with mutations affecting codons 844–848 tend are more likely to harbor OPGs (50% of children).[58]

Other risk factors include race/ethnic background, birth weight, and allergic conditions. In this respect, Caucasians with NF1 are more likely to be diagnosed with OPG than those who identify as Black or Asian.[59] High birth weight is associated with increased brain tumor incidence in children with NF1,[60] whereas allergic conditions, like eczema and asthma, are associated with a reduced risk of OPG development.[61]

Risk factors for vision loss include tumor location, subject age, and sex. NF1-OPGs involving the posterior visual pathway (optic tracts and radiations) have a greater likelihood of vision loss.[19,31,34,38] On the other hand, chiasmal location with hypothalamic involvement, along with young age of onset and older age at last endocrine evaluation, portend a higher risk for endocrine abnormalities.[46,47] The presence of clinical symptoms at diagnosis also increases the likelihood that OPGs will eventually require treatment.[35] Children younger than 2 or older than 8–10 years of age are more likely to experience vision loss.[19,37,62,63] Similarly, young age may also predict relapse after treatment.[31] Lastly, girls with NF1-OPGs involving the optic nerve are more 3–5 times more likely to require treatment for vision loss than boys.[64,65]

Screening and Monitoring

NF1-OPGs can exhibit highly variable clinical courses and visual outcomes. As such, not all children with an NF1-OPG will manifest symptoms or signs, and not all individuals with NF1-OPG-related vision loss will require treatment. For this reason, annual screening and longitudinal monitoring of individuals with NF1 for OPG-related signs and symptoms during childhood is crucial for prompt clinical decision making and treatment. Over the past two decades, consistent recommendations have been proposed by the NF1-OPG Task Force and the American Academy of Pediatrics (AAP; Figure 2): all children with NF1 should undergo ophthalmological exams annually by an experienced ophthalmologist, starting at 8–9 months of age until age 8, and then every two years until age 18.[66,67] These annual exams should include detailed assessments of visual acuity using age-appropriate methods (eg, Teller acuity cards, eye chart with standard letters (HOTV) or shapes (Lea), and Snellen acuity cards), and include assessments of color vision, visual fields, ocular motility, and eye alignment. The eyelids, orbits, pupils, irises, and fundi should also be thoroughly examined. Children with NF1 should also undergo annual physical examinations with assessments of weight, height, growth velocity, and sexual development to monitor for signs of precocious puberty. If an individual with NF1 develops any of the above symptoms, especially reduced visual acuity, endocrine disorders, or new neurologic deficits, a brain MRI should be obtained to evaluate for the presence of an OPG. However, "screening" baseline MRIs of the brain to detect asymptomatic OPGs in individuals with NF1 is not recommended.[35,62,67–69]

Screening guidelines for NF1-OPG from the French NF Network align well with those from the NF1-OPG Task Force and AAP with respect to the need for annual ophthalmological examinations and MRI screening of asymptomatic children.[70] In contrast, they recommend screening for OPG in asymptomatic children until 13, instead of 18, years of age. It is worth noting that both guidelines recommend screening well into the adolescent years in an effort to identify individuals with late-onset symptomatic OPGs.

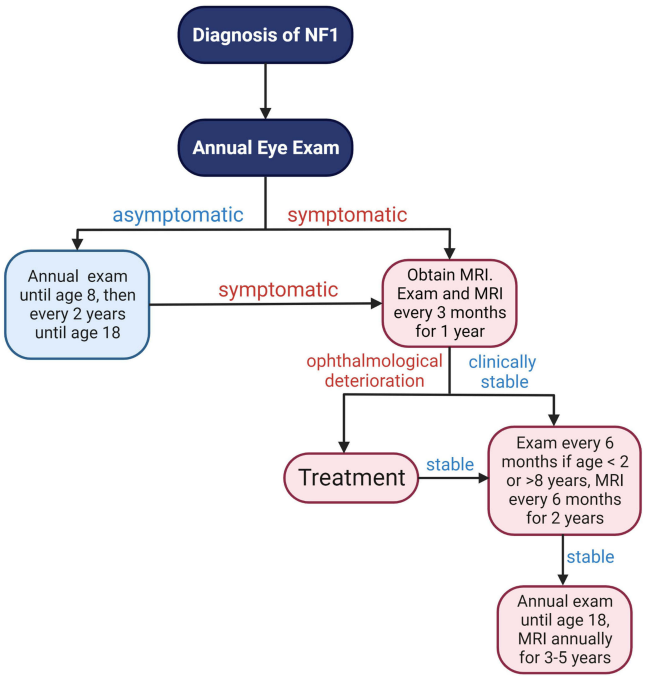

Figure 2 Proposed flow diagram for NF1-OPG screening and monitoring. Children with NF1 should undergo ophthalmological exam annually until 8 years of age, then every 2 years until age 18 if asymptomatic. Once symptoms develop, especially visual symptoms, MRI should be performed, and screening frequency should be increased to every 3 months for the first year. The intervals of the ophthalmologic examinations and MRIs can be gradually increased if stability of vision is achieved.

Once diagnosed with an OPG, either due to the development of symptoms or following incidental discovery, children with NF1-OPGs need close monitoring for the development or worsening of visual symptoms. Individuals should have ophthalmological exams and endocrinologic assessments every 3 months for the first year after diagnosis, given the fact that most decisions to initiate treatment are made within the first year.[19] If vision and endocrine function remain stable, exams should be conducted every 6 months for individuals younger than 2 years or older than 8 years of age, then annually until 18 years of age.[67,71] MRI should also be performed every 3 months for the first year after diagnosis and every 6 months for the next two years, especially for children with symptomatic OPGs or very young children in whom changes in vision cannot be confidently assessed.[67] Annual ophthalmologic evaluations and neuroimaging then continue annually for another 3–5 years if no clinical changes are noted. Afterwards, the interval of neuroimaging can be further increased in the absence of clinical progression until 18 years of age.[67]

A significant number of children will require MRI under general anesthesia, where the risk of anesthesia-related adverse events is approximately 1%. These events include neurotoxicity and aspiration, which occur more often in children than in adults, especially those younger than 3 years of age.[72,73] In addition to weighing the risk of MRI under anesthesia against the benefit of preventing lifelong disability due to visual loss, clinicians should also be aware of the rare phenomenon of spontaneous tumor involution on MRI, which has been reported to occur in the context of NF1-OPG.[74–76]

Complementary Assessments of Visual Function

Since many children with NF1 have co-morbid ADHD or autism spectrum symptomatology, other objective and quantitative methods have been developed to monitor for vision loss. The most commonly used assessments are optical coherence tomography (OCT) and visual evoked potentials (VEPs).[77] VEPs present a set of standardized visual stimuli and measure elicited visual cortical response detected using scalp electrodes. Decreased amplitudes or prolonged latencies may indicate injury to the visual pathway from an OPG.[67] While VEP has nearly 90% sensitivity at detecting the presence of an OPG, the specificity is much lower, and reports conflict on whether it correlates with vision loss.[78–80] In addition, VEP requires patient cooperation for reliable results, which can be difficult in children with NF1 due to their young age and cognitive comorbidities.

OCT measures the thickness of the retinal nerve fiber layer (RNFL) and ganglion cell layer-inner plexiform layer complex (GCL-IPL), the thinning of which correlates with declining visual acuity in children with NF1-OPG.[81–83] The advantage of OCT is its non-invasive nature and the automated measurements of RNFL and GCL-IPL thicknesses, which reduces inter-operator variability. RNFL thinning due to NF1-OPG may precede clinically measurable vision loss, making RNFL thickness an attractive biomarker for the early detection of vision loss.[84] However, good fixation is still required for reliable segmentation of the retinal layers, which may be difficult for young children and individuals who already have poor central vision. For very young children, OCTs with accurate assessment of RNFL and GCL-IPL layers may require anesthesia, usually performed in coordinated with a sedated MRI. While this method is attractive, there is also inter-device and inter-protocol variability that may cloud the interpretation of changes measured by OCT.[85,86]

Treatment

Treatment is usually initiated after clinical and/or radiographic progression is observed. The clinical criteria for treatment are defined as a visual acuity decrease of 0.2 logMAR units or more, or new visual field defect.[67,87] Tumor progression, especially in children whose visual acuity cannot be reliably assessed, may also be an indication for treatment.[67,87] While surgical resection is rarely performed, debulking or enucleation may be necessary in children with large OPGs that compress the surrounding brain tissue or cause severe proptosis and disfiguration with little functional vision left in the affected eye.[88,89] Surgical decompression or cerebrospinal fluid diversion may also be indicated if chiasmal OPGs cause compression of the third ventricle with associated hydrocephalus.[23,25]

The current first-line treatment for NF1-OPG is chemotherapy with vincristine and carboplatin.[90,91] Hypersensitivity to carboplatin can occur, the risk of which increases with repeated exposure.[92] For those individuals who develop carboplatin hypersensitivity, vinblastine has also been used as an alternative. Vinblastine has a more favorable side effect profile, but more clinical studies are needed to establish its efficacy for vision preservation and restoration in children with NF1-OPG.[92] Other second-line chemotherapies include vinorelbine and temozolomide, as well as bevacizumab and irinotecan.[93–97]

Although chemotherapy is often effective at limiting tumor growth, only a minority of individuals will experience improvements in vision following treatment. In a large multicenter study of 115 children treated for NF1-OPG between 1997 and 2007, 32% had improved visual acuity following treatment, while 40% and 28% had no change or deterioration of visual acuity, respectively.[19]

Genetics of NF1-OPG

All children with NF1 are born with one functional *NF1* allele and one non-functional *NF1* allele harboring a germline loss-of-function mutation. The presence of a germline *NF1* gene mutation alone is not sufficient for tumorigenesis. Optic glioma formation requires somatic loss of the remaining functional *NF1* allele.[98–100] This is consistent with the "two-hit" model of tumorigenesis, first proposed to explain the origin of retinoblastoma.[101,102] Examination of NF1-associated pilocytic astrocytomas revealed that somatic inactivation of the second *NF1* allele can occur through either loss of heterozygosity, loss-of-function mutations, or epigenetic modification.[103–105] All of these events lead to undetectable levels of the *NF1* protein (neurofibromin) in the tumor cells.[106]

Neurofibromin is a large 2818 amino acid protein that forms a functional homodimer.[107,108] It contains a 300-amino-acid domain that binds to and negatively regulates the RAS proto-oncogene.[3,109] By binding to RAS, neurofibromin functions as a GTPase-activating protein (GAP) and accelerates the conversion of RAS from its GTP-bound active form to an inactive GDP-bound form.[110,111] *NF1* loss-of-function mutations result in increased RAS activity and cell growth through hyperactivation of RAS downstream pathways (RAS-MEK-ERK or RAS-AKT-mTOR).[112–114] Consistent with its role as a RAS-GAP, increased RAS activity is also detected in surgical specimens of human NF1-OPG.[115,116]

Insights from Preclinical Models

Because surgical resection or biopsy of NF1-OPGs is rarely performed, the majority of our understanding of these tumors derives from preclinical animal models. Genetically engineered mice are the most widely used and best characterized models of *Nf1*-OPG,[117,118] although minipigs with germline *NF1* mutations also develop OPGs.[119] Because mice

homozygous for *Nf1* loss (*Nf1*^{null}) die in utero, conditional transgenesis (Cre-LoxP) methods have been employed to develop mice in which somatic *Nf1* loss could be targeted to specific cell types.[117] Using this method, numerous *Nf1*-OPG mouse models have been generated.[117,118,120] In these *Nf1*-OPG models, tumors arise in >95% of mice by 3–4 months of age, with loss of RGCs and thinning of the RNFL, similar to that observed in humans.[81,121] Leveraging these murine strains, several key insights have been revealed relevant to improved patient risk assessment and treatment.

Tumor Cell of Origin

First, the likely cell of origin for murine *Nf1*-OPGs is a GFAP-, CD133-, and BLBP-expressing neural progenitor cell (NPC), rather than a NG2-expressing glial cell.[118,122,123] Second, the NPCs capable of tumorigenesis are anatomically restricted to the subventricular zone of the third ventricle,[124,125] where during normal development, they give rise to oligodendrocyte precursor cells that migrate into the optic nerve.[126] The regional differences between NPCs in the third ventricle (*Nf1*-OPG cell of origin) and the lateral ventricle (unlikely *Nf1*-OPG cell of origin) result from increased expression of the mTOR complex protein, rictor, which controls Akt activation.[124] Third, *Nf1* somatic loss in Olig2-expressing oligodendrocyte precursor cells also induces *Nf1*-OPG formation, albeit with a longer latency (~6 months).[123] To complement these studies in mice, human induced pluripotent stem cells (hiPSCs) harboring biallelic *NF1* mutations have also been used to generate diverse types of cells in the central nervous system and investigated for their ability to form low grade gliomas.[127] Consistent with the mouse model findings, hiPSC-derived neuroglial progenitors, but not astrocytes, generate tumors following transplantation into immunocompromised mice.

Immune Tumor Microenvironment

While biallelic *Nf1* loss in the tumor cells of origin is necessary, it is not sufficient by itself, for tumorigenesis. In this regard, bi-allelic *Nf1* loss in susceptible NPCs does not result in *Nf1*-OPG formation.[128] *Nf1* loss in third ventricle NPCs must be coupled with a germline *Nf1* mutation in the non-cancerous cells in order for tumors to form.[118] Examination of these non-neoplastic cells reveals the presence of monocytes (resident microglia) and T cells that form an immune microenvironment through the production of soluble chemokines[129–131] (Figure 3).

The importance of microglia to glioma progression was revealed by genetic and pharmacologic studies, resulting in delayed optic glioma formation and reduced *Nf1*-OPG growth, respectively.[132,133] Tumor-associated microglia produce a key growth factor for optic glioma tumor cells (Ccl5), such that its inhibition blocks *Nf1*-OPG growth.[134,135] Following recruitment by the tumor cells (Ccl2 chemoattraction), T cells regulate microglia function and Ccl5 production through the elaboration of another cytokine (Ccl4).[131,135] However, in contrast to RAS/RAS pathway inhibition, where cessation of drug treatment results in continued tumor growth,[121,136] blocking T cell infiltration or microglia Ccl5 production during tumorigenesis has durable effects on *Nf1*-OPG growth following the cessation of treatment.[137]

Because T cells likely infiltrate the tumor from the systemic circulation, they may also serve as bellwethers of systemic disease. In *Nf1*-OPG mice, experimental asthma induction causes T cells to express decorin, which blocks microglial expression of Ccl5 and suppresses optic glioma formation.[138] This experimental finding provides a mechanistic explanation for the reduced risk of OPG development in children with NF1 and asthma.[61] In addition to suggesting potential immune therapies, the ability of T cells to function as sentinels of systemic disease make them possible convergence points for other NF1-OPG risk factors.

Neurons as Key Drivers of NF1-OPG

Neurons can also participate in NF1-OPG pathobiology. First, they can be the targets of OPG-induced damage. In this regard, *Nf1*-mutant retinal ganglion cells (RGCs) whose axons course through the optic nerve, have smaller growth cones, shorter neurites, and increased death due to impaired generation of intracellular cyclic AMP (cAMP).[139] The importance of intracellular cAMP to the intrinsic vulnerability of *Nf1*-mutant neurons is underscored by the finding that pharmacologic cAMP elevation in *Nf1*-OPG mice rescues RGC death in vivo.[139]

Second, *Nf1*-mutant RGCs also play key roles in the initiation and progression of NF1-OPG. Increased neuronal activity in response to light stimulation (visual experience) is critical for *Nf1* optic glioma initiation, such that rearing *Nf1*-OPG mice in the dark blocks tumor formation.[140] This activity-dependent initiation of optic glioma by *Nf1*-mutant RGCs is mediated through neuronal shedding of neuroligin-3 (Nlgn3), a potent growth factor for gliomas. Additionally, *Nf1* mutation also

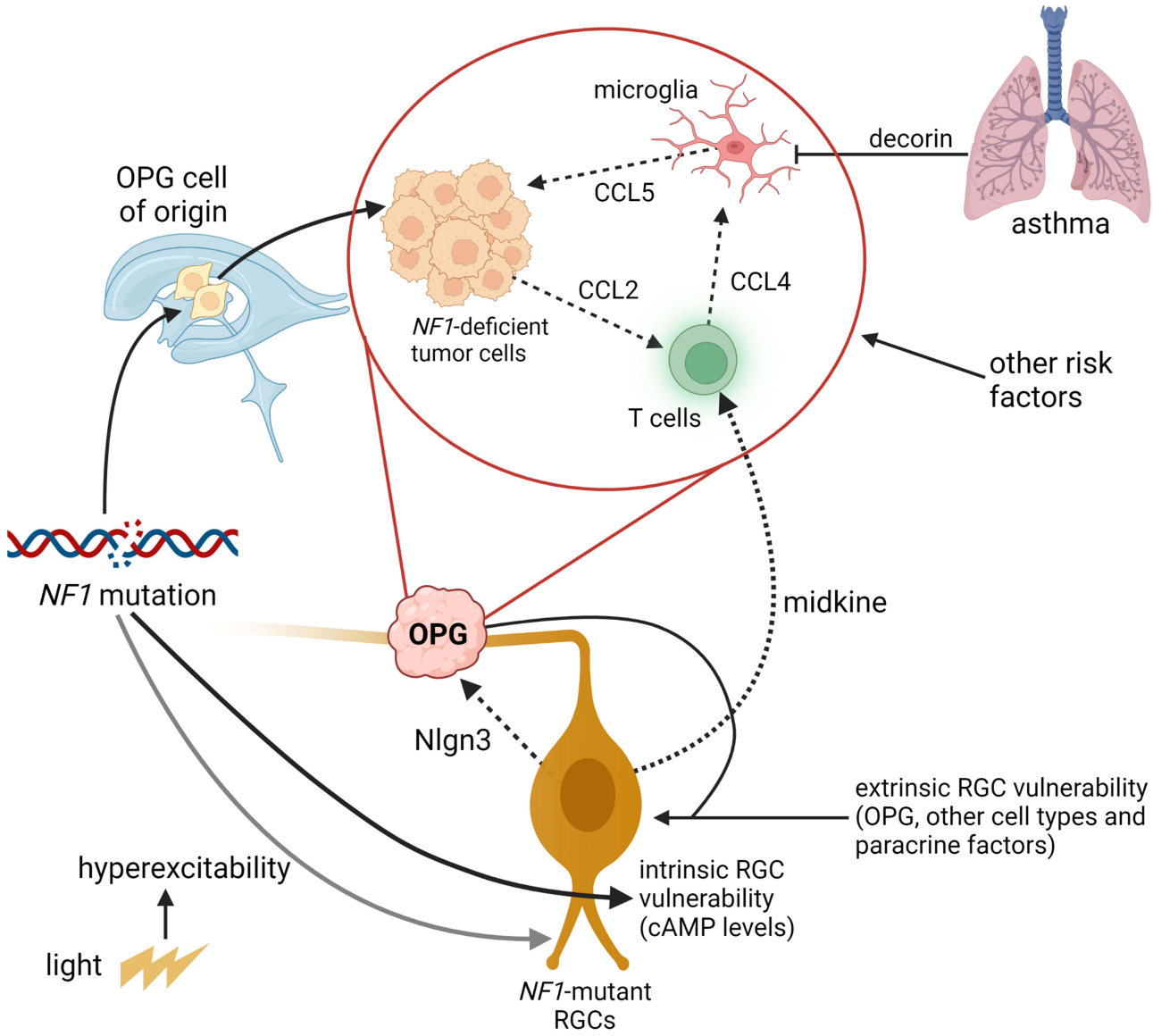

Figure 3 Interaction of tumor cells, neurons, and immune cells in murine *Nf1*-OPGs. *Nf1*-deficient tumor (glioma) cells produce Ccl2 to attract T cells, which release Ccl4 following exposure to *Nf1*-mutant neuronal midkine to induce Ccl5 secretion from *Nf1*-mutant microglia. Ccl5 functions as a potent mitogen for glioma cell growth. In addition, *Nf1*-mutant RGCs also promote tumor initiation and expansion through the elaboration of neuroligin-3 (Nlgn3) in response to light (visual experience). The establishment of a supportive microenvironment for *Nf1*-OPG formation and growth allows for risk factor convergence at the level of neurons (light, specific *Nf1* mutation), T cells (asthma), and microglia (other systemic exposures).

increases RGC neurons baseline excitability, acting at the level of the hyperpolarization activated cyclic nucleotide gated potassium channel (HCN), such that HCN pharmacological targeting with lamotrigine blocks optic glioma progression.[141] In contrast to light-induced regulation of *Nf1*-mutant neuronal excitability, this HCN-controlled effect is mediated by *Nf1*-mutant neuronal production of midkine, which stimulates T cells to produce Ccl4 and activate the immune axis supportive of tumor growth. Taken together, these findings establish *Nf1*-mutant RGCs as active drivers of optic glioma initiation and growth, as well as targets of optic glioma-related vision loss, making them important cells to consider in future clinical trials.

Challenges and Future Prospects

Risk Assessment

Recent studies using *NF1*-mutant hiPSCs and *Nf1*-GEM models with patient-derived germline *NF1* gene mutations demonstrate that not all germline *NF1* gene mutations are functionally equivalent.[130,141–143] In these experiments, mice

with different germline *Nf1* gene mutations exhibit a wide range of tumor phenotypes, including no tumors, reduced tumor penetrance, and faster tumor growth. These mice could be used to identify serum biomarkers for glioma formation and growth, and provide unique opportunities to perform preclinical studies on mouse strains with different tumor characteristics. The use of mice coupled with human epidemiologic studies may reveal additional predictive risk factors for precision medicine.[144]

Screening and Monitoring

In addition to OCT and MRI, which are now an integral part of monitoring children with NF1-OPGs, several new tools are being evaluated. These include tractography or diffusion tensor imaging (DTI) and volumetric MRI, which are techniques that map white matter tracts and calculate the volume of OPGs, respectively. Decreased functional anisotropy and increased diffusion on tractography may be associated with decreased visual acuity in individuals with NF1-OPG.[145–149] Similarly, larger tumor size on volumetric MRI correlates with greater retinal nerve fiber layer thinning.[150] DTI and volumetric MRI share some of the disadvantages of traditional brain MRI, such as the need for sedation in young patients and a relatively high cost. Additionally, these protocols call for experienced operators, which may also limit their widespread use. Further studies on the threshold of changes necessary to influence treatment decisions and the utility of these radiographic assessments for monitoring treatment response remain to be addressed.

Treatment

While carboplatin/vincristine has long been the primary first-line therapy for NF1-OPG, numerous molecularly-targeted therapies that block RAS pathway signaling have entered clinical trials (Table 1). Among them, MEK inhibitors have emerged as particularly promising drugs. MEK inhibition effectively suppressed tumor growth in animal models of *Nf1*-OPG,[151] and in early clinical trials on NF1- and non-NF1-associated OPGs (selumetinib and trametinib).[152–155] While these results are encouraging, it should be noted that more than a third of patients in two of these trials reported significant adverse events (mainly dermatological, gastrointestinal, and hematological sequelae) that were dose limiting.[153,154] Disease rebound has also been observed in some individuals after withdrawal of MEK inhibition.[153] In addition to MEK inhibitors, one immunomodulatory therapy (Poly-ICLC) is currently being evaluated.[156–160]

Due to the limited vision restorative potential of the current mainstream cytotoxic agents, there is a pressing need to develop alternative treatment strategies to promote vision preservation and restoration. While no neuroprotective or

Table 1 Active Clinical Trials for NF1-OPG

Agent	Study Number	Status	Sponsor	Phase	Ages	Primary Outcome
Selumetinib	NCT03326388	Recruiting	Great Ormond Street Hospital	I/II	3 to 18 years	Maximum Tolerated Dose
Selumetinib	NCT01089101	Active, not recruiting	NCI	I/II	3 to 21 years	Maximum tolerated dose and response rate
Selumetinib	NCT03871257	Recruiting	NCI	III	2 to 21 years	Event-free survival and visual acuity improvement
Vinblastine ± bevacizumab	NCT02840409	Recruiting	The Hospital for Sick Children	II	6 months to 18 years	Response rate
Lenalidomide	NCT01553149	Active, not recruiting	NCI	II	Up to 21 years	Response rate
Poly-ICLC	NCT04544007	Recruiting	University of Alabama at Birmingham, NFCTC	II	Up to 22 years	Response rate

Abbreviations: Poly-ICLC, Polyinosinic-Polycytidylic; NCI, National Cancer Institute; NFCTC, Neurofibromatosis Clinical Trials Consortium.

vision-restorative agents are currently approved for NF1-OPG, a few promising candidates are in preclinical or early clinical trials. Topical nerve growth factor (NGF) delivery to the eye was shown to improve visual fields in a small cohort of individuals with NF1-OPG who completed chemotherapy.[161] Future compounds could be considered, including those that elevate neuronal cyclic AMP or attenuate neuronal hyperexcitability (eg, lamotrigine).[139,141] Other strategies are also being considered, such as viral delivery of pro-survival transcription factors and transplantation of stem cell-derived human RGCs.[162–165]

Platforms for Future Research

To ensure that future research continues to offer valuable insights into the molecular determinants of tumor initiation, progression, and vision loss, and that preclinical studies of novel therapeutic interventions have good chances of efficacy, there is a great need for additional experimental platforms that capture the inherent clinical heterogeneity seen in children with NF1-OPG. These platforms should include multiple small-animal models harboring different patient-derived germline mutations, as well as additional animal models in which optic gliomas arise within the optic tracts and optic radiations. Moreover, while the visual system of mice is easily accessible and well characterized, it may not accurately represent the complex structure and function of the human visual system. In this respect, the use of NF1 genetically engineered pig models that share many similarities with humans with respect to ocular anatomy and development of the visual system, could be employed.[166,167] Other animals with highly developed visual systems, such as ferrets, are amendable to CRISPR/Cas9-mediated genomic engineering, and could be developed as future models of NF1-OPG.[168]

Disclosure

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