Brain Tumor Pathology (2019) 36:74–83
https://doi.org/10.1007/s10014-019-00340-3

REVIEW ARTICLE

Molecular genetics and therapeutic targets of pediatric low-grade gliomas

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Received: 13 February 2019 / Accepted: 19 March 2019 / Published online: 30 March 2019

Abstract

Pediatric low-grade gliomas (PLGGs) have relatively favorable prognosis and some resectable PLGGs, such as cerebellar pilocytic astrocytoma, can be cured by surgery alone. However, many PLGG cases are unresectable and some of them undergo tumor progression. Therefore, a multidisciplinary approach is necessary to treat PLGG patients. Recent genomic analysis revealed a broad genomic landscape underlying PLGG. Notably, the majority of PLGGs present MAPK pathway-associated genomic alterations and MAPK signaling-dependent tumor progression. Following preclinical evidence, many clinical trials based on molecular target therapy have been conducted on PLGG patients, some of whom exhibited durable response to target therapy. Here, we provide an overview of PLGG genetics and the evidence supporting the application of molecular target therapy in these patients.

Keywords Pediatric low-grade glioma · Genetic alteration · Molecular target therapy

Abbreviations

PLGG	Pediatric low-grade glioma
PA	Pilocytic astrocytoma
PXA	Pleomorphic xanthoastrocytoma
DNET	Dysembryoplastic neuroepithelial tumor
GG	Ganglioglioma
TSC	Tuberous sclerosis complex
SEGA	Subependymal giant cell astrocytoma
DA	Diffuse astrocytoma
d-OT	Diffuse oligodendroglial tumor

Introduction

Pediatric low-grade gliomas (PLGGs) are clinically and genetically distinct from adult LGG [63]. PLGGs include pilocytic astrocytoma (PA), dysembryoplastic neuroepithelial tumor (DNET), ganglioglioma (GG), pleomorphic astrocytoma (PXA), subependymal giant cell astrocytoma (SEGA), diffuse astrocytoma (DA) and diffuse oligodendroglial tumors (d-OT), and other tumors [70]. Recent large-scale genomic analysis uncovered the genetic landscape of pediatric brain tumors, including PLGG. Importantly, there is a tight relationship between specific genetic alterations and anatomical tumor location in PLGG. Several clinical trials, based on molecular target therapy, are ongoing in PLGG patients. Herein, we summarize the genetic characterization of PLGG and the relevant molecular therapeutic targets potentially suitable for precision medicine.

Genetic characterization of PLGG

Somatic gene abnormalities

MAPK signaling pathway

Although, histologically, PLGGs comprise different tumors, the vast majority of PLGGs are caused by various genetic alterations affecting the MAPK pathway (Fig. 1) [53]. In particular, genetic alterations to promote MAPK pathway activation are found in almost the totality of PA cases [29, 56, 75].

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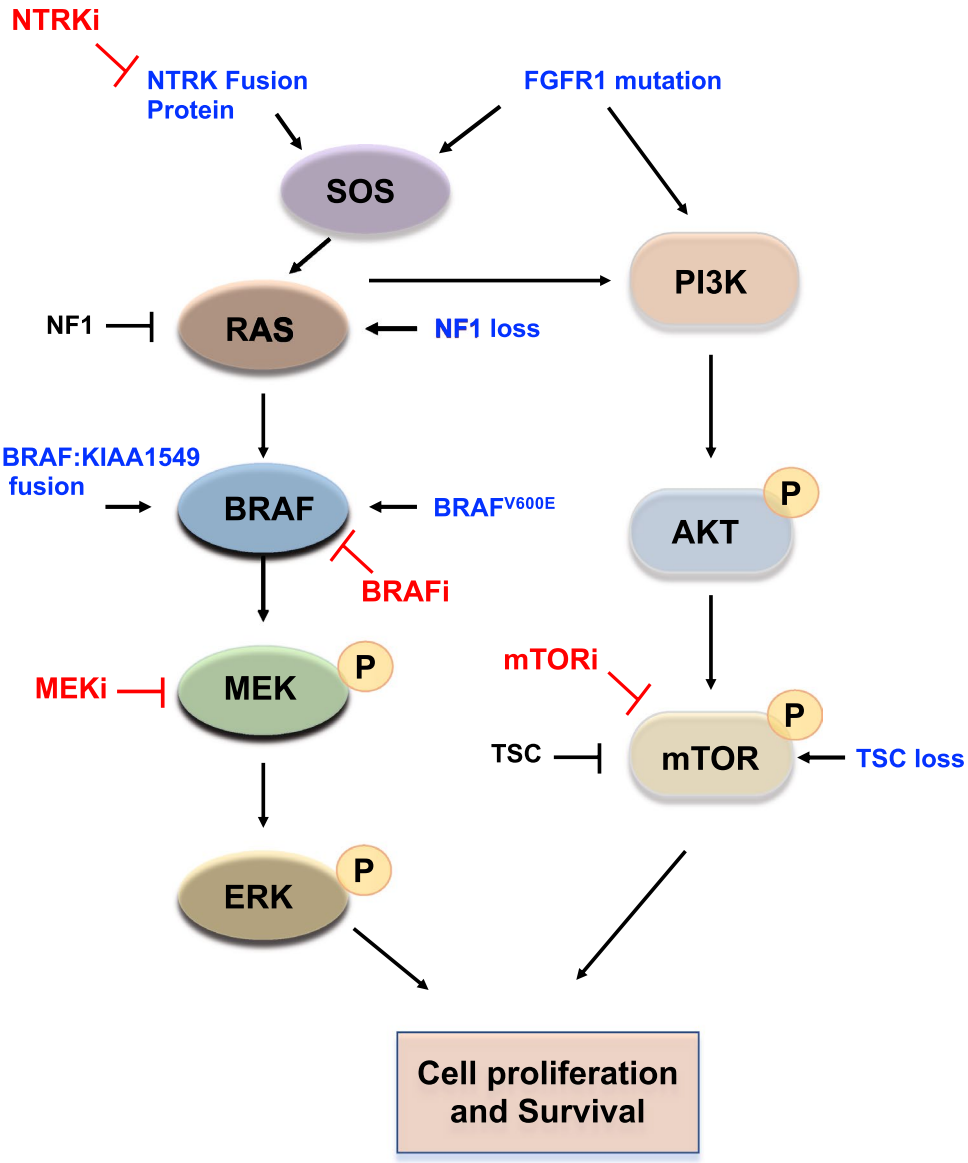

Fig. 1 Major oncogenic pathways (MAPK pathway and PI3K/AKT/mTOR pathway) in pediatric low-grade gliomas (PLGG). Blue fonts. Major oncogenic alterations in PLGG. Red fonts. Proposed molecular therapeutic inhibitors for suppressing major oncogenic pathways

KIAA1549: *BRAF* fusion

A 2-Mb tandem duplication of 7q34, encompassing the *BRAF* gene, was commonly detected in PA cases [11]. Importantly, younger patients with infratentorial posterior fossa PA tend to display a high frequency of the *BRAF* fusion [23, 30]. In the tandem duplication, the N-terminal end of the KIAA1549 protein replaces the N-terminal regulatory region of BRAF, while the BRAF kinase domain is retained, resulting in constitutive activation of the MAPK pathway [30, 75]. Other BRAF fusions, involving *FAM131B, RNF130, CLCN6, MKRN1, GNA11, QKI, FZR1*, and *MACF1*, were also identified. These events also induce loss of the N-terminal regulatory region of the BRAF protein and constitutive activation of the kinase domain. The *BRAF* fusions arise from various genetic mechanisms, including deletions and translocations in PA [29, 75]. In addition to *BRAF* fusions, *BRAF* small insertions, activating BRAF kinase signaling, were also observed in a small proportion of PA [29]. BRAF fusions are almost exclusive to PA [70]. PAs carrying the *KIAA1549:BRAF* fusion occur in almost all anatomical locations, but most frequently in the cerebellum (Fig. 2A) [10].

BRAF ^{V600E} mutation

PLGGs bearing the *BRAF* ^{V600E} mutation comprise a heterogeneous group of tumors with divergent histology, location, cooperating genetic alterations, and outcomes [31]. The *BRAF* ^{V600E} status alone is not a sufficient diagnostic or prognostic biomarker of PLGG [31]. A strong association between the *BRAF* ^{V600E} mutation and tumor location was

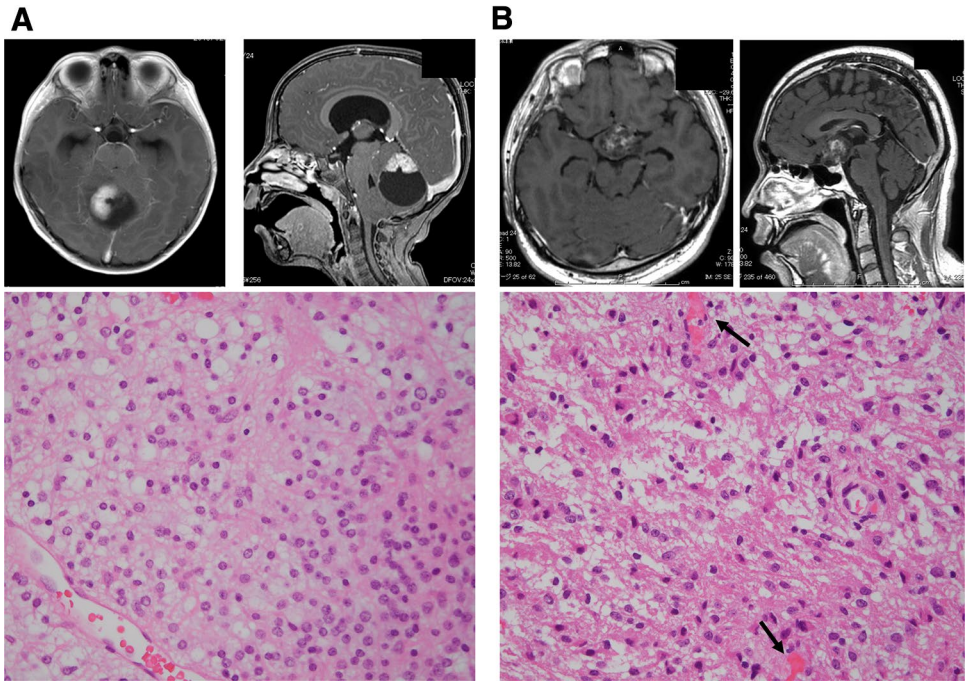

Fig. 2 **a** Axial (left) and sagittal (right) contrast enhancing MR imaging indicating contrast-enhanced lesion with cyst in cerebellum. Hematoxylin and eosin staining indicating pseudo-oligodendroglial pattern. **b** Axial (left) and sagittal (right) contrast enhancing MR imaging indicating weak contrast-enhanced lesion in suprasellar lesion. Hematoxylin and eosin staining showing typical biphasic pattern with Rosenthal fibers (arrows). These tumors are histologically diagnosed as pilocytic astrocytoma, but harboring distinct genetic alteration. Magnification, ×400

observed in PA (WHO grade I). More specifically, 20% of extra-cerebellar PA were found positive for the *BRAF*^{V600E} mutation, whereas only 2% cerebellar PA harbored the mutation [65, 70].

The *BRAF* ^{V600E} mutation was observed in approximately 65% of PXA cases (WHO grade II and grade III) [14, 64], and is highly correlated with age. PXA patients carrying the *BRAF*^{V600E} mutation were mainly observed in young subjects (mean age; 18 years), while PXA tumors related to wild-type *BRAF* display a later onset (mean age; 38 years) [64]. The *BRAF*^{V600E} mutation was also found in 18–50% of GG (WHO grade I), 30–51% of DNET (WHO grade I), and 43% of SEGA (WHO grade I), respectively [8, 42, 55, 65].

FGFR1 mutations, fusions, and kinase domain duplications

Recent large-scale genetic analysis uncovered recurrent *FGFR1* somatic mutations (p.N546K, p.K656E), *FGFR1–TACC1* fusions, and a novel internal tandem *FGFR1* kinase domain duplication in patients with PA and DNET [29, 56, 76]. Abnormalities in *FGFR1* are frequent in PLGGs with oligodendroglial phenotype and composed of primary of oligodendrocyte-like cells, being present in 82% of DNETs and 40% of d-OT, respectively [56].

Fusions of the *NTRK* gene family

NTRK receptor transcript fusion is a very rare event in adult and pediatric tumors (0.3%), but relatively frequent in pediatric melanoma (11.1%) and PLGG (2.5%), as well as pediatric high-grade glioma (PHGG, 5.3%) [50]. Among *NTRK* family members, *NTRK2* fusions (*QKI-NTRK2* and *NACC2-NTRK2* fusions) were identified in PA [29]. The *NTRK* gene fusions are characterized by various 5′partners with a dimerization domain that presumably leads to constitutive dimerization and kinase activation in PA [29, 75].

Homozygous *CDKN2A* deletion

CDKN2A is a tumor-suppressor gene and key regulator of cell cycle. A *CDKN2A* homozygous deletion inactivates cell cycle regulation and promotes malignant cancer progression. Consistently, loss of CDKN2A (p16) in immortalized human astrocytes abrogated the senescent features [26]. Although activated BRAF alone is not sufficient for tumorigenesis, the combination of BRAF activation and CDKN2A loss results in cell transformation [61], indicating a critical role for *CDKN2A* homozygous deletion in tumor progression. Indeed, *BRAF*^{V600E} mutation and *CDKN2A* deletion were found to be early genetic events in PLGG with malignant transformation [46]. In *BRAF*^{V600E} mutant PLGGs, *CDKN2A* deletion was rated as a poor independent prognostic factor [40]. *CDKN2A* homozygous deletion was found in 25% of the *BRAF*^{V600E} mutant PLGGs [40], 60% of PXA, and 16.7% of *BRAF*^{V600E} mutant GG. However, the number of available studies is relatively small [55, 72].

Amplification and/or rearrangement of *MYB/MYBL1* and *MYB–QKI* fusion

A triple alteration consisting of *MYB* truncation, increased expression through enhancer hijacking, and loss of *QKI*

tumor suppressor function was identified in a proportion of PLGGs with astrocytic phenotype (diffuse astrocytic and angiocentric glioma). An *MYB–QKI* fusion characterizes almost all angiocentric gliomas (87%), while *MYB–ESR1* fusion and *QKI* rearrangement was also identified in a subset of angiocentric gliomas [56]. In contrast, *MYB* or *MYBL1* rearrangement was detected in 41% of DA [56]. *MYB*/*MYBL1* alterations were co-occured with *BRAF* alteration in a subset of DA [56, 57, 75].

ROS1 or *ALK* fusions

ALK or *ROS1* rearrangements, which activate RAS/MAPK, PI3K, and JAK/STAT pathways, have been identified in a subset of PHGG and PLGG [9, 28, 48, 52]. These genetic events were found in infants and younger children.

Germline gene abnormalities

TSC1/TSC2

Tuberous sclerosis complex (TSC) is an autosomal dominant neurocutaneous disorder caused by mutations in either hamartin-encoding *TSC1* or tuberin-encoding *TSC2*. In the central nervous system, TSC is characterized by the development of SEGA, subcortical heterotopic nodule, and cortical tuber [47]. SEGAs belong to the group of astrocytic neoplasms, even though they are also expressed in neurons. The majority of SEGAs exhibit loss of heterozygosity in the same gene in which the mutation of *TSC1* or *TSC2* was identified [3], while no evidence of *BRAF* ^{V600E} or other *BRAF* mutations was found in these tumors.

Neurofibromatosis type I (NF1)

The *NF1* gene encodes an RAS GTPase-activating protein known as neurofibromin and is one of several genes that affect RAS–MAPK signaling [58]. The somatic *NF1* loss occurred by frameshift mutation, loss of heterozygosity, and methylation and no additional gene alteration was identified in NF-1 associated PA, indicating *NF1* loss is likely sufficient for PA formation [22]. About 20% of NF1 patients develop PAs [47], most of which are located in the supratentorial midline (Fig. 2B) [70].

Molecular target therapy for pediatric low-grade tumors

Target for *BRAF*^{V600E} mutation in pediatric gliomas

A large clinical study indicated that patients with *BRAF*^{V600E} mutant PLGG exhibited poorer prognosis compared to patients with wild-type *BRAF*. Moreover, conventional therapies were scarcely effective in *BRAF*^{V600E} mutant PLGG patients [40]. Thus, novel therapeutic strategies are needed for *BRAF*^{V600E} mutant gliomas.

Since *BRAF*^{V600E} triggers the constitutive activation of MAPK signaling pathway (Fig. 1), the latter has been proposed as a therapeutic target. An early preclinical study demonstrated that *BRAF* knockdown and pharmacological BRAF inhibition induce p-ERK inactivation and antiproliferative activity in *BRAF*^{V600E}-expressing, but not in wild-type *BRAF*-expressing malignant gliomas. The first-generation BRAF inhibitor, PLX4720, extended the overall survival in a *BRAF*^{V600E} mutant orthotopic xenograft model, indicating that *BRAF*^{V600E} is a promising therapeutic target in *BRAF*^{V600E}-expressing brain tumors [49].

Burger et al. demonstrated a durable response to dabrafenib (a first-generation BRAF inhibitor) in three patients with disseminated leptomeningeal *BRAF*^{V600E}-positive glioma. Of note, one patient was stable for up to 27 months. In addition, they established a patient-derived cell line and found that dabrafenib reduced the cell density and inhibited p-ERK [5], indicating that drug sensitivity is through on-target effect. A phase-1/2 clinical trial demonstrated that the objective response rate of dabrafenib is 38% in PLGG [13]. Another clinical trial for pediatric *BRAF*^{V600E} mutant relapsed/refractory PLGG demonstrated that dabrafenib was also effective (44% overall response rate) and tolerable (clinicaltrials.gov, NCT01677741). Another first-generation BRAF inhibitor, vemurafenib (a PLX4720 analog), controlled tumor progression in patients with recurrent PXA [7, 43]. In addition, a vemurafenib-based regimen decreased tumor size in patients with brain stem GG expressing the *BRAF*^{V600E} mutation [62]. In another study, all six *BRAF*^{V600E}-mutant PLGG patients favorably responded to BRAF inhibitors [40]. The VE-BASKET study, focusing on *BRAF*^{V600E}-mutant non-melanoma cancers, demonstrated the characterization of 24 patients with glioma received vemurafenib until disease progression. The objective response rate was 42.9% (3/7) in PXA, 9.1% (1/11) in malignant diffuse glioma, and 33.3% (2/6) in other tumors, including one pilocytic astrocytoma [32]. Another phase-2 basket study also indicated a 75% (3/4) response after vemurafenib monotherapy in PXA patients with the *BRAF*^{V600E} mutation [25].

Unfortunately, resistance to the BRAF inhibitor is frequently observed due to MAPK pathway reactivation, which is mediated by RAF-independent activation of MEK and ERK [69]. Additionally, acquired gene alterations conferring drug resistance, including *NRAS, BRAF, MEK1*, and *MEK2*, were identified after treatment with BRAF inhibitors [71]. In contrast, combined BRAF/MEK inhibition was reported to block p-ERK signaling and prevent the acquisition of resistance in melanoma cell lines [54]. In addition, a phase-1/2 clinical trial demonstrated that a

combination of dabrafenib and trametinib (MEK inhibitor) prolonged progression-free survival (PFS) in patients with metastatic melanoma [44]. Various phase-3 studies demonstrated improved overall survival after treatment of naïve unresectable or metastatic melanoma patients with *BRAF*^{V600E} mutation [45, 60]. Similar combination effects were also observed in other solid cancers, including colorectal cancer [12].

Consistently, whereas monotherapy with a BRAF inhibitor results in transient MEK-ERK inhibition in BRAF^{V600E} mutant glioma cell lines, combined BRAF/MEK inhibition prevented MAPK reactivation, resulting in enhanced antitumor effects, both in vitro and in vivo [77]. Moreover, in a *BRAF*^{V600E} mutant-expressing glioma cell line, combined BRAF/MEK inhibition was found to be more effective compared to the combination between BRAF and mTOR inhibitors (everolimus) or that between an MEK1/2 inhibitor (AZD6244) and everolimus [51]. A higher efficacy of the combined BRAF/MEK inhibition was also observed in a *BRAF*^{V600E} mutant-expressing and *CDKN2A*-deficient syngenic mice glioma model [21], which is considered a high-risk group in *BRAF*^{V600E} mutant PLGG [40]. Brown et al. reported a clinical–radiological response in two cases of anaplastic PXA treated with a combination of BRAF and MEK inhibitors [4]. Another group described the results of BRAF/MEK inhibitor treatment of two patients with *BRAF*^{V600E}-positive tumors (one anaplastic PXA and one glioblastoma (GBM)) after conventional treatment. Accordingly, the anaplastic PXA case exhibited a partial response for 14 months, although progression was observed thereafter. On the other hand, the GBM patient was stable after 16 months of treatment [66]. In a phase-2 open-label trial (clinicaltrials.gov, NCT02034110), patients with the *BRAF*^{V600E} mutation received dabrafenib plus trametinib until unacceptable toxicity, disease progression, or death. In that study, 37 high-grade glioma (HGG) patients were enrolled, 31 of whom were evaluable for response. The overall response rate was 26% (8/31), including one complete response. Of note, five of eight (62.5%) responding patients exhibited a response duration of more than 12 months. A global, open-label phase-2 study (clinicaltrials.gov, NCT02684058), evaluating dabrafenib in combination with trametinib in pediatric patients with *BRAF*^{V600E}-mutant HGG, is currently ongoing, as well as a phase-1/2 study employing the trametinib/dabrafenib combination in PLGG (clinicaltrials.gov, NCT02124772). In addition to MAPK pathway reactivation, it has been demonstrated that resistance to BRAF inhibitors may occur through activation of the EGFR signaling pathway in glioma [74]. Therefore, a combination of BRAF inhibition and EGFR target therapy might be an alternative therapeutic option for *BRAF*^{V600E}-mutant glioma.

Target for *KIAA1549-BRAF* fusion gliomas

Importantly, a paradoxical activation of MAPK signaling after treatment with PLX4720 (first-generation BRAF inhibitor) was reported in *KIAA1549-BRAF* fusion cells [68]. Similarly, sorafenib, a multi-kinase inhibitor targeting BRAF, VEGFR, PDGFR, and c-kit induced MAPK-dependent stimulation of tumor growth, mostly in recurrent/progressive PLGGs carrying the *BRAF1549-KIAA* fusion [33]. To overcome this issue, a second-generation BRAF inhibitor was developed and found to prevent the paradoxical MAPK activation [68]. However, another study reported that after treatment with the second-generation BRAF inhibitor, PLX8394, inhibitor-resistant cells emerged because of PI3K/AKT/mTOR pathway activation in cells stably expressing the *KIAA1549-BRAF* fusion [27], further emphasizing the difficulty in controlling *KIAA1549-BRAF* fusion tumors using a single BRAF inhibitor.

In addition to the BRAF inhibitor, the MEK1/2 inhibitor demonstrated antitumor effect in a *BRAF*^{V600E} mutant xenograft model [38]. A phase-1 Pediatric Brain Tumor Consortium study indicated that selumetinib (AZD6244, MEK1/2 inhibitor) displays promising antitumor activity in PLGG [1]. Currently, selumetinib effects are under examination in young patients with recurrent or refractory LGG (clinicaltrials.gov, NCT01089101). Preliminary results indicated partial response in 29% (2/7) of *BRAF*^{V600E} mutant tumors and 33% (6/18) of tumors carrying the *BRAF-KIAA1549* fusion.

A preclinical study demonstrated that the *KIAA1549-BRAF* fusion regulates neuroglial cell growth in an mTOR-dependent manner [34], implying that targeting of mTOR and downstream pathways may be another suitable therapeutic strategy for *KIAA1549-BRAF* fusion tumors. Notably, *KIAA1549-BRAF*-containing cells were sensitive to the MEK1/2 inhibitor, AZD6244, and the combination of AZD6244 and everolimus-induced enhanced effect, when compared with *BRAF* wild-type cells [51]. AZD6244 and everolimus reduced p-ERK and p-S6, respectively, and combination treatment enhanced suppression in both signaling [51]. Additionally, an acquired PI3K/AKT/mTOR pathway-mediated resistance to the MEK inhibitor emerged in *KIAA1549-BRAF* fusion cells, whereas the combination treatment of MEK and mTOR inhibitors enhanced cell toxicity in vitro and in vivo [27].

NF1 mutation targeting in pediatric gliomas

The *NF-1* gene encodes neurofibromin, a negative regulator of Ras activity, and loss of NF-1 leads to Ras dysregulation and activation of downstream pathways, including MAPK and PI3K pathway, as well as tumorigenesis [59]. Initial preclinical experiment demonstrated that an MEK inhibitor sensitized an *NF-1*-deficient acute myeloid leukemia model

[41]. Of note, the MEK1/2 inhibitor, selumetinib, decreased tumor size in 71% (17/24) of NF-1-related pediatric plexiform neurofibromas [16]. Therefore, Ras–MAPK signaling may be a novel therapeutic target in gliomas carrying the *NF-1* mutation. See et al. demonstrated that *NF-1* deficiency is associated with MEK inhibitor sensitivity in GBM cell lines and an MEK inhibitor (PD0325901) suppressed *NF-1*-deficient GBM orthotopic xenograft formation. In addition, they found that inhibition of PI3K/AKT/mTOR signaling enhanced the sensitivity to MEK inhibition [67]. In the NCT01089101 trial, 10 of 25 (40%) NF-1-associated LGGs under treatment with selumetinib achieved partial response, with a 2-year PFS of 96%. Further large-scale studies are required to establish the efficacy of MEK inhibition in *NF-1*-deficient PLGG.

In addition, it has been demonstrated that the NF-1-related mTOR pathway regulates glial cell growth and gliomagenesis [2]. Kaul and colleagues reported that the growth of *NF-1*-deficient optic glioma is suppressed by both AKT- or MEK-mediated mTOR inhibition in vitro and in vivo [35]. Moreover, rapamycin suppressed the proliferation of NF-1+/-^{GFAP}CKO mice optic glioma [24]. Interestingly, when an mTOR inhibitor and the tyrosine kinase inhibitor, erlotinib, were tested on recurrent PLGG, two NF-1 patients had disease control for more than 1 year [73]. A phase-2 study employing everolimus for recurrent or progressive low-grade gliomas, with or without *NF-1* deficiency, is currently recruiting patients (clinicaltrials.gov, NCT01734512).

Other molecular targets in pediatric gliomas

A breakthrough in molecular target therapy has been the employment of everolimus for tuberous sclerosis-associated SEGA. SEGAs are the most common brain tumors in TSC and occur in 5–20% of these patients. Mutations in *TSC1* (hamartin) or *TSC2* (tuberin) upregulate the mTOR complex 1, leading to cell proliferation in SEGA, raising the possibility that mTOR inhibitor may be a specific therapeutic agent. Several case reports demonstrated that rapamycin caused the regression of TSC-related astrocytomas [19, 37]. Importantly, large clinical trials (ClinicalTrials. gov number, NCT00789828, NCT00411619, and NCT01713946) indicated that everolimus reduced tumor volume and seizure frequency in patients with TSC-associated SEGA [18, 20, 39]. Additionally, treatment with everolimus provided long-term clinical benefit to patients with SEGA [17].

Furthermore, recurrent genetic alterations, such as those involving *NTRK, FGFR1*, and *MYB*, were identified in PLGG and are promising therapeutic targets [29, 56, 76]. Receptor tyrosine kinase tropomyosin-related A, B, and C (TRKA, TRKB, and TRKC) are encoded by *NTR1, NTRK2*, and *NTRK3*, respectively. These *NTRK* oncogenic fusions lead to downstream activation of signaling pathway, including the PI3K pathway and MAPK pathway [36].

Various inhibitors targeting TRK family members have been developed and tested in clinical trials. In 2018, the U.S Food and Drug Administration (FDA) approved the use of larotrectinib for solid tumors containing *NTRK* gene fusions. Importantly, larotrectinib led to dramatic tumor regression in a pediatric HGG patient with *ETV6-NTRK3* fusion [78]. Clinical trials testing larotrectinib for *NTRK* fusion-positive solid tumors, including brain tumors, are currently ongoing (NCT02576431). Further studies are required to assess the therapeutic potential of TRK inhibition in PLGG.

Recurrent *FGFR1* mutations (hotspot residues at N546 and K656), as well as *PTPN11* mutations, were identified in a subset of PAs [29]. Moreover, duplication of the FGFR1 tyrosine kinase domain and *FGFR1-TACC* fusion were identified in PLGG [76]. These mutations were found to be mutually exclusive with RAF/RAS alterations and also result in MAPK pathway activation [29]. Anti-FGF/FGFR targeting drugs have been introduced and are being tested in clinical trials [6, 15].

In summary, large-scale genomic analyses uncovered the genetic landscape of pediatric low-grade gliomas, which are distinct from adult gliomas. Since most of the PLGGs harbor gene alterations that activate the MAPK pathway, the efforts to develop a therapeutic strategy targeting this pathway are intensifying. The results of several ongoing clinical trials are expected to improve PLGG patients' outcome by novel molecular target therapies.

Compliance with ethical standards

Conflict of interest The authors declare no potential conflict of interest.

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