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The FGF/FGFR System in the Biology and Therapeutic Landscape of Pediatric CNS Tumors

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ABSTRACT

Central nervous system (CNS) tumors are the most common solid malignancies in children, comprising a highly heterogeneous group of neoplasms defined by distinct molecular alterations and clinical behaviors. Advances in molecular genetics have underscored the relevance of specific signaling pathways in driving pediatric tumorigenesis, among which the fibroblast growth factors (FGFs) and their receptors (FGFRs) have emerged as critical regulators of CNS development and tumor biology. The strict regulation of this system is frequently disrupted in cancer contexts, leading to abnormal activation that promotes tumor growth, invasion, and therapy resistance. Recent genomic profiling studies confirm that *FGFR* gene aberrations (i.e., activating point mutations, amplifications, and fusions) occur in a non-negligible fraction of pediatric CNS tumors. Notably, *FGFR* alterations are found in approximately 9% of pediatric gliomas, representing a higher incidence compared to adult gliomas. Across a broader survey of pediatric solid and brain tumors, activating FGFR aberrations were measurable in approximately 3% of cases. This prevalence establishes the FGF/FGFR axis as a measurable therapeutic vulnerability in defined patient subsets. Therefore, a deeper understanding of the role of the FGF/FGFR system across different pediatric CNS tumor subtypes is essential for elucidating disease mechanisms and identifying novel therapeutic opportunities. This review outlines the characteristics of major pediatric CNS tumors and discusses the role and potential therapeutic targeting of the FGF/FGFR system.

1 | Introduction

Central nervous system (CNS) tumors represent the most common solid malignancies in children and encompass a highly heterogeneous group of neoplasms [1, 2]. Their diversity reflects differences in histopathology, molecular alterations, developmental origin, and clinical behavior. Pediatric CNS tumors include embryonal tumors such as medulloblastoma, gliomas

Abbreviations: BDNF, brain-derived neurotrophic factor; CAFs, cancer-associated fibroblasts; CAMs, cell adhesion molecules; ClpP, caseinolytic protease P; CNS, central nervous system; CV, carboplatin and vincristine; DFMO, difluoromethylornithine; DHGs, diffuse hemispheric gliomas; DIPG, diffuse intrinsic pontine glioma; DMGs, diffuse midline gliomas; DRD2, dopamine receptor D2; ECM, extracellular matrix; EFS, event-free survival; EGL, external granule layer; EPN, ependymoma; EZHIP, enhancer of zeste homolog inhibitory protein; FGF, fibroblast growth factor; FGFR, fibroblast growth factor receptor; FRS2, FGFR substrate 2; GNP, granule neuron precursor; GPCR, G protein coupled receptor; HSPGs, heparan sulfate proteoglycans; IDH, isocitrate dehydrogenase; LOH, loss of heterozygosity; LRL, lower rhombic lip; MB, medulloblastoma; MBEN, MB with extensive nodularity; NF2, neurofibromatosis type 2; NGF, nerve growth factor; ODC, ornithine decarboxylase; PF, posterior fossa; pHGGs, pediatric-type diffuse high-grade gliomas; PKC, protein kinase C; PLCγ, phospholipase Cγ; pLGGs, pediatric-type diffuse low-grade gliomas; PLNTY, polymorphous low-grade neuroepithelial tumor of the young; PR, progesterone receptor; RTK, receptor tyrosine kinase; SHH, sonic hedgehog; SP, spinal; ST, supratentorial; TK, tyrosine kinase; TKIs, TK inhibitors; URL, upper rhombic lip; WHO, World Health Organization.

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ranging from low- to high-grade, ependymomas, and other less frequent entities, each characterized by distinct biological and prognostic profiles [3].

Over the past decade, advances in molecular genetics have reshaped their classification, underscoring the relevance of signaling pathways in driving tumorigenesis and influencing therapeutic response. Among these pathways, the fibroblast growth factors (FGFs) and their receptors (FGFRs) have emerged as critical regulators of CNS development and tumor biology [4, 5]. Indeed, recent genomic profiling studies have reported that *FGFR* gene aberrations occur in a non-negligible fraction of pediatric CNS tumors [6]. A deeper understanding of the role of the FGF/FGFR system across different pediatric CNS tumor subtypes is, therefore, essential for elucidating disease mechanisms and identifying novel therapeutic opportunities.

In this review, we will consider the major pediatric tumors of the CNS outlining their main characteristics and discussing the role of the FGF/FGFR system in the pro-tumor mechanisms of these cancers, as well as its potential targeting as a novel therapeutic option.

2 | The FGF/FGFR System

2.1 | FGF/FGFR System Biology

Comprising 22 members classified by sequence homology and biological activity into three functional groups and seven subfamilies, the FGF family is one of the most heterogeneous groups of growth factors in vertebrates [7, 8]. Canonical FGFs are secreted factors acting as local paracrine signaling molecules, while the hormone-like FGFs act as endocrine factors that control metabolic homeostasis [7, 9, 10]. On the other hand, the so-called intracellular FGF subfamily consists of non-secreted factors mainly involved in neuronal development and in regulating the electrical excitability of neurons [9, 11]. Both canonical and hormone-like FGFs mediate their biological functions by activating cell surface tyrosine kinase (TK) receptors, encoded in mammals by four distinct genes (FGFR1-4), which, through alternative splicing events, generate seven receptor isoforms with distinct ligand-binding properties [11] (Figure 1A). Structurally, FGFRs present an extracellular domain, a transmembrane domain, and an intracellular TK tail, which is responsible for FGF-related signaling [15, 16]. Receptor dimerization provides docking sites for downstream signaling molecules, such as the specific adapter protein FGFR substrate 2 (FRS2) and phospholipase Cγ (PLCγ). FRS2 phosphorylation drives the activation of the RAS-MAPK pathway, resulting in proliferation, differentiation, or cell cycle arrest. On the other hand, activation of PLCγ results in the activation of protein kinase C (PKC), promoting cell migration [7, 17] (Figure 1A).

Due to its widespread tissue expression and its mediation of such a wide range of cellular activities, the FGF/FGFR system plays key regulatory roles in the earliest stages of embryonic development and during organogenesis. In the adult, the FGF/FGFR system exerts homeostatic functions, being involved in tissue repair, metabolism, and remodeling processes [10, 16]. Given its ubiquitous and extensive biological activities, the FGF/FGFR system requires tight regulation at different levels. Ligand-receptor binding specificity and spatiotemporal expression of FGFs, FGFRs, and HSPGs are necessary to avoid aberrant or inappropriate activation. Epigenetic mechanisms, small noncoding RNAs, and post-translational modifications are also involved in the regulation of FGF/FGFR signaling component expressions [7, 18]. At the extracellular level, the interaction of FGFs with HSPGs and other FGF-binding proteins modulates ligand availability [11, 19], while receptor exposure on the cell membrane is affected by FGFR internalization, degradation, and recycling following activation [20]. Furthermore, negative feedback mechanisms occur at the intracellular level in response to FGF/FGFR activation, including induction of MAPK phosphatases and/or negative modulators (e.g., sprouty proteins), which act at different levels of the signaling cascade [17, 21].

2.2 | FGF/FGFR System in Cancer

In cancer contexts, the strict regulation of the FGF/FGFR system is frequently disrupted, leading to its abnormal activation in both the neoplastic and stromal compartments, thus promoting tumor growth, invasion, angiogenesis, metastatic spread, and therapy resistance [7, 22]. FGFR aberrations are widely distributed in all malignant tumors, and include gene amplification, translocations, and dysregulation of transcriptional control mechanisms, which results in FGFR overexpression [7, 18] (Figure 1B). Moreover, FGFR-activating mutations and the generation of fusion protein following gene rearrangements can induce ligand-independent receptor dimerization and aberrant signaling activation [23, 24]. On the other hand, FGF overexpression by cancer cells or by the surrounding stroma results in signaling hyperactivation, thereby sustaining tumor growth through autocrine/paracrine mechanisms [24]. Besides their protumor activity exerted on cancer cells, tumor-derived FGFs drive tumor–stroma interactions, sustaining the formation of a pro-tumor microenvironment. Accordingly, FGFs have been reported to promote angiogenesis [12], activate cancer-associated fibroblasts (CAFs) [25], and recruit tumor-associated macrophages, thus supporting tumor progression and immune evasion [26, 27].

2.3 | Anti-FGF/FGFR Therapeutics

Given its pivotal role in cancer progression, the FGF/FGFR system constitutes a promising target for the development of anticancer therapies. To date, FGF/FGFR targeting approaches include: (i) TK inhibitors (TKIs), (ii) monoclonal antibodies (mAbs), and (iii) FGF traps (Table 1) [22, 23]. First-generation multitarget or non-selective tyrosine kinase inhibitors (TKIs) [12, 24, 26], such as dovitinib (TKI258), ponatinib, nintedanib, lenvatinib, regorafenib, pazopanib, sorafenib, sunitinib, cediranib, and lucitanib, were initially developed to simultaneously inhibit multiple TK receptors, including VEGFR and PDGFR, by competing with ATP at the intracellular kinase domain [22]. While this broad-spectrum activity may provide combinatorial pathway suppression, these agents typically display suboptimal potency against FGFRs and are associated with significant off-target toxicities, including hypertension, proteinuria, and

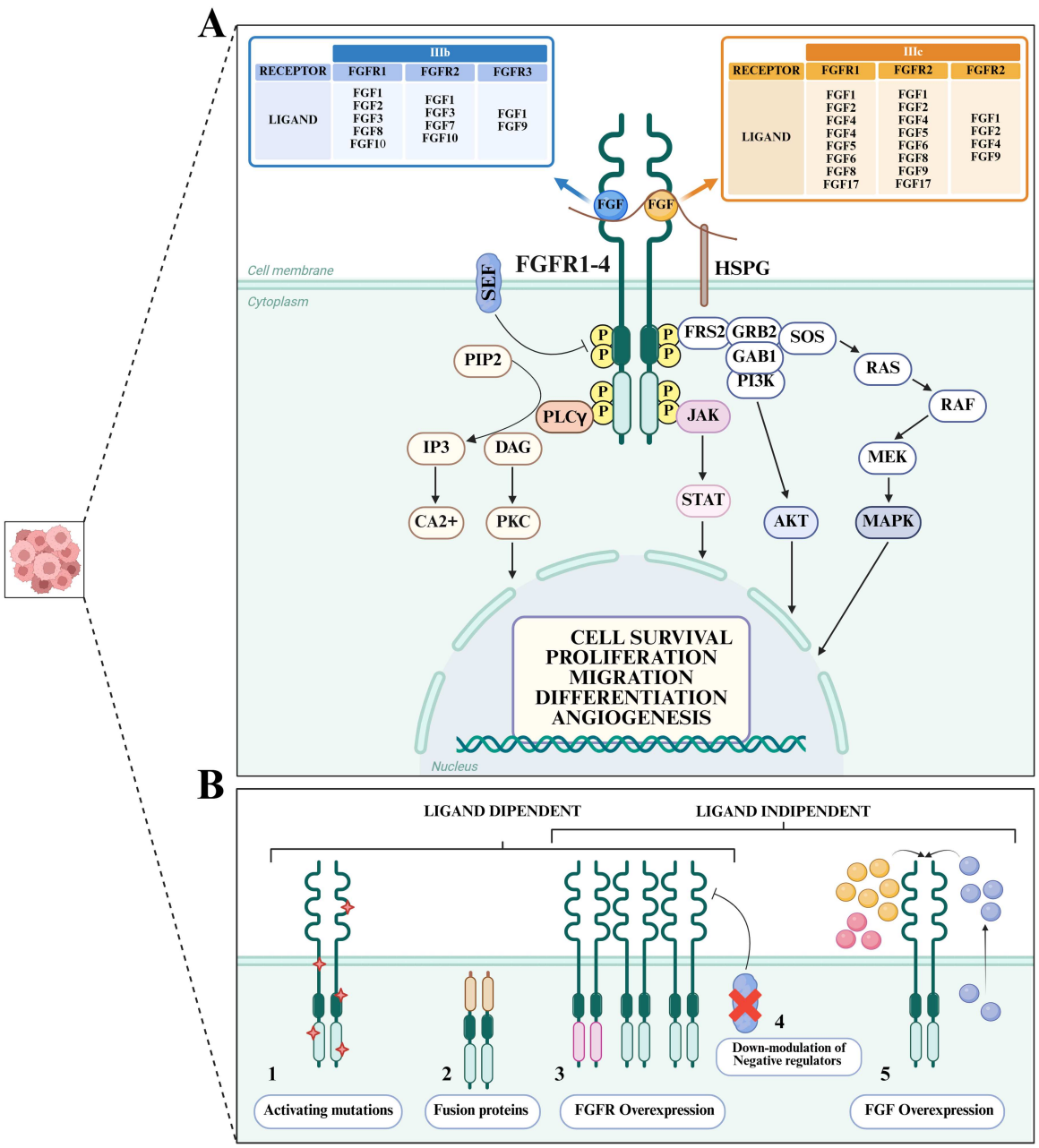

FIGURE 1 | FGFR/FGF Signaling Pathways in cancers. (A) FGFs bind to FGFRs, initiating receptor dimerization and transphosphorylation of the tyrosine kinase (TK) domain. This activation facilitates the recruitment of adapter proteins, triggering multiple downstream signaling cascades. Binding specificity between FGFs and FGFRs is here specified for the IIIb and IIIc splice variants and is influenced by co-factors like heparan sulfate proteoglycans (HSPGs), which stabilize ligand–receptor interactions. While FGFR signaling can be inhibited by SEF (similar expression to FGF), which interferes with ligand binding. (B) Activating mutations (red diamonds) can arise within the extracellular, transmembrane, or TK domains of FGFRs (1). These mutations promote ligand-independent dimerization and persistent activation of the receptor. Structural chromosomal alterations may result in intragenic translocations, leading to the formation of FGFR fusion proteins (2). These chimeric proteins undergo spontaneous dimerization, driving constitutive FGFR signaling. FGFR overexpression can derive from gene amplification, chromosomal translocation, or dysregulated transcription (3). This overexpression is often accompanied by aberrant splicing at the C-terminal region (highlighted in pink), which can impair receptor internalization and cause its accumulation at the cell membrane. Downregulation of negative modulators such as SEF can enhance FGFR pathway activity by removing inhibitory constraints (4). Tumor cells may stimulate surrounding stromal cells to secrete FGFs (shown in orange), establishing a paracrine signaling loop (5). Additionally, cancer cells themselves can produce FGFs (light red), reinforcing signaling through autocrine mechanisms. Alterations in FGFR splicing patterns can lead to the expression of receptor isoforms with modified ligand-binding preferences (blue), resulting in dysregulated and imbalanced signaling (6). Adapted from [12–14]. *Created in BioRender. Ronca, R. (2026)* https://BioRender.com/aj9grce. [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 1 | Summary of the main FGF/FGFR system inhibitors available at preclinical and clinical level.

Drug type	Function	Mechanism of action	Examples/Clinical use
Tyrosine kinase inhibitors (TKIs)	Inhibit FGFR kinase activity and downstream oncogenic signaling	Small molecules blocking the ATP-binding site of FGFRs. • 1st generation: non-selective, off-target toxicity • 2nd generation: selective FGFR inhibition with improved safety	1st generation: Dovitinib, Ponatinib, Nintedanib, Lenvatinib, Regorafenib, Pazopanib, Sorafenib, Sunitinib, Cediranib, Lucitanib 2nd generation: Erdafitinib (urothelial carcinoma) Pemigatinib (cholangiocarcinoma) Futibatinib (intrahepatic cholangiocarcinoma) Rogaratinib (FGFR mRNA overexpression) Derazantinib (cholangiocarcinoma) Infigratinib (cholangiocarcinoma) AZD4547 (breast Cancer) Debio 1347 (gastrointestinal cancer) Fisogatinib (hepatocellular carcinoma) Roblitinib (hepatocellular carcinoma)
Monoclonal antibodies (mAbs)	Block FGF/FGFR interaction	High-affinity antibodies targeting specific FGFs or FGFR isoforms, preventing receptor activation and signaling	Bemarituzumab (anti-FGFR2b, advanced gastric/gastroesophageal cancer) Vofatamab (anti-FGFR3) MGFR1877S (anti-FGFR3) GP369 (anti-FGFR2-IIIb) GAL-F2 (anti-FGF2) KM1334 (anti-FGF8b)
FGF traps	Neutralize multiple FGFs and inhibit tumor–stroma communication	Soluble decoy receptors or small molecules sequestering extracellular FGFs to block receptor engagement and signaling	FP-1039 (soluble fusion protein) NSC12 (PTX3-derived small molecule) sFGFR3 (bind canonical FGFs) SM27 (bind FGF2) LHT7 (mimics heparan sulfate interactions)
Allosteric inhibitors	Bind to the extracellular domain of FGFR	Modulate receptor activity without directly competing with ligand binding, thereby inducing a partial inhibitory effect that preserves basal signaling	SSR128129E

cardiovascular effects, largely attributable to VEGFR inhibition [12]. The development of second-generation selective FGFR TKIs has therefore aimed to enhance target specificity and improve tolerability. Among pan-FGFR inhibitors, erdafitinib (JNJ-42756493) [23] is a potent, reversible inhibitor of FGFR1-4 and has received regulatory approval for urothelial carcinoma harboring FGFR alterations, whereas futibatinib (TAS-120) [28] represents an irreversible covalent inhibitor that binds a conserved cysteine residue within the kinase domain, conferring activity against certain resistance-associated mutations. Other pan-FGFR inhibitors include rogaratinib (BAY 1163877) [29] and derazantinib (ARQ-087) [30], both showing promising efficacy and safety profiles in phase I/II clinical trials on advanced solid tumors [23]. Among FGFR1-3 selective inhibitors, infigratinib (BGJ398) [23] and pemigatinib (INCB054828) [23] are orally bioavailable agents with demonstrated clinical efficacy, the latter approved for FGFR2 fusion-positive cholangiocarcinoma. Additionally, AZD4547 [31] is characterized by a flexible ("plastic") binding mode that allows interaction with multiple receptor conformations, and Debio 1347 (CH5183284) [22], a highly selective compound under clinical investigation. On the other hand, FGFR4-specific inhibitors, such as fisogatinib (BLU-554) [32] and roblitinib (FGF401) [33], have been developed to target FGF19-driven hepatocellular carcinoma, exploiting the restricted physiological role of FGFR4. Despite these advances, class-specific toxicities remain prominent, particularly hyperphosphatemia resulting from inhibition of FGFR1-mediated FGF23 signaling, along

with dermatologic and mucosal adverse effects [12, 28]. Moreover, acquired resistance frequently arises through gatekeeper mutations (e.g., V561M in FGFR1 or V555M in FGFR3) that sterically hinder drug binding [7, 27].

Monoclonal antibodies (mAbs) provide an alternative extracellular targeting strategy with high isoform specificity. For instance, both bemarituzumab (FPA144) [34] and GP369 [35] selectively bind FGFR2-IIIb and suppress ligand-dependent receptor phosphorylation, while bemarituzumab has been specifically engineered to enhance antibody-dependent cellular cytotoxicity (ADCC) [36]. Likewise, vofatamab [23] targets FGFR3 hampering its activation, while MGFR1877S [7] interferes with FGFR3 dimerization. Antibodies directed against FGF ligands, such as GAL-F2 (anti-FGF2) [37] and KM1334 (anti-FGF8b) [38], further expanded this approach. However, their limited efficacy as monotherapy and the need for combination with chemotherapy or immunotherapy, together with toxicity concerns (notably severe weight loss observed with FGFR1-targeting agents due to hypothalamic effects), constrain their broader application. Ligand traps, including soluble decoy receptors such as FP-1039 (GSK3052230) [39], a fusion protein comprising the extracellular domain of FGFR1-IIIc linked to an IgG1 Fc fragment, and experimental constructs like soluble FGFR3 (sFGFR3) [40], function by sequestering canonical FGFs in the extracellular space, thereby preventing receptor activation. In parallel, small-molecule and peptide-based traps, such as NSC12 (a pan-FGF trap) [41], SM27 (an FGF2-binding compound derived from thrombospondin-1) [42], and polysulfated agents including pentosan polysulfate and heparin mimetics (e.g., LHT7) [43], mimic heparan sulfate interactions to inhibit ligand availability. Nonetheless, the inability of certain ligand traps, such as FP-1039, to neutralize endocrine FGFs (e.g., FGF23) may represent both a safety advantage and a therapeutic limitation in tumors driven by these ligands. Finally, allosteric inhibitors, exemplified by SSR128129E [44] bind to the extracellular domain of FGFR and modulate receptor activity without directly competing with ligand binding, thereby inducing a partial inhibitory effect that preserves basal signaling. This "ceiling effect" may maintain cellular homeostasis and reduce adverse events, highlighting a promising direction for next-generation FGFR-targeted therapies.

Representative chemical structures of the most relevant FGFR inhibitors discussed in this review are summarized in Figure 2, highlighting the structural diversity of currently available ATP-competitive kinase inhibitors.

2.3.1 | *Experimental and Clinical Data*

The experimental and clinical data provide a more nuanced picture. Infigratinib has been described as a brain-penetrant FGFR inhibitor; nevertheless, preclinical and clinical observations indicate that its activity in gliomas may be transient, suggesting that achieved intracerebral concentrations may be insufficient for sustained therapeutic efficacy [6]. Consistently, a phase II study in recurrent gliomas reported a low objective response rate [45]. Similarly, AZD4547, despite its potent FGFR inhibitory activity, has shown limited efficacy in glioma trials, a finding that may be partly attributable to suboptimal brain penetration or to intrinsic resistance mechanisms [31].

For other agents, evidence of BBB permeability remains indirect. Erdafitinib, for example, has not been formally characterized in terms of CNS pharmacokinetics, yet clinical observations in glioblastoma patients harboring FGFR3–TACC3 fusions have shown tumor growth deceleration and disease stabilization, suggesting at least partial CNS activity [45]. Pemigatinib has also demonstrated activity in FGFR-altered CNS tumors, with partial responses reported in selected cases [23]. Dovitinib has been proposed to cross the BBB, although robust clinical validation is still lacking [46]. Conversely, ponatinib appears to have limited brain penetration, as it is a known substrate of efflux transporters such as P-glycoprotein (P-gp) and ABCG2, which actively restrict drug accumulation within the CNS [46]. Notably, Debio 1347 has shown encouraging disease control in a small pediatric cohort, although data remain preliminary [45].

Importantly, BBB permeability in brain tumors is not a static parameter but rather a dynamic feature influenced by multiple factors [42, 43]. Tumor-associated disruption of BBB integrity, frequently observed in high-grade gliomas and various CNS cancers, may facilitate drug entry, partially compensating for otherwise poor penetration. In parallel, the activity of efflux transporters, including P-gp and breast cancer resistance protein (BCRP), represents a major barrier to effective CNS drug delivery and is not accounted for by passive diffusion models.

Overall, these considerations highlight the need for dedicated pharmacokinetic and pharmacodynamic studies specifically designed to assess CNS drug exposure, including measurements in cerebrospinal fluid and tumor tissue. Such investigations are particularly warranted in pediatric populations, where data remain scarce. A more precise characterization of BBB penetration will be essential to optimize the clinical development and therapeutic positioning of FGFR-targeted agents in CNS malignancies.

3 | Pediatric CNS Tumors and FGF/FGFR

It has been widely reported that members of the FGF family play multiple roles in the formation of the CNS [5]. Indeed, in the brain, 10 members of the FGF family have been reported to be expressed [47]. Among these, FGF3, FGF8, FGF15, FGF17, and FGF18 play crucial roles during early brain development by providing positional cues and regulating gene expression involved in brain patterning [48]. In adulthood, FGFs primarily function as homeostatic factors, contributing to tissue repair and cellular proliferation. Several FGFs and their corresponding receptors have been implicated in the pathogenesis of neurological disorders such as Parkinson's and Alzheimer's disease [4]. FGFR1 is the most abundant receptor within the nervous system, showing predominant expression in neurons, astrocytes, and radial glial cells [49]. FGFR2 and FGFR3, on the other hand, are preferentially expressed in astrocytes and oligodendrocytes [47].

Genetic abnormalities and dysregulation of FGFRs are increasingly being investigated in pediatric cancers [50]. Although genomic alterations of FGFR genes are rare in pediatric tumors, being found in only 0.2% to 0.3% of cases [51–54],

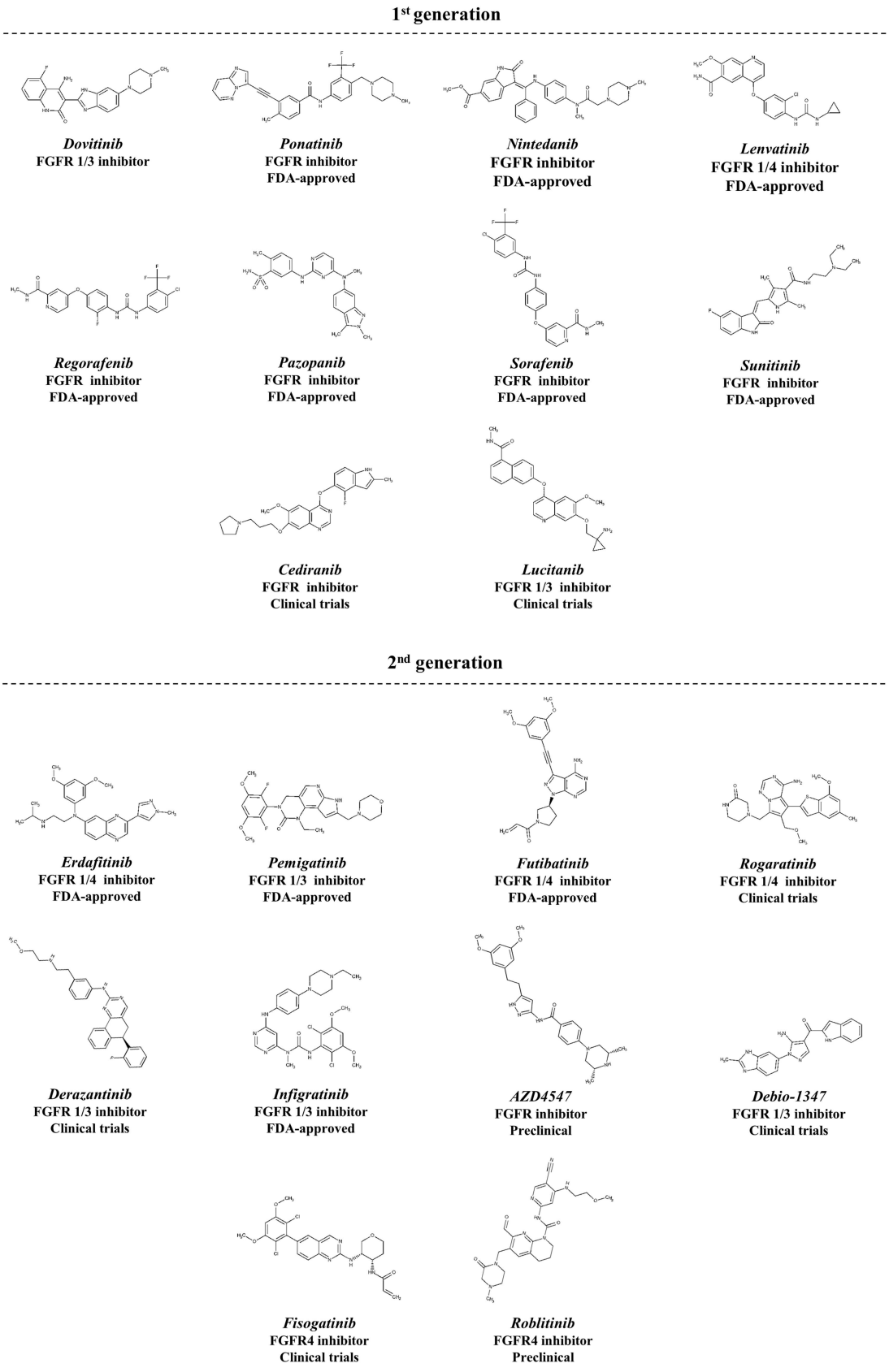

FIGURE 2 | Legend on next page.

high expression levels of FGFR1, FGFR2, and FGFR3 are associated with a worse prognosis, even when genomic alterations are absent [54, 55].

Most FGFRs (and mainly FGFR1) are expressed in the most common pediatric cancers of the CNS, as revealed by a dataset analysis performed by our group (Figure 3). Moreover, recent genomic profiling studies indicate that aberrations in FGFR genes occur in a non-negligible fraction of pediatric CNS tumors. In a large analysis of gliomas ($n = 11{,}635$, including 1344 pediatric cases), ~5.3% of all gliomas harbored FGFR alterations, with a higher incidence in pediatric gliomas (~8.9%) compared to adult tumors [6]. In a broader survey of 1395 pediatric solid and brain tumors, activating FGFR aberrations (including mutations, amplifications, and fusions) were identified in approximately 3% of cases [53]. Among specific FGFR family members, FGFR1 alterations were the most frequent in pediatric gliomas, FGFR2 and FGFR3 alterations were less common, and FGFR4 alterations were relatively rare [54]. Thus, while FGF/FGFR pathway dysregulation is not pervasive, it is clearly measurable, ranging from approximately 3% to 9% depending on tumor subtype and grade, suggesting a subset of pediatric CNS tumors that may benefit from FGFR-targeted strategies.

The following sections will describe the main types of the most common pediatric CNS tumors, outlining their key biological characteristics and the currently available therapeutic approaches. In addition, the role of the FGF/FGFR system and its potential use as a therapeutic target will be discussed (Figure 4; Table 2).

3.1 | Medulloblastoma

Medulloblastoma (MB) is an aggressive neuroectodermal tumor of the cerebellum and represents the most common malignant brain tumor of childhood, accounting for approximately 25% of all intracranial tumors in children [56, 57]. Diagnosis occurs mainly in children aged between 3 and 9 years, although in some individuals MB can also occur during adulthood [56]. In children, MB typically originates in the cerebellar vermis and often spreads into the fourth ventricle, while in adults, it usually arises from the cerebellar hemispheres. The main cause of death in MB patients is tumor relapse, which is estimated to occur in 30%–40% of the cases [58]. Indeed, around 30% of MB patients at diagnosis present metastatic disease with mainly focal or multifocal localization within the spinal and intracranial leptomeninges [59]. Advances in methylomic and transcriptomic analyses have reshaped our understanding of MB, now recognized as a biologically heterogeneous disease rather than a single entity [60–62]. At the molecular level, the updated World Health Organization (WHO) framework defines four principal genetic subgroups: WNT-activated, SHH-activated (further stratified by TP53 status), and non-WNT/non-SHH MB, which include the Group 3 and Group 4 [63]. Survival outcomes differ substantially among subtypes, with the most aggressive forms having an overall survival rate of 55%, while less aggressive forms may reach a survival rate of 95% [61–64]. Moreover, accumulating evidence has demonstrated that MB subgroups recapitulate the phenotypic and transcriptional programs of distinct cerebellar progenitor cell populations, thereby establishing a strong link between tumor biology and specific developmental lineages within the embryonic cerebellum [65, 66].

3.1.1 | *Treatment of Medulloblastoma*

MB is managed through a multimodal approach comprising maximal safe surgical resection followed by adjuvant radiotherapy and/or chemotherapy [67, 68]. Risk stratification into standard- and high-risk categories is central to define prognosis and therapeutic intensity, while infant MB is recognized as a separate clinical entity due to distinct biological and therapeutic considerations. Chemotherapy has further improved outcomes when added to surgery and radiotherapy, and the most frequently employed regimens include vincristine in combination with cisplatin and lomustine, or with cisplatin and cyclophosphamide. Despite these advances, conventional therapy is associated with substantial neurocognitive toxicity, and recurrence occurs in 30%–40% of patients [69, 70]. For these reasons, ongoing investigations aim to optimize risk-adapted therapy. For standard- and low-risk disease, efforts focus on treatment de-escalation to reduce late effects, whereas in high-risk disease, strategies emphasize biologically informed treatment intensification and incorporation of novel agents [67, 68]. These approaches are intended to reduce both treatment- and tumor-related morbidity and mortality across all patient groups [67]. Risk-adapted therapy in MB is increasingly guided by molecular subgrouping. WNT-activated tumors, and Group 4 are endowed with a good prognosis and are the focus of treatment de-escalation strategies [71, 72]. For SHH-MB, radiation-sparing regimens such as intraventricular or myeloablative chemotherapy have yielded encouraging outcomes, with efforts directed toward further de-intensification. Indeed, Group 3 tumors remain associated with poor survival (<60%) under standard

FIGURE 2 | Chemical structures of FGFR tyrosine kinase inhibitors currently approved or under clinical development. Representative chemical structures of first-generation multitarget FGFR tyrosine kinase inhibitors (TKIs) and second-generation selective FGFR inhibitors are shown. First-generation inhibitors are characterized by broad kinase selectivity and target multiple receptor tyrosine kinases, including FGFRs, VEGFRs and PDGFRs, whereas second-generation compounds were specifically developed to achieve greater FGFR selectivity and improved pharmacological profiles. The current clinical status of each inhibitor (Approved, Phase I, Phase II, or Preclinical) and its main FGFR selectivity profile are indicated below each compound. Chemical structures were obtained from DrugBank Online (DrugBank ID: DB05928 for Dovitinib; DrugBank ID: DB08901 for Ponatinib; DrugBank ID: DB09079 for Nintedanib; DrugBank ID: DB09078 for Lenvatinib; DrugBank ID: DB08896 for Regorafenib; DrugBank ID: DB06589 for Pazopanib; DrugBank ID: DB00398 for Sorafenib; DrugBank ID: DB01268 for Sunitinib; DrugBank ID: DB04849 for Cediranib; DrugBank ID: DB11845 for Lucitanib; DrugBank ID: DB12147 for Erdafitinib; DrugBank ID: DB15102 for Pemigatinib; DrugBank ID: DB15149 for Futibatinib; DrugBank ID: DB15078 for Rogaratinib; DrugBank ID: DB14889 for Derazantinib; DrugBank ID: DB11886 for Infigratinib; DrugBank ID: DB12247 for AZD4547; DrugBank ID: DB12903 for Debio-1347; DrugBank ID: DB16167 for Fisogatinib; DrugBank ID: DB16845 for Roblitinib; accessed July 2026). Adapted from DrugBank Online (https://go.drugbank.com; accessed July 2026).

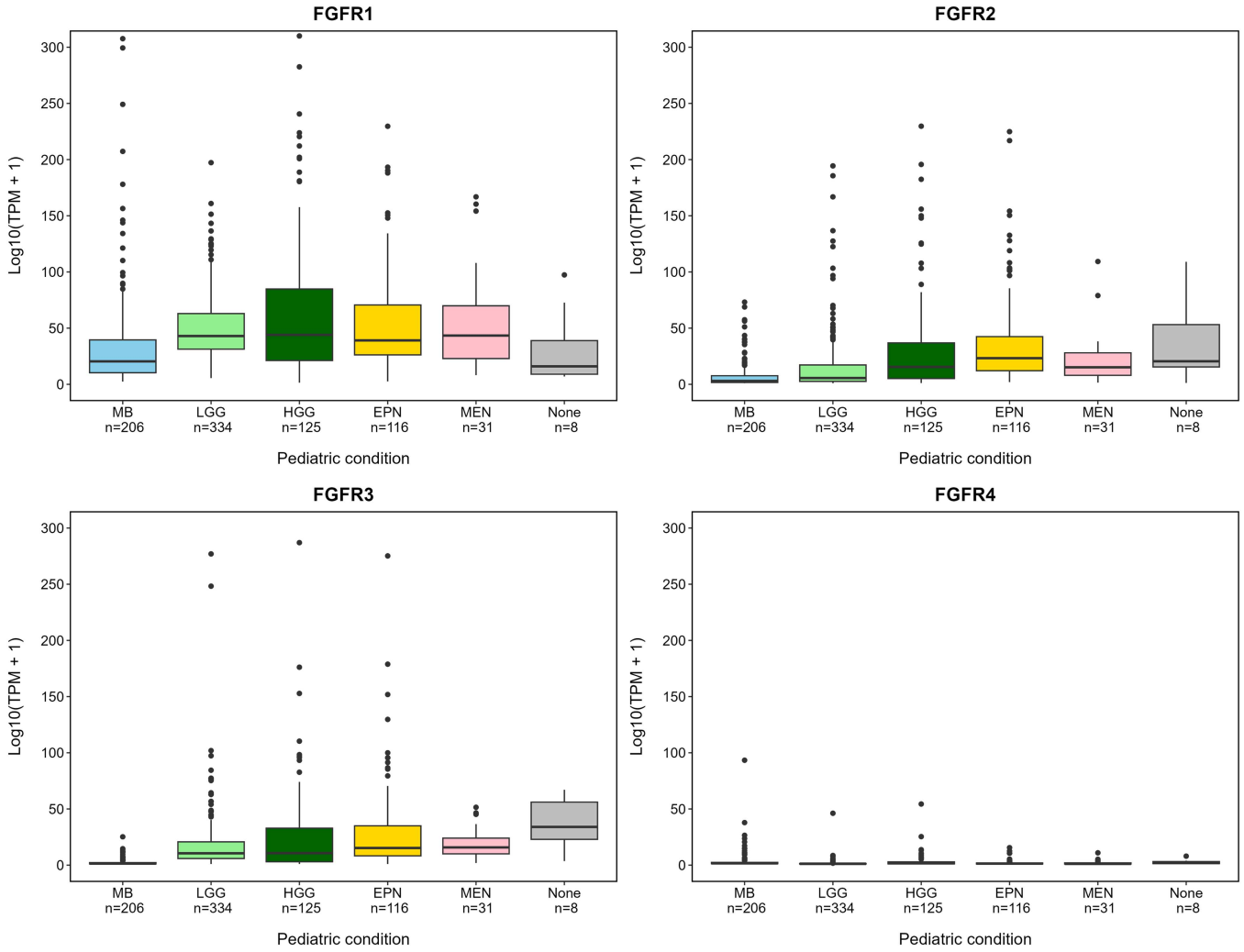

FIGURE 3 | Boxplots of the expression levels of FGFR1-4 across the selected pediatric CNS tumoral entities: Medulloblastoma (MB), low-grade glioma (LGG), high-grade glioma (HGG), Ependymoma (EPN), Meningioma (MEN) as compared to the not tumoral condition (None). This is an original figure generated by the Authors using publicly available RNA-seq datasets. Individual data points represent pediatric patient samples retrieved from publicly available datasets: open Pediatric Cancer Gene Expression for tumor entities and open Pediatric Brain Tumor Atlas (PBTA) and Expression Atlas for non-tumor pediatric conditions. Expression values were derived from RNA-seq data and log-transformed to normalize for skewness and facilitate comparison across genes and conditions. Data were plotted using the ggplot2 package in R. n = number of cases/patients. [Color figure can be viewed at wileyonlinelibrary.com]

therapy, and for high-risk non-infant patients, the addition of carboplatin during craniospinal irradiation improved outcomes in the ACNS0332 trial [58]. Promising therapeutic strategies include pemetrexed-gemcitabine combinations for MYC-amplified tumors (tested in the SJMB12 trial) [73], as well as CDK inhibitors and HDAC inhibitors, reflecting frequent chromatin and histone pathway alterations of the subgroup [74, 75].

3.1.2 | *FGF/FGFR System in MB*

Recurrent FGFR genomic alterations are uncommon in MB. Notably, two original cases of germline mutations in FGFR2 and FGFR3 were reported, accompanied by craniosynostosis, and associated with MB [76]. Additionally, a rare case described in 2018 involved a 23-month-old child, who developed anaplastic MB 5 months after successful treatment for stage IV neuroblastoma. DNA sequencing revealed both somatic mutations and germline variants in several cancer-related genes, including FGFR3 [77]. Despite the low frequency of such mutations, overexpression of FGFRs (particularly FGFR1 and FGFR3) and their corresponding FGF ligands has been observed in MB cohorts. Most of the existing evidence regarding the impact of FGF/FGFR signaling in MB is in the SHH-MB group. In contrast, data supporting its involvement in WNT, Group 3, or Group 4 MB are limited. In these subgroups, FGFR3 overexpression has been identified as a marker of treatment resistance, although the mechanisms underpinning this association remain largely unexplored. Notably, combination therapy using FGFR and PI3K inhibitors was evaluated across multiple MB cell lines (DAOY, UW228-3, Med8a, D425, and D283), resulting in enhanced sensitivity in all models, most prominently in chemotherapy-resistant cell lines [78].

In the context of SHH-MB, the role of FGF2 remains controversial. Indeed, conflicting findings regarding its impact on tumor growth, invasiveness, and modulation of Hedgehog

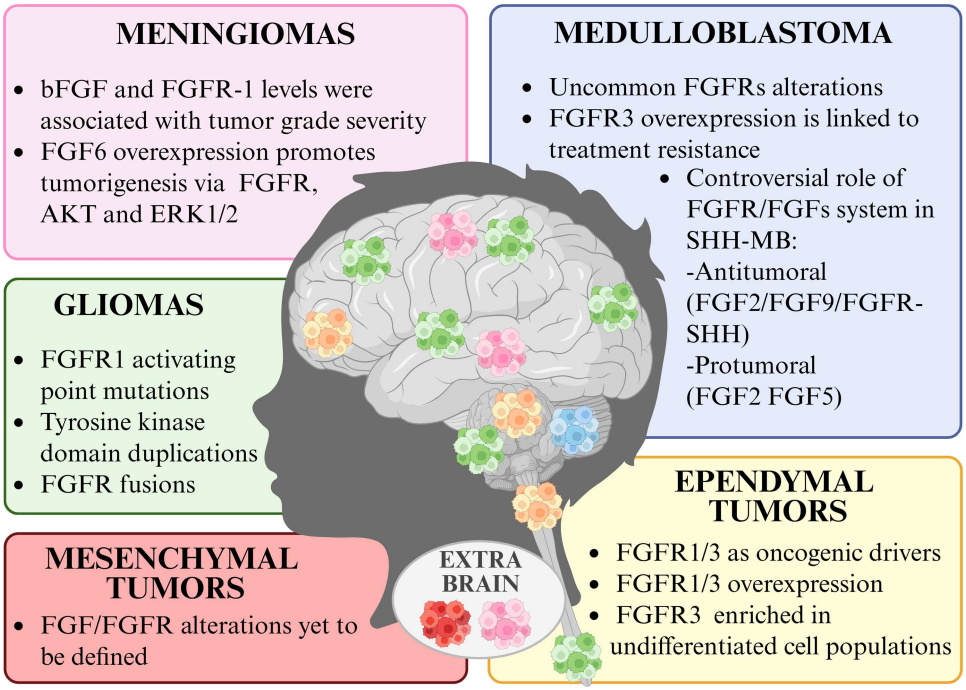

FIGURE 4 | Overview of the major pediatric CNS tumor entities discussed in this review and their principal FGF/FGFR alterations. The figure summarizes the most representative molecular alterations, signaling abnormalities and therapeutic opportunities associated with the FGF/FGFR axis across medulloblastoma, pediatric low-grade gliomas, pediatric high-grade gliomas, ependymomas, meningiomas and mesenchymal tumors. *Created in BioRender. Ronca, R. (2026)* https://BioRender.com/e2irlg0. [Color figure can be viewed at wileyonlinelibrary.com]

(Hh) signaling highlight the uncertain functional significance of FGFR-SHH pathway crosstalk in SHH-MB. Early studies have shown an anti-tumor role of FGF signaling, since it can antagonize SHH activity. In particular, Kenigsberg et al. have demonstrated that among the five FGFs expressed in the developing cerebellum, only FGF2 and FGF9 exhibit anti-tumor activity in MB by inducing neuronal-like differentiation, reducing cellular proliferation, and promoting apoptosis [79]. Additionally, an *in vivo* study reported that the absence of FGF signaling in GNPs does not significantly affect their proliferation or differentiation. However, activation of FGF signaling exerts a pronounced antitumor effect: administration of FGF2 to MB cells inhibited the formation of tumor mass upon transplantation, and administration of FGF2 to tumor-bearing mice significantly suppressed tumor growth [80]. Moreover, it has been reported that in SHH-MB DAOY cells, Hh signaling can be repressed by FGF2 through MEKK2 and MEKK3 activation [70].

In a more complex context, Neve et al. reported a bidirectional crosstalk within FGFR and SHH, demonstrating that the activation of SHH signaling via Smoothened (SMO) agonists induces robust GLI1 expression and enhances tissue invasiveness, whereas FGFR activation promotes ERK nuclear translocation, suppresses GLI1 expression, thereby attenuating invasive behavior. Indeed, co-activation of both pathways results in an intermediate phenotype characterized by reduced invasion compared to single-pathway stimulation, while proliferative capacity remains unaffected, suggesting that FGFR-SHH crosstalk primarily modulates invasive potential rather than proliferation, and its impact may vary depending on tumor subtype and microenvironmental context [81].

In contrast, the pro-tumoral role of the FGF/FGFR system in MB (SHH and Group 3) was described by Kumar et al. showing that FGF2 is locally produced by tumor-resident or infiltrating cells, and this enhanced cell motility and invasion, especially when co-activated with TGF-β signaling pathway [82]. Moreover, a recent article reported the pro-tumoral role of FGF5 in SHH-MB demonstrating that its suppression can reverse early tumorigenic events. In particular, it has been shown that FGF5 is upregulated in infantile SHH-MB and its aberrant upregulation, particularly in a Sufu-deficient mouse model (Sufu-cKO), leads to ectopic activation of FGFR signaling. This promotes excessive proliferation of GNPs within the external granule layer (EGL), contributing to early tumorigenic expansion [83]. Finally, Lukoseviciute et al. demonstrated that the combination treatment of PI3K, FGFR and CDK4/6 inhibitors efficiently decreased the viability of SHH-MB cells, suggesting that it may provide possible therapeutic opportunities for MB therapy [84].

3.1.3 | *Considerations on the Context-Dependent Roles of FGF/FGFR in MB*

The apparently contradictory roles of FGF/FGFR signaling in MB likely reflect a strong context dependency, emerging from the interplay of molecular, cellular, and microenvironmental factors rather than representing true inconsistencies across studies. Several key determinants can be identified.

First, the molecular context and the position of oncogenic alterations within the SHH pathway appear to critically influence FGF activity. When tumors are driven by upstream mutations, such as PTCH1 or SMO, FGF signaling can exert an antitumor effect by repressing GLI1 through MEKK2/3-mediated

TABLE 2 | CNS tumor-specific roles of FGF/FGFR signaling.

Tumor type	Role of FGF/FGFR signaling	Evidence/Main mechanisms	Therapeutic relevance of FGFR targeting
Pediatric low-grade gliomas (pLGGs)	Predominantly pro-tumoral (driver role)	FGFR1 mutations (N546K, K656E), TKD duplications, FGFR1/3-TACC fusions drive MAPK and PI3K/AKT activation, proliferation and recurrence	High relevance FGFR is actionable driver in a subset; erdafitinib and ponatinib show preclinical and early clinical activity
Pediatric high-grade gliomas (pHGGs)	Predominantly pro-tumoral	FGFR fusions/mutations contribute to constitutive signaling, chromosomal instability, survival pathways	Moderate but promising relevance Lower frequency than pLGG, but actionable subgroup may benefit from FGFR inhibitors
Ependymoma (EPN)	Predominantly pro-tumoral	FGFR1/3 overexpression supports stemness, migration, survival; FGFR signaling linked to malignant phenotype	High preclinical relevance Ponatinib/AZD4547 impair growth and induce differentiation
Medulloblastoma (MB)	Context-dependent (pro- and anti-tumoral)	Anti-tumoral: FGF2/FGF9 can suppress SHH signaling, induce differentiation/apoptosis Pro-tumoral: FGF2/FGF5 can promote proliferation, invasion, therapy resistance depending on subtype/context	Emerging relevance No approved FGFR therapies, but strong rationale in SHH and Group 3, especially in combinations (FGFR + PI3K/CDK4/6)
Pediatric meningiomas	Predominantly pro-tumoral	FGF2–FGFR1 autocrine/paracrine loop promotes proliferation, angiogenesis, invasion; FGF6 amplification can drive aggressive disease	Potential relevance Especially aggressive/high-grade or FGF6-amplified cases; evidence still limited
Pediatric CNS mesenchymal tumors	Unknown	Role not defined	Currently unclear Open area for investigation

mechanisms. In contrast, when pathway deregulation occurs downstream, as in SUFU-deficient settings, this regulatory control is bypassed, and FGF signaling may instead promote proliferation through alternative cascades, including MAPK activation. This highlights how the same pathway can shift from suppressive to oncogenic depending on the hierarchical level of pathway disruption. Second, differential expression and composition of FGFRs further contribute to functional variability. The biological outcome of FGF stimulation is highly dependent on receptor context: for instance, FGFR1 expression has been associated with growth-inhibitory and differentiation-inducing effects, whereas alternative receptor isoforms or altered receptor balance may favor mitogenic and pro-survival responses [85, 86]. This receptor-level heterogeneity likely underlies part of the divergent experimental observations. Third, histological variants and molecular subgroups introduce an additional layer of complexity. Classical SHH-MB appears more responsive to FGF-induced differentiation and growth arrest, whereas desmoplastic variants and more aggressive entities such as Group 3 tumors tend to exhibit enhanced proliferation or invasiveness upon FGF pathway activation. These differences reinforce the concept that FGF/FGFR signaling does not operate uniformly across MB subtypes but is instead integrated into subtype-specific regulatory networks.

Finally, the pleiotropic nature of FGFR downstream signaling provides a mechanistic basis for these divergent outcomes. FGFR activation can engage multiple intracellular pathways, including MAPK/ERK, cytoskeletal remodeling programs, and modulators of GLI1 stability and localization. Depending on which signaling axis predominates within a given cellular and microenvironmental context, FGF signaling may either enhance invasive behavior or suppress tumor growth and promote differentiation.

Taken together, these observations indicate that FGF/FGFR signaling in MB cannot be classified as strictly oncogenic or tumor-suppressive, but rather as a highly plastic pathway whose functional output is dictated by tumor-specific context. This complexity underscores the need for more refined, subgroup-informed investigations. Although no FGFR-targeted therapies are currently approved for MB, increasing attention is being directed toward SHH and Group 3 subtypes, where pathway activity appears more prominent. In this setting, rationally designed combination strategies targeting FGFR alongside cooperating pathways may represent a promising avenue to overcome resistance and improve therapeutic outcomes.

3.2 | Pediatric-Type Diffuse Low-Grade Gliomas

Pediatric-type diffuse low-grade gliomas (pLGGs) are a biologically distinct group of childhood brain tumors formally defined in the fifth edition of the WHO classification of central nervous

system (CNS) tumors, CNS5 [3]. pLGGs are considered the most common tumor affecting children's brain (30% of childhood CNS tumors) [87], with an incidence of 2.1 per 100,000 children [88] and an overall survival after 15 years from the diagnosis around 85% [89]. Unlike adult-type diffuse gliomas, which are primarily driven by Isocitrate Dehydrogenase (*IDH*) 1/2 mutations, pLGGs lack *IDH* alterations and instead show frequent dysregulation of the MAPK signaling pathway. These are typically slow-growing tumors, with a favorable overall prognosis compared with pediatric high-grade gliomas (pHGGs), although recurrence and progression may occur after subtotal resection [3, 90]. At the molecular level, all pLGG subgroups are characterized by the constitutive activation of the MAPK-ERK signaling cascade, and *BRAF* alterations [91]. Moreover, *FGFR* alterations have been identified as important oncogenic drivers (see below).

3.2.1 | *Treatment of pLGGs*

When feasible, maximal safe resection is the preferred and potentially definitive treatment. For unresectable, asymptomatic or minimally symptomatic tumors, active surveillance is used to delay cytotoxic therapy and limit long-term toxicities, particularly in younger children. Systemic therapy is initiated upon clinical progression or morbidity. Standard regimens include carboplatin plus vincristine or weekly vinblastine, both providing meaningful disease control [92].

Molecularly guided targeted therapies are increasingly used. Dabrafenib plus trametinib is FDA-approved for children ≥1 year with BRAF V600E mutant pLGG, showing superior outcomes compared with chemotherapy, while tovorafenib has received accelerated approval for relapsed or refractory BRAF-altered pLGG [93, 94]. The MEK inhibitor selumetinib has demonstrated sustained responses and visual improvement in patients with optic pathway and hypothalamic tumors [95]. TRK inhibitors, such as larotrectinib and entrectinib, achieve rapid and durable responses in NTRK fusion-positive tumors [96]. Finally, radiotherapy can achieve durable disease control but is generally reserved for older children or refractory cases, and deferred in younger patients due to the risk of long-term neurocognitive, endocrine, and vascular toxicities.

3.2.2 | *FGF/FGFR System in pLGGs*

A unifying feature of pLGGs is the dysregulation of the MAPK signaling pathway, which promotes cellular proliferation and survival. FGFR family members, particularly FGFR1, play a critical role in this oncogenic signaling. FGFR1 alterations in pLGGs include activating point mutations (e.g., N546K, K656E), tyrosine kinase domain duplications, and gene fusions such as FGFR1–TACC1 [97, 98]. These alterations lead to ligand-independent FGFR1 activation, downstream MAPK and PI3K/AKT signaling pathway, and increased mitogenic activity in tumor cells [98, 99]. FGFR1 alterations are particularly enriched in midline or thalamic glioneuronal tumors, including PLNTY and pilocytic astrocytomas, though they are also observed in a subset of diffuse low-grade gliomas with MAPK pathway alterations [100].

In pLGGs FGFR fusions, in particular FGFR1–TACC1 and FGFR3–TACC3, are less common than point mutations or duplications but are associated with distinct histopathological and epigenetic signatures. Tumors harboring FGFR fusions may show oligodendroglioma-like morphology, calcifications, branching vasculature, and CD34 immunoreactivity [101]. These fusions result in constitutive activation of the receptor tyrosine kinase, promoting oncogenesis and potentially contributing to progression or recurrence.

The clinical relevance of FGFR alterations in pLGGs extends to targeted therapy. Preclinical studies have demonstrated that FGFR inhibitors, such as erdafitinib and ponatinib, can effectively reduce proliferation and induce apoptosis in FGFR-altered glioma cells [102]. Early-phase clinical studies in pediatric populations have shown disease stabilization and partial responses in low-grade gliomas harboring FGFR fusions or mutations, supporting the feasibility of FGFR-targeted interventions [101]. These findings are particularly relevant when complete surgical resection is not achievable or when tumors recur after conventional therapy.

In conclusion, the FGF/FGFR signaling pathway is a key molecular driver in pLGG, particularly through FGFR1 alterations and FGFR–TACC fusions. The molecular characterization of these tumors enables a more precise classification according to the WHO CNS5 guidelines and identifies a subset of patients who may benefit from targeted FGFR inhibition, optimizing the already existing therapeutic approaches.

Although the oncogenic role of FGFR1 alterations in pLGGs is well established, most available evidence derives from genomic and preclinical studies, whereas prospective clinical validation of FGFR-targeted therapies remains limited. Future studies should clarify which specific molecular alterations best predict therapeutic response and long-term clinical benefit.

3.3 | Pediatric-Type Diffuse High-Grade Gliomas

Pediatric-type diffuse high-grade gliomas (pHGGs) represent a biologically and clinically distinct group of glioblastomas, IDH-wild type, despite overlapping histopathological features. They have an incidence around 1.5 per 100,000 individuals and a 5-years survival below 10% [103], accounting over 40% of brain-related tumors in children [104]. Within the pHGGs, four molecularly defined entities are recognized: diffuse midline glioma, H3 K27-altered; diffuse hemispheric glioma, H3 G34-mutant; diffuse pediatric-type high-grade glioma, H3-wildtype and IDH-wild type; infant-type hemispheric glioma. These distinctions, driven by advances in methylation profiling and sequencing, highlight the inadequacy of histology alone for accurate classification [105]. Diffuse midline gliomas (DMGs) are defined by global loss of H3K27 trimethylation, typically caused by H3 K27M mutations or EZHIP overexpression [106, 107]. Diffuse hemispheric gliomas (DHGs) harbor H3 G34R/V mutations, with altered *H3K36* methylation and impaired DNA repair [108, 109]. Pediatric high-grade gliomas, lacking both H3 and IDH mutations, represent a heterogeneous methylation-defined group frequently enriched for alterations involving PDGFRA, EGFR, FGFR1, MYCN, or TERT [110, 111]. Infant-type hemispheric gliomas, presenting in the first year of life, are driven by *ALK*, *NTRK*, *ROS1*, or *MET* gene fusions and show sensitivity to selective kinase inhibitors [99, 112].

3.3.1 | *Treatment of pHGGs*

The management of pHGGs remains extremely challenging, as current treatments offer limited survival benefits and are predominantly palliative. Standard therapy consists of maximal safe surgical resection followed by focal radiotherapy, while chemotherapy, typically temozolomide, offers limited benefit due to the frequent absence of MGMT promoter methylation in these tumors [113]. Given these limitations, therapeutic development has increasingly shifted toward targeted therapies. As an example, since many pHGGs harbor histone mutations such as H3 K27M, which drives oncogenesis through epigenetic dysregulation, ONC201 (dordaviprone), a dopamine receptor D2 (DRD2) antagonist and caseinolytic protease P (ClpP) agonist [114], has shown tumor shrinkage in a subset of patients, received FDA approval for H3 K27M-mutant diffuse midline gliomas, and pediatric trials confirmed its safety and occasional long-term survival [115, 116]. Also, immunotherapy is emerging as an additional strategy, and CAR-T cells targeting GD2 have demonstrated promising preclinical efficacy in DIPG models and early clinical improvements in initial pediatric trials [117].

3.3.2 | *FGF/FGFR System in pHGGs*

Studies regarding FGFR involvement in glioblastoma revealed that oncogenic fusions between FGFRs and TACC proteins, in particular FGFR3–TACC3 and FGFR1–TACC1, occur in a small percentage (around 3%–4%) of adult high-grade glioma. These fusions result in the constitutive activation of tyrosine kinase signaling, with the consequent dysregulation of the mitotic spindle, a chromosomal instability and oncogenic transformation, both *in vitro* and in murine models [118]. In pediatric contexts, FGFR alterations have been observed across a range of high-grade glioma specimens. Through a multi-cohort genomic analysis of pediatric solid tumors, including brain cancers, FGFR aberrations were identified, including activating point mutations, amplifications, and fusions such as FGFR3–TACC3 and FGFR1–TACC1. These molecular alterations have been observed in approximately 3% of cases (41 of 1.395 tumors) [53]. Notably, among these, some pediatric patients achieved clinical benefit from FGFR-targeted therapies.

Rarely, but in a few cases, FGFR anomalies in pediatric gliomas reflect those seen in adult ones. As in pLGGs, FGFR3–TACC3 fusion-positive gliomas are commonly identified through histopathological and epigenetic peculiarities, which may display oligodendroglioma-like morphology, calcifications, branching vasculature, and CD34 immunoreactivity [119]. Although these features have been observed in pHGGs (to date, fewer than 15 pediatric cases have been reported), the discovery of these cases opens the door to the possibility to extend similar clinical management also to this subgroup of pediatric patients [120].

Beyond fusions, the pHGGs scenario can include FGFR1 mutations and duplications, frequently studied in pLGGs. FGFR1 hotspot mutations, such as N546K and K656E, tyrosine kinase domain duplications, and FGFR1–TACC1 fusions are frequently observed in FGFR-driven glioneuronal pediatric tumors, particularly when midline or glioneuronal-located [91]. Although less prevalent, these alterations are also seen in high-grade settings, contributing to sustain MAPK and PI3K-AKT pathway activation, underscoring the oncogenic potential of FGFR signaling across tumor grades.

While direct preclinical or clinical data of FGFR-targeted therapy in pHGGs remain quite limited, FGFR inhibitors such as ponatinib and erdafitinib have demonstrated CNS penetrance and early activity against FGFR-altered pediatric gliomas in broader pediatric brain tumor studies, representing a possible future therapeutic strategy [102].

In summary, although FGFR activation via fusions or mutations is less frequent in pHGGs than in low-grade counterparts, the similarity in pathogenic mechanisms could open the way to new therapeutic approaches. Recognition of FGFR anomalies improves the molecular taxonomy of pHGGs and highlights a potentially actionable target for a subset of cases, where the use of FGFR inhibitors might help improve outcomes for these tumor patients.

In contrast to pLGGs, the biological and therapeutic significance of FGFR alterations in pHGGs remains less clearly defined. The rarity of these alterations, together with the limited number of pediatric patients treated with FGFR inhibitors, currently prevents definitive conclusions regarding their predictive value or clinical utility.

3.4 | Ependymomas

Ependymoma (EPN) is a rare neuroepithelial tumor of the CNS occurring in all age groups, accounting for 1.6% of all brain tumors, and it is one of the most common pediatric malignant brain tumors (5.4% of pediatric brain tumors) [121]. EPNs are divided into 10 diagnostic categories based on integration of anatomical location, histopathology, genetic abnormalities, and DNA methylation patterns, reflecting the biology and prognosis of tumor [3]. Although EPNs may occur in any part of the CNS, most occur in the posterior fossa (PF), followed by the supratentorial (ST) and spinal (SP) compartments. Among all EPNs, the PF EPN is the most common in the pediatric age (60%–70% of EPNs) and is further subclassified as PFA and PFB subtypes [122]. PFA tumors are inherently found in younger children and have a relatively balanced genome, besides the alterations in 1q and 6q genes [123]. PFA tumors are more clinically aggressive and are distinguished from PFB by methylation profiling or by demonstrating the global loss of H3 K27me3 by immunohistochemistry, associated with the expression of EZHIP (Enhancer of Zeste Homolog Inhibitory Protein). On the other hand, PFB tumors have a more typical chromosomal instability and a much more favorable outcome, with a 5-year overall survival of around 70%–75% [123]. Finally, the SP EPNs are generally observed in older children through adulthood and mostly lack a specific gene signature.

3.4.1 | *Treatment of EPNs*

Irrespective of molecular subgroups, the significant predictors of survival in EPNs include location, extent of resection and radiotherapy. EPNs are mainly localized tumors rather than infiltrating, so a gross total resection is usually feasible, but the 5-year progression-free survival remains poor (23%–45%) [124].

As a matter of fact, a complete resection of a SP EPN is generally curative, whereas a complete resection of a PF EPN is rarely that way. EPNs tend to recur within the previous resection cavity [125], while metastatic recurrence is not common, or could be iatrogenic. The combination with radiation therapy adds benefit for progression-free survival and overall survival (63%–93%) [126]. The current literature did not report clear evidences about the efficacy of chemotherapy as a tool to facilitate further surgical resection prior to radiotherapy [127]. In general, almost 40% of EPNs remain incurable [128] and there are very few EPN-specific clinical trials due to the lack and complexity of targets/drivers to hit with therapies.

3.4.2 | *FGF/FGFR System in EPNs*

Depending on the anatomical location of the tumor, there appears to be heterogeneity based on the molecular subtypes of EPNs [129]. Intracranial EPNs are characterized by a dysregulation of FGFR and EGFR (Epidermal Growth Factor Receptor) [130, 131]. It has already been demonstrated that FGFR1 and FGFR3 act as potential oncogenic drivers of EPN [132–134]. In particular, Lötsch et al. [46], by screening 467 EPN tissue samples in three independent cohorts, uncovered FGFR1 and FGFR3 overexpression throughout all molecular EPN groups. Moreover, FGFR3 has been demonstrated to be further enriched in malignant ST EPN. As a matter of fact, ST-RELA tumors exhibited the highest expression of both FGFR1 and FGFR3, but FGFR3 was found enriched in undifferentiated cell populations, particularly in radial glia and embryonal astrocytic cells which are considered the EPN cells of origin [135]. Indeed, FGFR-related transcriptomic signatures were induced by oncogenic ZFTA-RELA activity [136], suggesting a potential role for FGFRs as mediators of EPN malignant phenotype. To validate this hypothesis, Lötsch et al. tested a panel of FGFR inhibitors on different EPN cell models reporting that FGFR blockade impairs MAPK and PI3K signaling cascade, thereby hampering cell survival, stemness features and the migratory potential of ST-RELA and PFA EPN cells. Moreover, FGFR inhibition had a central impact on multiple cell biological processes, including lipid and RNA metabolism, as well as Notch1 or PD-1 signaling, some of which are deregulated or hyperactivated in EPNs [46]. The high sensitivity of EPN models to FGFR inhibitors was observed not only for the multi-RTK inhibitor ponatinib, but also for the more selective FGFR inhibitor AZD4547 (foxagratinib) molecule, proving FGFRs as a central therapeutic target in EPN cells. Besides cell viability, the efficacy of FGFR inhibitors was highlighted by the impairment of neurosphere-forming capacity, cell growth, differentiation patterns, and cell migration. Indeed, FGFR inhibition induced the maturation of cells in aggressive EPNs, a therapeutic concept currently considered of high potential in pediatric cancers [137].

Despite encouraging preclinical findings, the absence of prospective clinical studies currently limits the translation of FGFR inhibition into routine clinical practice. Whether FGFR overexpression represents a true oncogenic dependency or simply reflects the undifferentiated state of aggressive tumors remains to be clarified.

3.5 | Pediatric Meningiomas

Meningiomas are the most frequent CNS tumors in adults, but they are uncommon in the pediatric population, making up only 0.4% to 4.6% of all pediatric intracranial neoplasms [138, 139]. In children, meningiomas are often present in unusual locations, such as the intraventricular and infratentorial regions. They can be intraparenchymal (surrounded by brain parenchyma without dural attachment) and are frequently misdiagnosed. These tumors can appear at any age, including infancy or even during fetal development [140, 141]. Pediatric meningiomas often exhibit more aggressive behavior than their adult counterparts, with a higher frequency of elevated histological grades. In one series, 27.3% of pediatric cases were classified as grade II or III, suggesting an unfavorable prognosis in this age group [140]. Common predisposing factors for these tumors include neurofibromatosis type 2 (NF2) and previous radiation exposure [142]. Genetically, both sporadic and NF2-associated cases show a high incidence of NF2 (22q12) and Protein 4.1B (18p11.3) deletions, with mutations in the NF2 gene being strongly linked to their development. Furthermore, 1p and 14q deletions, which are generally associated with tumor progression, are commonly found in pediatric meningioma cases [142, 143].

3.5.1 | *Treatment for Meningiomas*

Surgical resection remains the main treatment for most meningiomas [140, 144]. For recurrent, clinically aggressive, or surgically untreatable cases, radiotherapy is the only currently accepted adjuvant therapy, and recent advances in surgery and radiotherapy have significantly improved survival [145]. A hormonal role in the tumorigenesis of meningiomas has long been suspected, given their higher incidence in women. The progesterone receptor (PR) is the best documented and is also detectable in men and children. However, clinical studies using anti-progestin agents have so far been disappointing, perhaps because meningiomas that require adjuvant therapy (e.g., high-grade ones) are less likely to express PR. Other hormonal receptors, such as those for androgens, somatostatin, growth hormone, and prolactin, have been detected, but their precise biological roles remain to be determined [146, 147]. Chemotherapy (together with interferon and somatostatin analogs) is under investigation for malignant meningiomas, but none of these options has an established role in prolonging progression-free or overall survival. Traditional chemotherapy does not yet have a defined role [148].

3.5.2 | *FGF/FGFR System in Meningiomas*

FGF2 has been shown to be produced in over 90% of human meningioma tissues, and FGFR1 is expressed in all meningioma tissues examined. The level of FGFR1 expression correlates with that of FGF2, suggesting the presence of an autocrine loop of stimulation in the autonomous growth and tumorigenesis of meningioma cells. Also, endothelial cells of capillaries express FGFR1, indicating that tumor-derived FGF2 may play a key role in tumor angiogenesis through a paracrine mechanism. Moreover, the presence of FGF2 and FGFR1 confirms their importance in carcinogenesis, proliferation, and tumor infiltration [149–151]. Indeed, FGF2 and FGFR1 protein levels in meningiomas correlate with the pathological grade of the tumor, thus providing a useful indicator to distinguish benign from malignant forms and assess the histological and malignant grade [149]. In terms of specific alterations, a rare case of primary

mediastinal malignant meningioma showed frequent FGF6 amplification in both primary and metastatic lesions. FGF6 overexpression promoted the proliferation, migration, and invasion of malignant meningioma cells by boosting the phosphorylation of FGFR, AKT, and ERK1/2 [148].

In the frame of targeted therapy, selective TKIs (anlotinib and apatinib) have been evaluated in the clinics. Indeed, a rare case of primary malignant mediastinal meningioma with pulmonary and bone metastases, characterized by FGF6 amplification, showed benefit from treatment with apatinib (a TKI targeting VEGFR) for more than 33 months and subsequently with anlotinib (a broad-spectrum TKI targeting VEGFR, PDGFR, FGFR, and c-Kit). This suggests that anlotinib can effectively inhibit disease progression in patients with FGF6 amplification by blocking the FGFR and the downstream AKT/ERK signaling pathway [148, 152]. Additionally, the TKI inhibitor dovitinib was shown to suppress FGFR1/3 activation and their downstream signaling in high-grade anaplastic meningioma cell lines, resulting in a relevant therapeutic profile for more aggressive pediatric meningiomas [153].

However, the available evidence is mainly based on isolated clinical observations and small experimental studies. Therefore, the relevance of the FGF/FGFR pathway in pediatric meningiomas remains largely exploratory and requires further validation.

3.6 | Mesenchymal Tumors

Pediatric mesenchymal tumors of the CNS are a diverse group of neoplasms that possess unique clinical, histological, and molecular features. In children, these tumors account for a small fraction of primary CNS neoplasms, but they exhibit a broad biological spectrum, ranging from benign to highly aggressive sarcomas. The WHO CNS5 synchronized the nomenclature for CNS mesenchymal tumors with their soft tissue equivalents, removing some entities common in soft tissues but exceptionally rare in the CNS, while adding new entities based on their histomolecular profiles [3]. The landscape of pediatric CNS mesenchymal tumors is changing rapidly, with a growing focus on molecular diagnosis for more precise classification and the development of targeted, personalized therapies. Indeed, specific molecular signatures, represented by characteristic gene fusions and mutations helped in the identification of different mesenchymal tumor subtypes and are essential for accurate diagnosis, prognostication, and therapeutic planning. However, for many new entities, a definitive WHO grade has not yet been assigned, and further research is necessary to fully characterize their clinical, radiological, and outcome aspects [154].

Unfortunately, as yet, no relevant data are available on the role of FGF/FGFR in mesenchymal tumors, thus remaining an open field for future research.

4 | Conclusions

In summary, the evidence reviewed here highlights the emerging, multifaceted role of the FGF/FGFR signaling axis in the biology of pediatric CNS tumors. Aberrant activation of this pathway contributes to key oncogenic processes, including proliferation, survival, stemness, angiogenesis, and therapy resistance, supporting its rationale as a therapeutic target [155]. However, a unifying conclusion that emerges from the available data is that FGF/FGFR signaling cannot be considered a uniform oncogenic driver across tumor entities. Rather, it operates through context-dependent modalities that reflect tumor lineage, developmental origin, and molecular background. These include: (i) a direct tumor-driving function mediated by activating mutations, kinase-domain duplications, or oncogenic fusions, as observed most prominently in subsets of pLGGs; (ii) a lineage-associated regulatory program linked to undifferentiated cellular states and impaired differentiation, as suggested in EPNs; and (iii) a microenvironmentally modulated signaling network shaped by ligand availability and extensive crosstalk with pathways such as SHH, PI3K/AKT, MAPK, TGF-β, and Notch (Box 1).

This framework provides a basis to interpret the heterogeneity and, in some cases, the apparent contradictions reported in the literature. MB represents a paradigmatic example of such complexity, where FGF signaling may exert either tumor-suppressive or tumor-promoting effects depending on the molecular subgroup, the level at which the SHH pathway is deregulated, and the broader signaling context. Rather than representing conflicting observations, these findings underscore the plasticity of FGF/FGFR signaling and its dependence on cellular and microenvironmental determinants. Similar considerations apply across tumor types, where FGFR alterations, overexpression, or pathway activation may reflect distinct

BOX 1 | Anti-FGF/FGFR drugs and BBB-penetrance.

The ability of FGF/FGFR pathway inhibitors to effectively penetrate the blood–brain barrier (BBB) remains an important yet insufficiently characterized aspect of their clinical application in CNS tumors. Current evidence is limited and largely derives from indirect assessments or early-phase clinical observations, with a substantial reliance on theoretical models based on physicochemical drug properties.

In this context, BBB permeability has been estimated using *predictive scoring* systems based on passive diffusion parameters. One such model assigns a "BBB score" [158] ranging from 0 to 6, with higher values indicating a greater likelihood of CNS penetration. According to this approach [45], erdafitinib displays a relatively low score (2.77), corresponding to a limited probability of passive CNS penetration, while ponatinib shows a slightly higher but still modest score (3.11). In contrast, vandetanib [159] (a multikinase inhibitor used as a comparator) reaches an intermediate score (4.26), suggesting a comparatively higher probability of BBB permeability. However, these models only account for passive transport and fail to capture critical determinants such as active transport mechanisms or tumor-induced alterations of BBB integrity, thereby limiting their predictive value in vivo.

biological states with different therapeutic implications (Figure 5; Table 2).

Here, we integrated recent genomic and epigenomic insights reported in the literature with functional and translational evidence across the major pediatric CNS tumor entities. Although FGFR alterations are not pervasive, their presence in a measurable subset of tumors, together with recurrent patterns of pathway activation, supports their biological and clinical relevance. At the same time, the available data indicate that FGFR expression or genetic alteration alone is unlikely to serve as a sufficient predictive biomarker, emphasizing the need for a more refined, context-aware stratification of patients.

Under a translational and therapeutic perspective, accumulating preclinical and early clinical evidence supports the potential of FGFR-targeted strategies. Selective FGFR tyrosine kinase inhibitors, such as pemigatinib, futibatinib, and erdafitinib, have demonstrated activity in FGFR-altered malignancies and show initial promise in pediatric CNS tumors, where they can reduce proliferation and induce apoptosis in glioma models and promote differentiation in aggressive EPN (Table 2). Moreover, combination approaches have shown enhanced efficacy in MB and other pediatric tumor models, suggesting that pathway co-targeting may be required to overcome intrinsic and adaptive resistance mechanisms. In general, the clinical development of FGF/FGFR pathway inhibitors in pediatric oncology is progressively expanding, although it still lags behind adult oncology, reflecting both biological complexities and historical challenges in conducting pediatric trials (Box 2). These studies further emphasize the need for pediatric-specific clinical investigation strategies, including refined molecular stratification, optimization of dosing, and careful monitoring of long-term toxicities. Such efforts will be essential to fully define the therapeutic role of FGFR-targeted agents in pediatric cancers.

The successful clinical implementation of FGFR-targeted therapies will require overcoming several important translational challenges. First, accurate patient selection will depend not only on the identification of FGFR mutations or fusions, but also on the development of reliable predictive biomarkers capable of distinguishing true oncogenic dependence from secondary pathway activation. Second, both primary and acquired resistance mechanisms, including bypass signaling and secondary kinase-domain mutations, are expected to limit the long-term efficacy of FGFR inhibitors, as already observed

BOX 2 | Clinical development of FGFR inhibitors in pediatric oncology.

Current clinical trials in pediatric oncology including CNS tumors are limited and largely based on a biomarker-driven approach, focusing on patients with tumors harboring specific FGFR alterations.

Among the most relevant ongoing trials, the *NCI-COG Pediatric MATCH* (APEC1621B, Arm B) is evaluating the pan-FGFR inhibitor erdafitinib in pediatric and young adult patients with solid tumors, including CNS malignancies, characterized by FGFR genomic alterations. Similarly, phase II trials (*NCT03210714* and *NCT03155620*) are investigating erdafitinib in relapsed or refractory neuroblastoma and medulloblastoma. In parallel, the phase II RAGNAR trial (*NCT04083976*) is assessing the efficacy and safety of erdafitinib across a broader population of pediatric patients with advanced FGFR-altered solid tumors.

Despite these efforts, emerging clinical evidence indicates that therapeutic responses to FGFR inhibitors in pediatric tumors are generally modest. In most cases, treatment leads to disease stabilization rather than objective tumor regression, suggesting a predominantly cytostatic effect. In tumor types for which dedicated trials are lacking, such as ependymoma, FGFR inhibitors have occasionally been used off-label, with reports of prolonged disease stabilization in selected patients.

An important aspect highlighted by pediatric studies is the safety profile of these agents. In particular, skeletal toxicities, including an increased risk of fractures, have been observed and are likely related to the inhibition of physiological FGFR signaling pathways involved in bone development and growth.

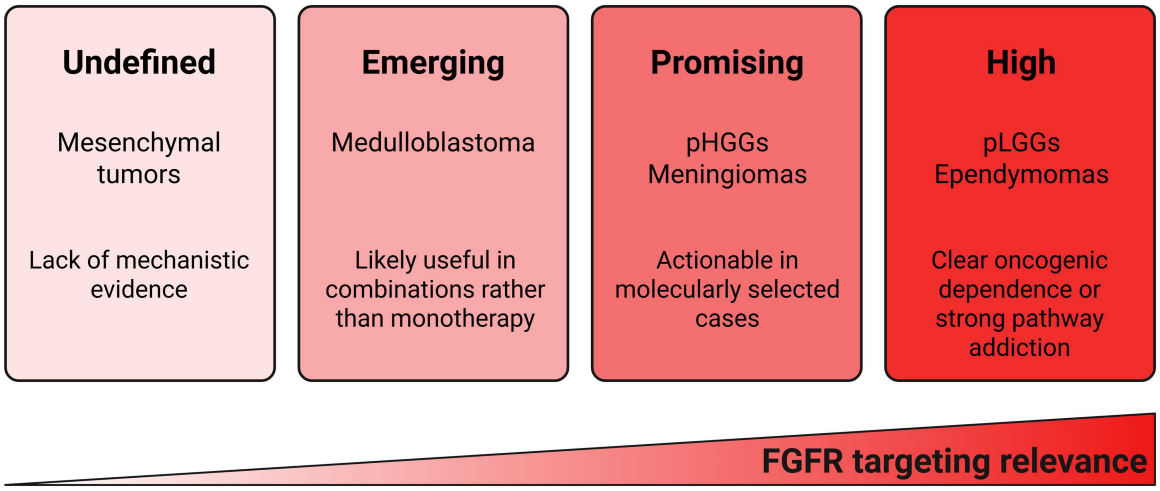

FIGURE 5 | Therapeutic relevance of FGFR targeting in pediatric CNS tumors. [Color figure can be viewed at wileyonlinelibrary.com]

in adult malignancies [156, 157]. Third, adequate drug delivery across the blood-brain barrier remains a major challenge, particularly for tumors retaining an intact BBB. Finally, because FGF/FGFR signaling extensively interacts with pathways such as MAPK, PI3K/AKT, SHH and immune regulatory networks, rational combination therapies may ultimately prove more effective than FGFR inhibition alone.

Despite these advances, several critical gaps remain. The functional relevance of FGF/FGFR activation must be distinguished from epiphenomenal overexpression, the determinants of context-specific signaling outputs remain incompletely defined, and robust predictive biomarkers are lacking. In addition, major translational challenges, including BBB penetration, intratumoral heterogeneity, and pathway redundancy, continue to limit clinical efficacy. Addressing these issues will require integrative approaches combining subtype-specific functional models, single-cell and spatial analyses, and biomarker-driven clinical trials. Particular attention should also be paid to long-term safety in pediatric patients, given the physiological role of FGF/FGFR signaling in skeletal development, tissue growth, and endocrine homeostasis, making prolonged pathway inhibition potentially associated with unique developmental toxicities.

Collectively, these considerations support the FGF/FGFR axis as a promising but highly context-dependent therapeutic target in pediatric neuro-oncology. Future progress will depend on integrating molecular profiling, functional validation, biomarker-driven clinical trials, and the development of next-generation FGFR inhibitors with improved CNS penetration and resistance profiles. Such efforts will be essential to identify the patients most likely to benefit from FGFR-targeted therapies and ultimately translate the growing biological knowledge of this pathway into effective precision medicine approaches for pediatric CNS tumors.

Author Contributions

S.F., C.T., E.S, M.T., and R.R. wrote the main manuscript text; S.F., C.T. prepared figures; A.d.M. and R.R. supervised the and revised the text. All authors reviewed the manuscript.

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Conflicts of Interest

The authors declare no conflicts of interest.

Declaration of AI Use

The authors used ChatGPT (OpenAI) exclusively to improve language clarity and readability during manuscript preparation. All scientific content, interpretation of the literature, conclusions, and final editing were performed by the authors, who take full responsibility for the content of the manuscript.

Data Availability Statement

Data sharing not applicable to this article as no datasets were generated during the current study.

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