Pediatric Low-Grade Glioma Classification

Pediatric Low-Grade Gliomas (PLGGs) display heterogeneity regarding morphology, genomic drivers and clinical outcomes.

They constitute the largest, yet clinically and (molecular-) a histologically heterogeneous group of pediatric brain tumors of WHO grade I and II occurring throughout all pediatric age groups and at all central nervous system (CNS) sites. The tumors are characterized by a slow growth rate and may show periods of growth arrest [1].

Pediatric low-grade gliomas were shown to be characterized by an array of distinct molecular aberrations. The cIMPACT-4 consensus proposed pediatric low-grade gliomas of the diffuse type to be characterized by distinct molecular changes rather than distinct histological features.

Fukuoka et al. described a small series of pediatric oligodendroglioma-like tumors with BRAF V600E mutations. Interestingly, they exhibited molecular changes usually associated with adult high-grade gliomas: chromosome instability, chromosome 7 gains, and chromosome 10 loss, but had an indolent natural history [2] [3].

Genetic abnormalities

Mobark et al. profiled a targeted panel of cancer-related genes in 37 Saudi Arabian patients with pLGGs to identify genetic abnormalities that can inform prognostic and therapeutic decision-making. THey detected genetic alterations (GAs) in 97% (36/37) of cases, averaging 2.51 single nucleotide variations (SNVs) and 0.91 gene fusions per patient. The KIAA1549-BRAF fusion was the most common alteration (21/37 patients) followed by AFAP1-NTRK2 (2/37) and TBLXR-PI3KCA (2/37) fusions that were observed at much lower frequencies. The most frequently mutated) genes were NOTCH1-3 (7/37), ATM (4/37), RAD51C (3/37), RNF43 (3/37), SLX4 (3/37) and NF1 (3/37). Interestingly, they identified a GOPC-ROS1 fusion in an 8-year-old patient whose tumor lacked BRAF alterations and histologically classified as low-grade glioma. The patient underwent gross total resection (GTR). The patient is currently disease-free. To the author's knowledge, this is the first report of GOPC-ROS1 fusion in PLGG. Taken together, they revealed the genetic characteristics of pLGG patients can enhance diagnostics and therapeutic decisions. In addition, we identified a GOPC-ROS1 fusion that may be a biomarker for pLGG [4].

Pediatric low-grade gliomas (PLGGs) are commonly associated with BRAF gene fusions that aberrantly activate the mitogen-activated protein kinase (MAPK) signaling pathway.

This has led to PLGG clinical trials utilizing RAF- and MAPK pathway-targeted therapeutics. Whole-genome profiling of PLGGs has also identified rare gene fusions involving another RAF isoform, CRAF/RAF1, in PLGGs and cancers occuring in adults. Whereas BRAF fusions primarily dysregulate MAPK signaling, the CRAF fusions QKI-RAF1 and SRGAP3-RAF1 aberrantly activate both the MAPK and phosphoinositide-3 kinase/mammalian target of rapamycin (PI3K/mTOR) signaling pathways. Although ATP-competitive, first-generation RAF inhibitors (vemurafenib/PLX4720, RAFi) cause paradoxical activation of the MAPK pathway in BRAF-fusion tumors, inhibition can be achieved with 'paradox breaker' RAFi, such as PLX8394.

Jain et al. report that, unlike BRAF fusions, CRAF fusions are unresponsive to both generations of RAFi, vemurafenib and PLX8394, highlighting a distinct responsiveness of CRAF fusions to clinically relevant RAFi. Whereas PLX8394 decreased BRAF-fusion dimerization, CRAF-fusion dimerization is unaffected primarily because of robust protein-protein interactions mediated by the N-terminal non-kinase fusion partner, such as QKI. The pan-RAF dimer inhibitor, LY3009120, could suppress CRAF-fusion oncogenicity by inhibiting dimer-mediated signaling. In addition, as CRAF fusions activate both the MAPK and PI3K/mTOR signaling pathways, we identify combinatorial inhibition of the MAPK/mTOR pathway as a potential therapeutic strategy for CRAF-fusion-driven tumors. Overall, we define a mechanistic distinction between PLGG-associated BRAF- and CRAF/RAF1 fusions in response to RAFi, highlighting the importance of molecularly classifying PLGG patients for targeted therapy. Furthermore, this study uncovers an important contribution of the non-kinase fusion partner to oncogenesis and potential therapeutic strategies against PLGG-associated CRAF fusions and possibly pan-cancer CRAF fusions [5)].

References

1)
Gnekow AK, Kandels D, Tilburg CV, Azizi AA, Opocher E, Stokland T, Driever PH, Meeteren AYNSV, Thomale UW, Schuhmann MU, Czech T, Goodden JR, Warmuth-Metz M, Bison B, Avula S, Kortmann RD, Timmermann B, Pietsch T, Witt O. SIOP-E-BTG and GPOH Guidelines for Diagnosis and Treatment of Children and Adolescents with Low Grade Glioma. Klin Padiatr. 2019 May;231(3):107-135. doi: 10.1055/a-0889-8256. Epub 2019 May 20. PubMed PMID: 31108561.

2)
Yang RR, Li KK, Liu APY, Chen H, Chung NY, Chan AKY, Li F, Tat-Ming Chan D, Mao Y, Shi ZF, Ng HK. Low-grade BRAF V600E mutant oligodendroglioma-like tumors of children may show EGFR and MET amplification. Brain Pathol. 2020 Oct 8. doi: 10.1111/bpa.12904. Epub ahead of print. PMID: 33032379.

3)
Fukuoka K, Mamatjan Y, Ryall S, Komosa M, Bennett J, Zapotocky M, Keith J, Myrehaug S, Hazrati LN, Aldape K, Laperriere N, Bouffet E, Tabori U, Hawkins C. BRAF V600E mutant oligodendroglioma-like tumors with chromosomal instability in adolescents and young adults. Brain Pathol. 2020 May;30(3):515-523. doi: 10.1111/bpa.12799. Epub 2019 Nov 10. PMID: 31630459.

4)
Mobark NA, Alharbi M, Alhabeeb L, AlMubarak L, Alaljelaify R, AlSaeed M, Almutairi A, Alqubaishi F, Ahmad M, Al-Banyan A, Alotabi FE, Barakeh D, AlZahrani M, Al-Khalidi H, Ajlan A, Ramkissoon LA, Ramkissoon SH, Abedalthagafi M. Clinical management and genomic profiling of pediatric low-grade gliomas in Saudi Arabia. PLoS One. 2020 Jan 29;15(1):e0228356. doi: 10.1371/journal.pone.0228356. eCollection 2020. PubMed PMID: 31995621.

5)
Jain P, Fierst TM, Han HJ, Smith TE, Vakil A, Storm PJ, Resnick AC, Waanders AJ. CRAF gene fusions in pediatric low-grade gliomas define a distinct drug response based on dimerization profiles. Oncogene. 2017 Aug 14. doi: 10.1038/onc.2017.276. [Epub ahead of print] PubMed PMID: 28806393.