Neuro-Oncology
19(4), 461–462, 2017 | doi:10.1093/neuonc/nox005

FGFR-TACC approaches the first turn in the race for targetable GBM mutations

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See article in this issue by Lasorella et al. pp. 475–483.

FGFR-TACC describes fusions of genes encoding fibroblast growth factor receptors (FGFRs) and transforming acidic coiled-coil domains (TACCs) that were discovered to be recurrent in glioblastomas (GBMs) in 2012.[1] As a family, FGFR-TACC is the most prevalent type of gene fusion yet identified in adult gliomas. Estimates vary, but they are found in roughly 3%–6% of adult and pediatric isocitrate dehydrogenase wild-type gliomas and have been found in all grades. The most common fusion joins the N terminus of FGFR3 to the C terminus of TACC3 by an in-frame rearrangement on chromosome 4p16. FGFR1-TACC1 is less prevalent, and multiple breakpoints have been identified for both fusions. Notably, FGFR-TACC fusions are prevalent in other cancer types, such as bladder and squamous cell lung cancer, and they comprise a subset of a larger family of FGFR fusions with non-TACC partners that are being investigated in both solid tumor and hematologic malignancies.[2] In this issue of *Neuro-Oncology*, Lasorella and colleagues present a contemporary review of what is known about FGFR-TACC in glioma and make a case for these fusions as biologically intriguing and promising therapeutic targets.[3]

FGFR-TACC fusion proteins have been demonstrated to be transforming and oncogenic, yet their biologic activity is not completely understood and appears to extend beyond canonical FGFR signaling: TACC domains promote dimerization and constitutive activation of FGFR at autophosphorylation sites but also lead to aberrant nuclear localization where at least one effect is to induce genomic instability.[1,3]The authors report that activation of FGFR canonical downstream pathways by the fusion protein is cell-type dependent and seemingly not strong in astrocytes, leading them to hypothesize that significant oncogenic effects are coming from accumulation in the nucleus and possible recruitment and phosphorylation of aberrant substrates. What is known of this biology is well summarized in the current review. It is clear that the effects of the fusion protein are highly sensitive to FGFR inhibitors in vitro and in vivo, leading to interest in several ongoing clinical trials.[1,3]

The data on clinical response is limited but promising. Two patients with FGFR3-TACC3 recurrent GBMs were treated in a first-in-man phase I trial of JNJ-42756493, an oral pan-FGFR kinase inhibitor, at 12 mg/day, leading to clinical improvements; one patient showed stable disease and the other a minor response.[4] Both patients progressed after 115 and 134 days on treatment, respectively. A separate phase I trial of JNJ-42756493 in a diversity of FGFR-altered solid tumors reported confirmed responses in 4 of 23 patients receiving at least a 6 mg dose.[5] All 4 responders had FGFR translocations (rather than amplifications or point mutations) and 2 were recurrent GBM patients with FGFR3-TACC3 fusions. Toxicity was largely manageable for the course of the study and was reduced by a schedule of intermittent dosing. These results suggest that inhibition of the fusion may be effective at least transiently. At least 6 other FGFR inhibitors are being investigated in ongoing clinical trials treating GBM, other solid tumors, and lymphomas.

In addition to FGFR-TACC, several other functional and recurrent gene fusions have been identified in gliomas to date, including EGFR-SEPT14, SEC61G-EGFR, and PTPRZ1-MET.[6,7] There are a larger number of fusions seen only sporadically in gliomas (eg, fusions with NTRK1 [neurotrophic tyrosine kinase receptor type 1] or ROS1) but which are prevalent in other cancers.[8] With increasing sequencing data, doubtless other fusions will emerge. But what characteristics make for a good therapeutic target? Some lessons may be taken from experience attempting to target activating gene rearrangements of epidermal growth factor receptor (EGFR), such as the common intragenic deletion mutation EGFR variant III. Like EGFRvIII, recurrent fusions of EGFR and platelet derived growth factor receptor alpha are typically associated with highly amplified DNA regions, often as “double-minute” extrachromosomal fragments that are prone to heterogeneous distribution cell-to-cell and region-to-region in growing tumors.[9] Oncogenes carried by double-minutes may be difficult to inhibit in cells harboring tens or hundreds of copies, and impossible in cells that have lost the amplicon altogether. In this context, it is notable that Lasorella et al describe FGFR-TACC fusions in gliomas resulting from duplication/inversions without high-level amplification, at least in most cases. This suggests that the rearrangements are more likely to be stably and clonally propagated, as

are, for example, translocations of EML4-ALK (echinoderm microtubule-associated protein-like 4–anaplastic lymphoma kinase) in lung cancer and other successfully targeted fusion genes prevalent in other cancers. Although single-cell sequencing of tumors with FGFR-TACC fusion have not yet been described, the authors demonstrate that FGFR overexpression appears uniform by immunohistochemistry in tumors harboring the fusion. More investigation is needed to confirm whether the translocation is retained uniformly in treated recurrences.

The prevalence of FGFR fusions (including FGFR-TACC) in other tumor types is arguably the most encouraging factor for clinical investigation. Foremost, the trials can move forward with reasonable accrual from more common cancers. A secondary benefit is that other tumor types offer an extended set of model systems and cellular contexts to better illuminate biological mechanisms of oncogenicity and tumor maintenance for FGFR-TACC and other FGFR fusions. There is the opportunity to test more selective drugs that might not have reliable CNS penetration, and to work out resistance mechanisms in tumor types more amenable to longitudinal tissue or cell-free DNA analysis. A recent analysis of 4 patients with FGFR2-driven intrahepatic cholangiocarcinoma treated with a selective inhibitor of FGFR1–3 found promising efficacy in 3 patients, as well as revealing early candidate mechanisms of resistance via FGFR point mutations.[10] These patients had FGFR2 fusions, although none had FGFR2-TACC fusion specifically.

The long-standing barriers to first successful mutation-targeted GBM therapy are beginning to show cracks. Basket trials are likely to be a key lever for studying rare GBM genotypes but they also seem unlikely to breach the barriers alone. One takeaway from these early investigations of FGFR-TACC is that further characterization of their odd biology may reveal novel mechanisms of gliomagenesis and lead to better therapeutic strategies than solely inhibiting the FGFR domain.

Conflict of interest statement. None.

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