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An allosteric inhibitor of SHP2 effectively targets PDGFRα-driven glioblastoma

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Glioblastomas (GBMs) are the most malignant primary brain tumors in adults. This highly aggressive malignancy lacks effective therapeutic interventions, reflected by a high mortality and a dismal survival of less than 14 months in patients diagnosed with GBM. Effective therapeutic strategies, particularly those which are tailored to target key oncogenic drivers in this heterogeneous tumor, are urgently warranted. Aberrant activation of receptor tyrosine kinases (RTKs), which primarily signals through the pathways of Ras/mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase (ERK) and Ras/phosphatidylinositol-3 kinase (PI3K)/AKT, promotes proliferation, survival, invasiveness, and angiogenesis and is tightly linked to the etiology of numerous neoplasms, including GBM.[1] In this context, platelet-derived growth factor receptor alpha (PDGFRα) is amplified in 13% of GBM patient samples and is a promising RTK therapeutic target.[2]

Signaling cascades triggered by activated RTK entail protein phosphorylation, a process tightly regulated by the opposing function of protein tyrosine kinases (PTKs) and protein tyrosine phosphatases (PTPs). Src homology 2 (SH2) domain containing protein tyrosine phosphatase 2 (SHP2), encoded by the Ptpn11 gene, is a bona fide oncoprotein and a master regulator of PDGFR-mediated activation of MAPK/ERK signaling.[3,4] In GBM, SHP2 promotes PDGFR-driven gliomagenesis,[5] and tumor progression via Ras activation.[6] A substantial interest in targeting SHP2 for cancer therapy led to the identification of several selective small-molecule SHP2 inhibitors. SHP099 is an allosteric SHP2 phosphatase inhibitor that inhibits Ras/MAPK/ERK signaling and proliferation of cancer cells.[7]

In this issue, Sang et al evaluate the therapeutic efficacy of SHP099 in GBM with activated PDGFRα signaling.[8] SHP099 decreased cell survival and self-renewal of patient-derived glioma stemlike cells (GSCs) in culture. On the other hand, neural progenitor cells, which, unlike GSCs, lack the aberrant RTK signaling, were less responsive to this inhibitor. Response to SHP099 was enhanced even further in GBM cells with activated PDGFRα signaling. Indeed, SHP099 impaired PDGF-A–induced ERK1/2 phosphorylation and cell proliferation by specifically targeting PDGFRα-mediated SHP2 activation. RNA sequencing efforts to reveal the underlying mechanisms of increased sensitivity to SHP099 in GBM with activated PDGFRα signaling identified downregulation of genes associated with cell cycle regulation. Accordingly, treatment with SHP099 increased the percentage of GBM cells in the G0/G1 phase of the cell cycle. Pharmacokinetic studies in mice which received SHP099 by oral gavage showed comparable brain and plasma concentrations, suggesting that this small molecule is able to effectively penetrate the brain. While these pharmacokinetic studies are certainly promising, more elaborate studies are needed to confirm that SHP099 is capable of penetrating the blood–brain barrier and blood–tumor barrier to achieve a functionally relevant therapeutic dose at the tumor site. The efficacy of this inhibitor was further evaluated in Ink4a/Arf-/- mouse astrocytes ectopically expressing PDGFRα/PDGF-A and in GSCs with activated PDGFRα signaling implanted in the brain of mice. Treatment with SHP099 significantly extended the overall survival in both models and reduced ERK1/2 activation. Further, combination of SHP099 with the conventional GBM chemotherapeutic temozolomide showed significantly prolonged survival compared with either treatment alone.

Collectively, the results presented by Sang et al suggest that GBM patients with amplified or mutated PDGFR are likely to benefit most from SHP2 inhibition. One of the remaining open questions is whether the inhibition of SHP2 could also benefit EGFR-mutated GBM tumors, given that EGFR is altered in 60% of primary GBM patients.[9] Both EGFR and PDGFR potentiate

Ras signaling and downstream activation of MAPK/ERK and PI3K/AKT. Further, SHP2-mediated activation of MAPK reportedly increases tyrosine phosphorylation of the EGFR variant III mutant (EGFRvIII),[10] and SHP2 activity is increased in EGFRvIII-expressing GBM cell lines.[6]

Therapeutic targeting of RTKs such as EGFR, PDGFR, and vascular endothelial growth factor receptor has been fairly disappointing and failed to significantly extend overall survival or halt disease progression in GBM patients. Conjoining factors such as moderate specificity, potency, and blood–brain barrier permeability of targeted agents, as well as redundant signaling pathways activated downstream of RTKs in highly heterogeneous GBMs limit durable responses and inevitably lead to the emergence of therapeutic resistance. As novel inhibitors with increased potency, specificity, and permeability are constantly being developed, combination therapies to target multiple oncogenic nodes should be explored. As such, combining inhibitors of RTK/RTP (such as EGFR) and PTP (such as SHP2) might effectively block oncogenic MAPK/ERK and PI3K/AKT signaling pathways, thus achieving a superior therapeutic outcome. Given the functional role of SHP2 in gliomagenesis and disease progression, selective targeting of SHP2 may have clinical implications for this incurable disease. Overall, the compelling preclinical evidence provided by Sang et al should motivate future efforts to translate SHP2-targeted therapy into the clinic for the treatment of GBMs and potentially other cancers with PDGFRα amplification.

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