Glioblastoma

Major finding: Fusion proteins combining *FGFR* and *TACC* are transforming in a subset of glioblastomas.

Mechanism: FGFR–TACC fusions promote constitutive FGFR kinase activity and induce aneuploidy.

Impact: FGFR inhibitors may provide therapeutic benefit to patients harboring this fusion.

FGFR–TACC FUSION PROTEINS ARE ONCOGENIC IN GLIOBLASTOMA

Defects in mitosis are thought to underlie the acquisition of chromosomal instability (CIN) and subsequent aneuploidy that are characteristic of solid tumors. One way this might occur is via chromosomal translocations that generate gain-of-function fusion proteins from genes that regulate mitosis and cell growth. Singh and colleagues investigated whether such fusions exist in human glioblastoma samples using computational approaches to analyze either whole-transcriptome or whole-exome sequencing. This analysis identified a recurrent intrachromosomal fusion of the kinase domain of fibroblast growth factor receptor (FGFR) genes *FGFR1* or *FGFR3* to the transforming acidic coiled-coil (TACC) domain of *TACC1* or *TACC3* in a small subset of glioblastomas. The resulting fusion protein was detected in primary tumor samples, and FGFR–TACC expression was sufficient to transform both fibroblasts and astrocytes in soft-agar assays in an FGFR kinase-dependent manner. Furthermore, FGFR–TACC fusions significantly enhanced the formation of highly proliferative, invasive glioma-like tumors in subcutaneous and intracranial tumor models. This oncogenic effect was mediated through constitutive FGFR kinase activity and noncanonical downstream signaling. In addition, FGFR–TACC fusions localized via the TACC domain to the mitotic spindle and the midbody, suggesting that this protein may promote chromosomal segregation errors. Indeed, expression of FGFR–TACC led to delayed, aberrant mitosis and increased aneuploidy; however, long-term FGFR–TACC expression conferred a proliferative advantage that allowed cells to overcome the growth-inhibitory effects of acute aneuploidy. Importantly, treatment with FGFR kinase inhibitors reversed the CIN and defective mitotic phenotypes *in vitro* and inhibited tumor growth driven by FGFR–TACC *in vivo*. These findings demonstrate an important role for this fusion protein in tumor initiation and suggest that FGFR inhibitors may be clinically useful in some cases of glioblastoma. ■

Singh D, Chan JM, Zoppoli P, Niola F, Sullivan R, Castano A, et al. Transforming fusions of FGFR *and* TACC *genes in human glioblastoma. Science 2012 July 26 [Epub ahead of print].*

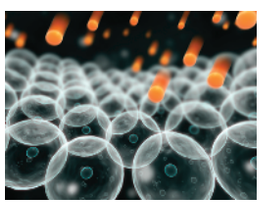
Drug Resistance

Major finding: Stromal cell–secreted HGF confers innate resistance to BRAF inhibition.

Clinical relevance: High plasma and stromal HGF levels were correlated with poor response to vemurafenib.

Impact: RAF inhibitors may be more effective when used in combination with inhibitors of HGF or MET.

STROMAL GROWTH FACTORS CONFER RESISTANCE TO TARGETED THERAPIES



Most kinase-addicted tumors have partial or complete innate resistance to targeted therapy. Straussman and colleagues hypothesized that the tumor environment plays a key role in mediating drug resistance, and they therefore systematically evaluated the stromal contribution to drug resistance by culturing cancer cell lines alone or in combination with human stromal cell lines in the presence of increasing doses of anticancer agents. Strikingly, the efficacy of most targeted therapies tested was diminished when cancer cells were cocultured with stromal cells due to the secretion of soluble factors. In another study, Wilson and colleagues similarly found that most kinase-addicted cancer cell lines they tested could be rescued from sensitivity to targeted therapies when exposed to several different soluble growth factors. In addition to identifying evidence for a general mode of drug resistance driven by the tumor microenvironment, both groups observed that hepatocyte growth factor (HGF) conferred resistance to the BRAF inhibitor vemurafenib on multiple *BRAF*-mutant melanoma cell lines through concurrent activation of the PI3K and MAPK pathways downstream of its receptor, MET. Furthermore, inhibition of MET with crizotinib restored sensitivity to vemurafenib *in vitro* and enhanced the effect of vemurafenib on melanoma xenograft tumor growth. In clinical samples, Wilson and colleagues observed that high pretreatment plasma HGF levels were predictive of worse progression-free and overall survival, and Straussman and colleagues found that HGF was frequently detected in stromal cells in pretreatment biopsy samples of *BRAF*-mutant melanomas and that patients with HGF-positive biopsies had a significantly poorer response to vemurafenib treatment. These findings may explain the high rate of innate resistance to vemurafenib in patients with *BRAF*-mutant melanoma and suggest that combining HGF- or MET-targeted therapy with BRAF inhibition may be a more effective therapeutic strategy. ■

Straussman R, Morikawa T, Shee K, Barzily-Rokni M, Qian ZR, Du J, et al. Tumour micro-environment elicits innate resistance to RAF inhibitors through HGF secretion. Nature 2012;487:500–4.

Wilson TR, Fridlyand J, Yan Y, Penuel E, Burton L, Chan E, et al. Widespread potential for growth-factor-driven resistance to anticancer kinase inhibitors. Nature 2012;487:505–9.