Glioblastoma Resistance to Anti-VEGF Therapy: Has the Challenge Been MET?

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In glioblastoma cells the receptor tyrosine kinase c-Met is upregulated in response to bevacizumab and plays an important role in promoting invasion and tumor recurrence. These data support novel links between VEGF-A and hepatocyte growth factor and suggest that c-Met and its signaling effectors may be effective targets for anti-invasive therapies. Clin Cancer Res; 19(7): 1–3. ©2013 AACR.
MET gene expression or pharmacologic inhibition of c-Met kinase activities blocks tumor cell invasion and resistance to bevacizumab. These results are consistent with a 2012 publication by Lu and colleagues, showing that c-Met is upregulated in bevacizumab-treated patient samples and in mouse mosaic models of glioblastoma genetically null for VEGF-A (9). Interestingly, in bevacizumab-sensitive tumors c-Met and VEGFR-2 form heterodimeric complexes that suppress HGF-mediated tumor cell growth and invasion. Met/VEGFR-2 heterodimers associate with the cytoplasmic tyrosine phosphatase PTP1B, which dephosphorylates the c-Met kinase domain and inhibits interactions with proinvasive signaling effectors. Collectively, the data from Aghi and colleagues and Bergers and colleagues (both articles were published collaboratively) reveal cross-talk between the HGF/SF and VEGF-A signaling pathways that negatively regulate tumor cell invasiveness during glioblastoma growth and progression. Met upregulation in response to bevacizumab, probably in combination with other cell-intrinsic and cell-extrinsic events that promote resistance, alters this negative regulation, and drives glioblastoma invasion (Fig. 1).

These data raise several important questions. First, in bevacizumab-resistant glioblastomas, what are the essential pathways that drive VEGF-independent angiogenesis? There are multiple proangiogenic factors; however, one obvious candidate is c-Met, which is expressed in endothelial cells and has proangiogenic functions via HGF/SF (8). Therefore, it is enticing to speculate that in addition to autocrine HGF/c-Met signaling events in invasive tumor cells, HGF/SF may also promote VEGF-independent neoangiogenesis via paracrine signaling between glioblastoma cells and blood vessels. Second, Jahangiri and colleagues have discovered multiple genes that are differentially expressed in glioblastoma samples upon development of bevacizumab resistance. Are these genes differentially expressed in the majority of glioblastoma cells or in select subpopulations of cells? Stem-like glioblastoma cells express VEGF-A and home to perivascular niches (10), suggesting that gene regulation in glioblastoma stem cells may contribute to acquired bevacizumab resistance. Alternatively, glioblastoma cell death may lead to enrichment of subpopulations of intrinsically resistant tumor cells that express high endogenous levels of c-Met. The U87 xenograft selection models suggest acquired resistance as U87 cell lines have been cultured for decades and lack stem-like properties. However, bevacizumab resistance in the U87 models and the primary glioblastoma cultures can be serially passaged, suggesting intrinsic stability. Delineating possible contributions by intrinsically resistant populations of glioblastoma cells in preclinical models and patient samples warrants further investigation. Third, can bevacizumab-resistant tumors be classified on the basis of their molecular genetic characteristics? Bevacizumab-sensitive glioblastoma cells are epithelial-like, whereas resistant cells upregulate some mesenchymal markers. However, the gene expression signatures of resistant tumors are distinct from mesenchymal glioblastomas (11), suggesting that antivascular therapies may generate unique tumor subtypes that should be classified and studied. Fourth, the exact Met-regulated intracellular signaling pathways that drive invasion of glioblastoma cell populations that should be classified and studied. Fourth, the exact Met-regulated intracellular signaling pathways that drive invasion of glioblastoma cell populations that should be classified and studied.
Glioblastoma cell invasion remain to be determined, and identifying these effectors may lead to new therapies. Jahangiri and colleagues report that Fak and Stat3 signaling effectors are hyperphosphorylated in invasive cells, and there are agents in the clinic that target these proteins. Another related question is whether the major c-Met signaling effector Gab-1 (8) is essential for proinvasive signaling and if Met phosphorylation of Gab-1 is functionally linked to Fak and Stat3. Finally, will combined inhibition of VEGF-A and HGF/SF pathways be effective antiangiogenic and anti-invasive therapies? The dual-specific kinase inhibitor cabozantinib, which targets Met and VEGFR-2, has shown encouraging results in preclinical models of pancreatic cancer (12) and has been approved for medullary thyroid cancers. However, it remains to be determined if clinical trials with this inhibitor or others will effectively impact glioblastoma recurrence and invasion.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

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References
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