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Dissecting the therapeutic determinants of MET inhibition: HGF-autocrine activation predicts sensitivity to MET inhibitor in Glioblastoma

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Due to its invasive nature, glioblastoma (GBM) is the most aggressive brain cancer. Hepatocyte growth factor (HGF) binds to MET tyrosine kinase receptor and induces invasive tumor growth. As MET inhibitors are entering clinical trials against several types of cancer including GBM, it is compelling to identify therapeutic determinants which could indicate which patient subsets are suitable for this therapy. We investigated *in vivo* three types of GBM models for their sensitivity to MET or EGFR inhibitors: 1) Tumors sustained by an HGF-autocrine loop; 2) tumors displaying paracrine HGF tumor growth; and 3) tumors with *MET* polysomy and *EGFR* amplificationOf the three tumor types, we observed that HGF- autocrine activation correlates with p-MET levels in the HGF autocrine GBM cell lines, which in turn are extremely sensitive to MET inhibition *in vivo*. Moreover, serum HGF levels in HGF-autocrine loop GBM xenografts correlate with MET inhibition. Paracrine HGF can enhance GBM growth *in vivo*, but they were not significantly sensitive to MET inhibition. In type three tumors, EGFR *VIII* amplification predicted sensitivity to erlotinib, but *MET* polysomy in the same tumor did not display MET activity and the cells did not show sensitivity to MET inhibition. We conclude that HGF- autocrine activation GBM tumors bear an activated MET signaling pathway that may be used to predict sensitivity to MET inhibitors in GBM patients. However, targeting MET alone may not be sufficient for treating GBM and the combination of MET with other RTK inhibitors, especially EGFR inhibitors should be considered.

Biography

Dr. Xie completed her doctorate in Oncology from Fudan University in China. She then joined the Laboratory of Molecular Oncology (LMO) at Van Andel Research Institute as a postdoctoral fellow. She has been continuously working on the MET signaling pathway, focusing mainly on brain cancer. Dr. Xie is currently a Senior Research Scientist in the (LMO) under the direction of Dr. George Vande Woude; her major research goal is to understand the mechanism of brain cancer malignancy and to develop novel strategies particular with MET inhibitors to target glioblastoma.