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Multiple targets to tackle tough tumours

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Targeting receptor tyrosine kinases (RTKs) has become an important therapeutic approach for a wide range of human cancers. However, most tumours do not respond to single RTK inhibition and those that do rapidly develop drug resistance. For glioblastoma multiforme (GBM), only PTEN intact tumours show a modest non-durable response to the single-target approach. The DePinho laboratory now shows that multiple RTKs are co-activated in untreated GBM and combinations of RTK inhibitors, but not single agents, may be used as a strategy for their treatment.

In GBM, single-agent anti-epidermal growth factor receptor (EGFR) or anti-platelet-derived growth factor receptor (PDGFRα and/or PDGFRβ) inhibition does not suppress phosphatidylinositol-3-kinase (PI3K) signalling, so the authors investigated the possibility that multiple PI3K activators co-exist in glioma cells. Immunoprecipitations identified the PI3K-activating proteins ERBB3 (an RTK), GAB1 (a docking protein that binds activated RTKs) and MET (an RTK co-immunoprecipitated with GAB1), among other RTKs.

The relationship between EGFR and MET was explored using glioma cells that express wild-type EGFR and constitutively activated EGFRvIII (EGFR*). In U87MG cells, MET is phosphorylated and bound to GAB1, but expression of wild-type EGFR and EGFR* displaced MET from the GAB1–PI3K complex. Downstream signalling did not change, indicating that MET and EGFR act as independent redundant inputs to the signalling network and suggesting that single-target inhibition of MET or EGFR would be ineffective.

To investigate this, single and combined inhibition was studied in U87MG-EGFR* cells using the EGFR inhibitor erlotinib and the MET inhibitor SU11274. Treatment with either inhibitor alone had little effect; however combination treatment not only reduced downstream signalling but also significantly decreased cell viability and growth. Addition of the PDGFR/KIT/ABL kinase inhibitor imatinib to the combination eliminated any residual downstream signalling and dramatically inhibited cell viability. Importantly — as lack of response to anti-EGFR treatment was reportedly associated with loss of the tumour suppressor PTEN — combination treatment reduced downstream signalling regardless of PTEN status, indicating that this could be a strategy for most GBM tumours refractory to single inhibitors.

Given the potential nonspecific actions of the RTK inhibitors, RNA interference (RNAi) was used to verify that blockade of RTKs is responsible for inhibiting downstream signalling. Transfection of glioma cells with small interfering MET in combination with erlotinib and imatinib resulted in a similar level of inhibition of cell growth observed with the combination of RTK inhibitors. RNAi against PDGFR and EGFR showed similar trends.

Finally, antibody array profiling of untreated primary GBM tumours showed co-activation of EGFR, MET and PDGFR, as well as RTKs not previously linked with GBM such as RET, MDT1R and CSF1R. This suggests that profiling the activated RTKs in individual tumours could help to tailor therapy. Taken together these data clearly demonstrate co-activation of RTKs in GBM that respond to *in vitro* multi-target inhibition. This strategy could be readily implemented for refractory tumours and clinical trials of combination treatments are currently underway.

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ORIGINAL RESEARCH PAPER Stommel, J. M. *et al.* Coactivation of receptor tyrosine kinases affects the response of tumor cells to targeted therapies. *Science* **318**, 287–290 (2007)
FURTHER READING Dancey, J. E. & Chen, H.X. Strategies for optimizing combinations of molecularly targeted anticancer agents. *Nature Rev. Drug Discov.* **5**, 649–659 (2006)