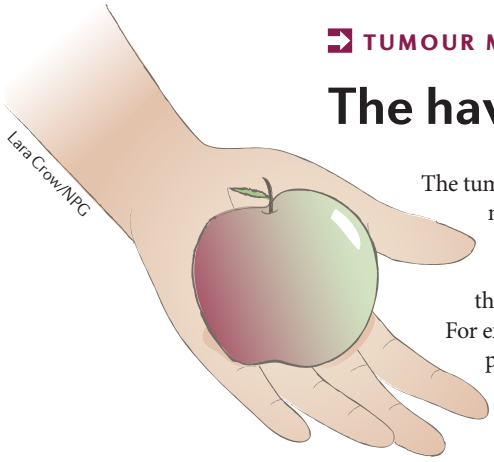


TUMOUR MICROENVIRONMENT

The haves and the have nots

The tumour microenvironment is emerging as an important determinant of therapeutic responses. For example, autocrine, paracrine and endocrine activation of oncogenic receptor tyrosine kinases (RTKs) can subvert therapeutic inhibition by maintaining the activation of common intracellular signalling pathways. Three papers have investigated this further — with interesting results.

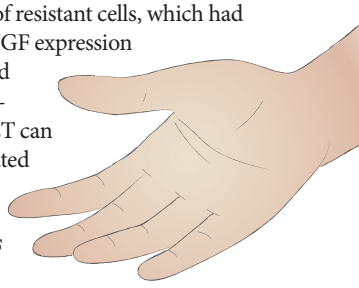
Using co-culture experiments, Straussman and colleagues assessed how 23 human stromal cell lines affected the sensitivity of 45 human cancer cell lines to 35 anticancer drugs. They found that BRAF-V600E melanoma cells became resistant to the BRAF inhibitor PLX4720 when cultured with fibroblasts. The presence of hepatocyte growth factor (HGF) in conditioned medium from these fibroblasts correlated with resistance. Moreover, the proportion of HGF^+ melanoma-associated stromal cells correlated with a poorer response to treatment with BRAF inhibitors than non-HGF^+ samples of human BRAF-V600E melanoma. The inhibition of HGF or MET (the HGF receptor, which was also activated in HGF^+ samples) resensitized melanoma cell lines to BRAF inhibitors, indicating that paracrine HGF–MET signalling mediates this innate resistance. Both the MEK–ERK and PI3K–AKT pathways were activated when BRAF-V600E melanoma cells were treated with HGF; other ligands activated either ERK or AKT, but these did not abrogate drug sensitivity, indicating that both pathways need to be activated to confer resistance.

> “HGF–MET signalling is an important determinant of therapeutic responses”

Finally, the authors found evidence of autocrine HGF–MET signalling in non-melanoma BRAF-V600E-mutant cancer cell lines, and combined BRAF and MET inhibition had synergistic effects in two such cell lines.

Wilson and colleagues assessed the effects on drug sensitivity of six different ligands on 41 human tumour-derived cell lines that have oncogenic RTK signalling. HGF, fibroblast growth factor (FGF) and neuregulin (NRG1) conferred drug resistance to the highest number of cell lines. Analyses of ligand-treated resistant cells revealed that either of the PI3K–AKT or MEK–ERK pathways, or both, were reactivated. Ligand-mediated drug resistance was overcome by inhibiting the corresponding RTK, but this had no effect as a monotherapy, indicating that the resistance conferred by ligand-RTK activation is a feedback response to the initial targeted therapy. These authors found various incidences of ligand-mediated therapeutic resistance, including HGF-induced resistance of BRAF-V600E melanoma cells to vemurafenib (a BRAF-V600E inhibitor). BRAF-V600E melanomas treated with MET agonistic antibodies were also resistant to vemurafenib *in vivo*. Finally, circulating levels of HGF (prior to treatment) correlated with poorer progression-free survival and overall survival in a cohort of 126 patients with BRAF-V600E melanoma who were treated with vemurafenib.

Kentsis and colleagues took a different focus. An RNA interference screen for genes that are required for the survival and proliferation of an acute myeloid leukaemia (AML) cell line identified 30 genes, one of which was *HGF*. Inhibiting HGF–MET signalling suppressed the growth of AML cells, indicating that autocrine HGF–MET signalling is important for the survival and growth of AML. Analyses of two cohorts of human AML samples confirmed that HGF and MET are commonly activated in a subset of AML cells (particularly those expressing oncogenic chimeric transcription factors). Indeed, the authors found that HGF expression and MET activation was induced in mouse haematopoietic cells transformed with a range of AML-associated chimeric transcription factors. Interestingly, they found that chronic treatment of HGF^+ AML cells with crizotinib (which inhibits MET) led to the outgrowth of resistant cells, which had increased HGF expression and regained MET activation. As MET can be co-activated with other RTKs, such as FGF receptor 1 (FGFR1), the authors treated KG1 cells (which have an *FGFR1OP2–FGFR1* translocation) with an FGFR1 inhibitor and crizotinib. This combination had synergistic effects *in vitro* and *in vivo* and prevented the re-expression of HGF and MET signalling and induced apoptosis, whereas the single agents had no effect. Therefore, FGFR1 activity is required for HGF induction to overcome chronic MET inhibition.



These three papers show that HGF–MET signalling is an important determinant of therapeutic responses and can be induced through paracrine, autocrine and endocrine production of HGF.

Gemma K. Alderton

ORIGINAL RESEARCH PAPERS Straussman, R. *et al.* Tumour micro-environment elicits innate resistance to RAF inhibitors through HGF secretion. *Nature* 4 Jul 2012 (doi:10.1038/nature11183) | Wilson, T. R. *et al.* Widespread potential for growth-factor-driven resistance to anticancer kinase inhibitors. *Nature* 4 Jul 2012 (doi:10.1038/nature11249) | Kentsis, A. *et al.* Autocrine activation of the MET receptor tyrosine kinase in acute myeloid leukemia. *Nature Med.* **18**, 1118–1122 (2012)