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TARGETED THERAPIES

Hepatocyte growth factor—a culprit of drug resistance

Two new studies have independently revealed that growth factors contribute to the innate drug resistance of many cancer types. Prime suspect number one is hepatocyte growth factor (HGF), which reactivates the MAPK and Akt signalling pathways to confer drug resistance.

The first study, led by Todd Golub, tested the hypothesis that cells outside the tumour—namely, stromal cells—not only promote tumour growth and metastasis but have a role in drug resistance. They treated a range of tumour cell lines (45 in total) alone or co-cultured with stromal cells (23 different types were used) with 35 commonly used cancer drugs. The results were marked: drugs otherwise capable of killing cancer cells alone were unable to do so when the cancer cells were co-cultured with stromal cells. Although different stromal cells had differing effects, resistance to targeted therapies was more pronounced than resistance to cytotoxic agents.

The researchers then went on to identify which factor or factors in particular were responsible for conferring resistance. Using *BRAF*-mutant melanoma cell lines as their model and PLX4720 (a RAF inhibitor) as their drug, they were able to home in on HGF as the likely candidate. Although HGF and its receptor MET have been implicated in melanoma growth, neither were known to have a role in resistance to RAF inhibition. Furthermore, they deduced that HGF activates the MAPK and Akt signalling pathways to override the tumour suppression caused by RAF inhibition. Looking at patient-derived samples, the investigators found that patients whose stromal cells secreted HGF had a poorer response to treatment ($P<0.05$). Overall, these results suggest that combining targeted therapy with HGF or MET inhibition might be a worthwhile endeavour.

This premise was supported by the work of another group, which showed that inhibition of MET blocked the HGF-mediated rescue in a *BRAF*-mutant xenograft model. The group, led by Jeff Settleman, identified HGF and other factors (such as EGF and FGF) as capable of rescuing a range of cancer cells that express mutationally activated kinases from growth inhibition by targeted therapy. The growth factors activate so-called redundant pathways to rescue the cell from therapy, just as HGF activates the MAPK and Akt pathways. Indeed, patients with cancer might benefit from the profiling of their kinase expression patterns. Such an approach would inform an effective strategy to treat patients. "In addition, efforts are underway to explore a much larger panel of growth factors that might also contribute to drug resistance," Settleman concluded.

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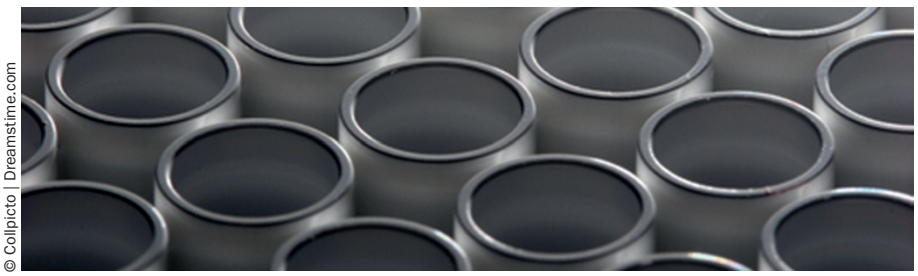

Original articles Straussman, R. *et al.* Tumour micro-environment elicits innate resistance to RAF inhibitors through HGF secretion. *Nature* doi:10.1038/nature11183 | Wilson, T. R. *et al.* Widespread potential for growth-factor-driven resistance to anticancer kinase inhibitors. *Nature* doi:10.1038/nature11246