Ligand-induced MET signaling as targetable codependence in acute myeloid leukemia

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Most, if not all, cases of acute myeloid leukemia (AML) are driven by mutations in signaling proteins, in particular tyrosine kinases.[1] However, signaling networks in AML are multilayered and exhibit considerable plasticity, which may account for the limited success of signal transduction inhibitors in clinical trials. A recent study reported by Kentis *et al.*[2] furthers our understanding of perturbed signaling in AML and, importantly, provides a potential new lead for development of targeted therapeutics in this disease.

Using large-scale RNA interference, Kentsis *et al.* discovered that the gene encoding hepatocyte growth factor (HGF) was essential in cultured human AML cells but not in cell lines derived from various lymphoid malignancies. Consistent with previous investigations,[3] elevated expression of HGF and activation of its cognate receptor, the MET receptor tyrosine kinase (RTK), was observed in nearly half of the AML cell lines and primary AML specimens tested. These findings point to autocrine MET signaling as a common pathogenetic event that also occurs in leukemias driven by other mutationally activated tyrosine kinases such as FLT3. Interestingly, aberrant HGF expression was not due to structural alterations of the *HGF* locus, suggesting the involvement of *trans*-acting factors that warrant further investigation. Genetic depletion of HGF or MET and pharmacological inhibition of MET kinase activity impaired the viability of multiple AML cell lines, demonstrating the functional relevance of the HGF-MET signaling axis. Surprisingly, treatment of HGF-expressing AML cell lines with crizotinib, a small-molecule inhibitor of MET and the related RTK ALK that was recently approved for the treatment of *ALK*-rearranged lung adenocarcinoma, led to rapid restoration of MET signaling and cell survival. This acquired resistance was found to be due to upregulation of HGF, which was mediated by another RTK, FGFR1, via an as yet undetermined molecular mechanism in cells harboring a chromosomal rearrangement that renders FGFR1 constitutively active. Accordingly, concomitant MET and FGFR1 inhibition blocked the adaptive response to crizotinib and resulted in sustained killing of human AML cells both *in vitro* and in immunodeficient mice. Collectively, these results demonstrate widespread dependence of AML cells on HGF-mediated MET signaling, and confirm compensatory ligand expression as an important mechanism of resistance to inhibition of cell surface receptors in AML that may be overcome by combination therapy.[4]

The findings of Kentsis *et al.* highlight several general principles relevant to the identification of new cancer drug targets. First, they underscore the potential of unbiased functional genetic screens for identifying gene products that promote tumorigenesis and may be targetable for therapeutic benefit, a strategy that has been applied successfully to the study of epithelial and lymphoid malignancies[5,6] and is now increasingly being used in AML.[7-10] Importantly, such genes may include typical oncogenes that are affected by structural alterations, as well as genes that are not mutated and may, therefore, evade detection by DNA sequencing or copy number analysis; a situation for which the term 'non-oncogene addiction' has been suggested.[11] Secondly, the data illustrate that many cancers, including AML, are likely not 'single kinase-dependent' but rely on simultaneous activation of multiple related signaling molecules, a finding that has obvious implications for the design of therapies targeting aberrant signal transduction. Finally, these results lend support to the concept that in-depth analysis of the vulnerabilities of specific cancers may uncover 'actionable' proteins that are targeted by drugs already in clinical use for other indications. Thus, studies such as that by Kentsis *et al.* can identify biomarker-guided therapeutic strategies with immediate translational potential.

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