Nature Reviews Clinical Oncology | Published online 19 Aug 2016; doi:10.1038/nrclinonc.2016.130

OVARIAN CANCER

Place your BETs on combination therapy

> BET-inhibitor-resistant cells showed exquisite sensitivity to RTK/MAPK/PI3K pathway inhibition

BET inhibitors can counter epigenetic mechanisms of oncogene expression, and are being evaluated in clinical trials for a range of cancers. New findings demonstrate that active kinome reprogramming can result in resistance to these agents, but also highlight novel drug combinations that might overcome this challenge.

James Duncan and colleagues used a proteomics approach involving multiplexed inhibitor beads (MIBs) to explore the changes in kinase expression and activity after acute or chronic exposure of a range of ovarian cancer cell lines to BET inhibitors. "MIBs consist of layers of immobilized ATP-competitive pan-kinase inhibitors that allow the selective enrichment of endogenous protein kinases from cell lysates," Duncan explains. Quantitation of the enriched kinases using mass spectrometry provides insights into the kinome profile of the cells.

Using this approach, BET-inhibitor-sensitive cell lines were found to upregulate kinases involved in apoptosis, and concomitantly downregulate pro-survival receptor tyrosine kinase (RTK)/MAPK/PI3K signalling. By contrast, overexpression or activation of various RTK/MAPK/PI3K pathway components was characteristic of cell lines with intrinsic or acquired resistance to BET inhibitors. Interestingly, many of the kinome changes in resistant cells were reversed upon removal of BET inhibition, opening important questions regarding intermittent dosing.

In addition, analysis of the MIBs-defined kinome signatures revealed candidate kinase-inhibitor combinations with synthetic lethality. Duncan summarizes: "BET-inhibitor-resistant cells showed exquisite sensitivity to RTK/MAPK/PI3K pathway inhibition, and the combined blockade of BET and RTK, MAPK, or PI3K signalling universally enhanced growth inhibition in ovarian cancer cells, strongly supporting the evaluation of such combinations for the treatment of ovarian cancer."

He concludes: "our findings suggest that BET inhibitors may have limited success as single agents in ovarian cancer owing to kinome reprogramming, and combination therapies targeting BET proteins and RTK/MAPK/PI3K signalling will be required. Importantly, BET, RTK, MAPK, and PI3K inhibitors are all being explored avidly in clinical trials and, therefore, combinations of these drugs could readily be incorporated into ongoing trials in patients with ovarian cancer."

David Killock

ORIGINAL ARTICLE Kurimchak, A. M. *et al.* Resistance to BET bromodomain inhibition is mediated by kinome reprogramming in ovarian cancer. *Cell Rep.* http://dx.doi.org/10.1016/j.celrep.2016.06.091 (2016)