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Abstract 1081: Genome-wide CRISPR screens reveal Hippo pathway activation as a resistance mechanism in BRAF mutant colon cancer FREE

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Abstract

BRAF V600E mutations occur in a subset of colon cancers. These are typically resistant to chemotherapy and are associated with a poor outcome. Combination treatment with BRAF and EGFR inhibitors is superior to standard chemotherapy and has recently received FDA approval, however the early emergence of drug resistance is a significant clinical problem. Clinical studies of resistant patients have identified mutations and amplifications in the MAPK pathway as important resistance drivers.

To identify novel non-MAPK dependent resistance mechanisms, genome-wide CRISPR/Cas9 knockout screens were performed to identify genes causing resistance to a combination BRAF/MEK/EGFR inhibitor regimen in the BRAF mutant HT29 and LS411N colon cancer cell lines. A number of strong resistance hits were identified but importantly, only 3 genes (CSK, ARID1A and STK11) were detected as significantly enriched in both cell lines screened. Two of these, CSK and ARID1A, have been shown to play a role in activation of the Hippo signaling pathway.

The generation of CSK knockout colon cell lines confirmed resistance to BRAF/MEK/EGFR inhibition both in vitro and in vivo using xenograft models. Furthermore, since CSK is a negative regulator of SRC, re-sensitisation of resistant BRAF mutant CSK knockout cells was achieved by adding Src inhibitors (Dasatinib and Saracatinib) to the combination therapy. Nuclear localisation of the transcription factors YAP1 and WWTR1 and binding to TEAD family members are required for Hippo pathway activation and we confirmed significantly increased nuclear YAP1/WWTR1 in CSK knockout cells. Furthermore, YAP1/WWTR1 nuclear localisation in these cells was reversed by

treatment with Src inhibitors. Novel pharmacological TEAD inhibitors have recently been developed and will also be used to confirm that resistance can be overcome by specifically targeting the Hippo pathway. Expression profiling of CSK knockout cells revealed significant enrichment of pathways associated with Hippo signaling. Genes involved in regulating Hippo pathway activation were also identified as CRISPR screen resistance hits in both lung and head and neck cancer cell lines, suggesting that this may be an important mechanism of resistance among other tumour types and not limited to the colon.

Here we show that activation of the Hippo pathway is a potential MAPK-independent resistance mechanism in BRAF mutant colon cancer, readily reversible by rational pharmacological targeting. Given the development of specific Hippo pathway inhibitors and plans for their use in clinical trials, activation of Hippo signaling should be considered in resistant BRAF mutant colon cancer where alterations in the MAPK pathway are not detected.

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