THE MAPK PATHWAY IS A THERAPEUTIC TARGET IN BRAF-MUTANT COLORECTAL CANCER

Mutations in the BRAF oncogene occur in 5–10% of metastatic colorectal cancer and are associated with poor prognosis. Although the BRAF inhibitors vemurafenib and dabrafenib and the MEK inhibitor trametinib are effective in BRAF-mutant melanoma, BRAFV600E-mutant colorectal tumors lack sensitivity to single-agent BRAF or MEK inhibition, likely due to feedback reactivation of MAPK signaling. Preclinical studies suggest that combined blockade of BRAF and MEK may result in enhanced MAPK suppression, prompting Corcoran, Atreya, and colleagues to assess the safety and clinical activity of dabrafenib plus trametinib in patients with BRAFV600E-mutant metastatic colorectal cancer as part of a phase I/II trial. Dual therapy was well tolerated, with the most common adverse events being nausea, pyrexia, and fatigue, consistent with those observed in patients with metastatic melanoma. Among 43 patients, ten patients (23%) remained on treatment for greater than six months, and a reduction in tumor size was detected in 16 patients, with a partial response in four patients (9%), a durable complete response lasting greater than 36 months in one patient (2%), and stable disease in 24 patients (56%). Pharmacodynamic analysis revealed a decrease in MAPK signaling in during-treatment biopsies compared with pretreatment samples; however, this reduction was markedly less than that reported for patients with BRAF-mutant melanoma. Consistent with this finding, the median progression-free survival was only 3.5 months, suggesting that suboptimal MAPK inhibition may limit the efficacy of this combination in BRAF-mutant colorectal cancer. Of note, genetic alterations in the PI3K pathway were detected in patients who achieved a decrease in tumor lesion size, suggesting a potential association with response to dual BRAF/MEK inhibition. Furthermore, therapeutic responses of patient-derived xenograft models generated from during-study biopsies correlated with clinical responses. These findings validate the MAPK pathway as a therapeutic target in BRAFV600E-mutant colorectal cancer and support the development of therapeutic strategies to improve suppression of MAPK signaling in these tumors.


Drug Resistance

SINGLE-CELL ANALYSIS OF PROSTATE CTCs HIGHLIGHTS RESISTANCE MECHANISMS

Androgen receptor (AR) inhibitors have shown some clinical efficacy in castration-resistant prostate cancer (CRPC), but responses are often not durable and vary among patients. Identification of the mechanisms underlying acquired resistance to AR inhibitors has been hampered by the challenge of obtaining serial bone biopsies in metastatic disease. As an alternative approach, Miyamoto, Zheng, and colleagues used microfluidic technology to isolate circulating tumor cells (CTCs), defined by expression of prostate lineage–specific genes and epithelial markers, from 13 patients with metastatic prostate cancer. RNA-sequencing (RNA-seq) analysis of single prostate CTCs revealed heterogeneity in transcriptional profiles within individual patients, as well as in CTCs compared with primary tumors. In addition, heterogeneous patterns in antiandrogen resistance mechanisms, including AR splice variants, were observed among the CTCs of patients with CRPC, with more than half of patients harboring more than one type of AR alteration. Retrospective analysis of CTCs from patients who experienced tumor progression during enzalutamide therapy also highlighted AR-independent drug resistance mechanisms; in particular, enrichment of noncanonical WNT signaling was detected in a distinct subset of prostate cancer cells from those with high glucocorticoid receptor expression, which has been implicated as a mechanism of antiandrogen resistance. Noncanonical WNT ligands were expressed by a subset of prostate cancer cells, and WNT5A expression was induced in enzalutamide-resistant cells. WNT5A knockdown diminished the proliferation of resistant cells, whereas ectopic expression of WNT5A decreased the sensitivity of androgen-sensitive prostate cancer cells to enzalutamide. Moreover, noncanonical WNT signaling was associated with enzalutamide resistance in a mouse xenograft model of prostate cancer. These findings support a role for the noncanonical WNT pathway in antiandrogen resistance and demonstrate that heterogeneous mechanisms contribute to drug resistance in advanced prostate cancer.

Single-Cell Analysis of Prostate CTCs Highlights Resistance Mechanisms

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