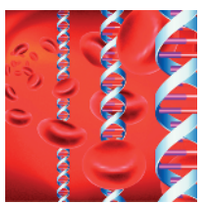
Colorectal Cancer

Major finding: Resistant colorectal cancer cells dynamically evolve in response to intermittent drug treatment.

Concept: Analysis of circulating tumor DNA in blood can be used to monitor clonal evolution in colorectal cancer.

Impact: Liquid biopsies can identify patient-specific resistance mechanisms and inform treatment decisions.

CIRCULATING TUMOR DNA CAPTURES MOLECULAR EVOLUTION IN COLORECTAL CANCER



Genomic profiling of single biopsies of primary tumors or metastases provides a spatially and temporally limited picture of the mutational landscape and may fail to capture tumor heterogeneity or therapy-induced molecular changes, emphasizing the need for repeated biopsies to monitor disease progression and drug resistance. Siravegna and colleagues evaluated whether analysis of circulating tumor DNA (ctDNA) in blood-based liquid biopsies could be used to track clonal evolution and therapeutic responses in patients with colorectal cancer. Indeed, the profiles of RAS pathway mutations in blood and tissue samples were highly concordant, and analysis of ctDNA highlighted mutations not detected in matched tumor tissue samples in eight patients. Furthermore, next-generation sequencing of ctDNA samples expanded the landscape of somatic genetic alterations associated with primary resistance to EGFR-targeted therapies by identifying *ERBB2* amplification and *MAP2K1* mutations, together with genomic changes previously implicated in acquired resistance to anti-EGFR antibodies, including *KRAS* mutations and *MET* amplification. Comparison of liquid biopsies taken at baseline and at relapse when anti-EGFR therapy was suspended revealed that the percentage of mutant *KRAS* alleles in ctDNA increased during treatment with EGFR-specific antibodies, but declined after treatment withdrawal. This decrease in mutant *KRAS* clones was also observed using *in vitro* preclinical models of acquired resistance and was associated with partial restoration of drug sensitivity. Consistent with this finding, rechallenge with EGFR-specific antibodies after additional lines of therapy was clinically effective in patients with colorectal cancer; longitudinal analysis of ctDNA from three patients receiving intermittent anti-EGFR treatment revealed a decline in mutant *KRAS* clones in the blood when the initial treatment was suspended, followed by an increase in the percentage of mutant *KRAS* alleles during rechallenge therapy. These findings indicate that the colorectal cancer genome dynamically adapts to pulsatile drug schedules and provide molecular support for the notion that rechallenge with EGFR-targeted therapies may be effective in colorectal cancer. ■

Siravegna G, Mussolin B, Buscarino M, Corti G, Cassingena A, Crisafulli G, et al. Clonal evolution and resistance to EGFR blockade in the blood of colorectal cancer patients. Nat Med 2015;21:795–801.

Drug Resistance

Major finding: Inactivation of SYK synergistically increases paclitaxel sensitivity in ovarian cancer cells.

Mechanism: SYK inhibition in the presence of paclitaxel stabilizes microtubules in paclitaxel-resistant cells.

Impact: Dual treatment with SYK inhibitors may overcome paclitaxel resistance in recurrent ovarian cancer.

SYK BLOCKADE ENHANCES PACLITAXEL RESPONSE IN OVARIAN CANCER

Patients with ovarian high-grade serous carcinoma (HGSC) initially respond to treatment with the chemotherapeutic agents carboplatin and paclitaxel, but frequently experience tumor relapse. However, the mechanisms underlying the development of resistance to these drugs remain poorly understood. Yu and colleagues found that the levels of spleen tyrosine kinase (SYK) and phosphorylated SYK were increased in recurrent ovarian tumors isolated from patients previously treated with carboplatin and paclitaxel compared with matched primary untreated tumors. In addition, SYK expression and activation were upregulated in paclitaxel-resistant ovarian cancer cell lines and positively correlated with paclitaxel response *in vitro*, suggesting that SYK overexpression may confer chemoresistance. SYK inactivation via knockdown or pharmacologic inhibition with the active metabolite of fostamatinib, R406, impaired the growth of ovarian cancer cells and synergistically enhanced the sensitivity of paclitaxel-resistant primary ovarian cancer cells and ovarian cancer cell lines to paclitaxel *in vitro*. Consistent with this finding, dual treatment with R406 and paclitaxel suppressed the growth of both naïve and paclitaxel-resistant ovarian tumor xenografts compared with single-agent treatment. Phosphoproteomic analysis in paclitaxel-resistant ovarian cancer cells identified substrate proteins phosphorylated by SYK, which were enriched in proteins implicated in cell growth pathways and cytoskeletal organization. In particular, SYK phosphorylated the microtubule components tubulin and the microtubule-associated proteins (MAP) MAP1B and MAP4; phosphorylation of these substrates was increased in paclitaxel-resistant cells and correlated with total and phosphorylated SYK levels in HGSC samples. Expression of an active SYK mutant enhanced MAP1B and MAP4 phosphorylation and was sufficient to confer paclitaxel resistance, whereas inhibition of SYK augmented paclitaxel-induced microtubule stabilization in paclitaxel-resistant ovarian cancer cells. These findings provide preclinical evidence for targeting SYK in ovarian cancer and suggest that SYK inhibition may enhance treatment response and overcome paclitaxel resistance in patients with HGSC. ■

Yu Y, Gaillard S, Phillip JM, Huang TC, Pinto SM, Tessarollo NG, et al. Inhibition of spleen tyrosine kinase potentiates paclitaxel-induced cytotoxicity in ovarian cancer cells by stabilizing microtubules. Cancer Cell 2015;28:82–96.