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Abstract 878: Tumor heterogeneity and lesion-specific response to targeted therapy in colorectal cancer

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Abstract

How genomic heterogeneity associated with acquired resistance to targeted agents affects response to subsequent lines of therapy is unknown. Exposure to therapy may result in selection of sub-clonal cell populations, capable of growing under drug pressures. Therefore, a single-lesion biopsy at disease progression may vastly underrepresent the molecular heterogeneity of resistant tumor clones in an individual patient and may fail to detect the existence of distinct but important resistance mechanisms that could impact clinical response.

We identified a colorectal cancer (CRC) patient in whom multiple tumor biopsies were obtained at resistance following prolonged response to with the anti-EGFR antibody cetuximab. Full-exome sequencing of 1000 cancer genes of both primary tumor and progression biopsy revealed a TP53 mutation in all samples and a novel MEK1 p.K57T mutation in one of the progressing liver biopsy. A mutation at the same MEK1 codon was identified in the cetuximab-resistant HCA46 CRC cell line. Biochemical analysis showed constitutive activation of MEK and ERK despite cetuximab treatment. However, the combination of the MEK inhibitor trametinib with either cetuximab or panitumumab restored sensitivity, suggesting a potential therapeutic strategy to overcome resistance to EGFR blockade caused by this mutation.

Accordingly, the patient was treated with the combination of panitumumab and trametinib. After 3 months, imaging demonstrated a reduction in size of the biopsied liver metastasis harboring the MEK1 mutation, but revealed that some other lesions had progressed. Plasma collected prior to therapy was analyzed by next-generation sequencing confirming the presence of both TP53 and MEK1 variants, but surprisingly unveiling a previously unrecognized KRAS mutation. ddPCR analysis of longitudinal timepoints of ctDNA unveiled that TP53 mutant levels dropped after initiation of therapy, but rose later during treatment in parallel with CEA tumor marker levels. However, MEK1 mutant levels declined sharply, indicating effective suppression of MEK1 mutant clones by panitumumab and trametinib; while KRAS mutant levels rose, indicating outgrowth of a resistant KRAS-mutant clone. Biopsy of a different liver metastasis that progressed despite panitumumab and trametinib revealed the same KRAS mutation identified in ctDNA.

In summary these findings illustrate how distinct acquired resistance mechanisms can arise concomitantly in separate metastases within the same patient, leading to mixed lesion-specific responses to subsequent targeted therapies. Liquid biopsy approaches, in association with single-tumor biopsies, have the potential to detect the presence of simultaneous resistance mechanisms residing in separate metastases in a single patient and to monitor the effects of subsequent targeted therapies.

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