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Concomitant blockade of EGFR and MEK overcomes acquired resistance to anti-EGFR therapy in colorectal cancer cells and patients' avatars.

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Abstract

2626

Background: The anti-EGFR antibodies cetuximab and panitumumab are approved for the treatment of RAS wild-type colorectal cancer (CRC) patients. The clinical efficacy of EGFR targeted antibodies is limited by the development of acquired (secondary) resistance. Here we investigated the molecular bases of relapse to anti-EGFR blockade in CRC cells and patients' samples and use xenotransplants to define a clinically applicable strategy to overcome acquired resistance. **Methods:** Molecular profiling of circulating tumor DNA was used to identify the emergence of mutations in plasma samples of patients who relapsed after anti EGFR therapies. Xenografted tumors (avatars) from patients who relapsed after EGFR blockade were established and exploited to assess the efficacy of drugs aimed at bypassing acquired resistance. **Results:** Emergence of concomitant mutations in KRAS and NRAS was detected in samples from 5 CRC patients who developed resistance to anti-EGFR antibodies. Acquired resistance to cetuximab and panitumumab was modeled in 4 CRC cell models. Resistant cells were a mixture of clones bearing alterations in KRAS, NRAS and BRAF thus closely recapitulating the patients' findings. Pathway analyses revealed that, although genetically polyclonal, resistant cells consistently displayed MEK and ERK activation but, surprisingly, were refractory to MEK inhibition. However, the resistant derivatives were sensitive to the concomitant inhibition of MEK and EGFR independently from their genetic status. Mouse xeno-transplants of lung and liver biopsies from two CRC patients who responded and subsequently relapsed upon EGFR therapy showed exquisite sensitivity to combinatorial treatment with the MEK inhibitor pimasertib and EGFR blockade with cetuximab. **Conclusions:** These observations provide a rational strategy to overcome the clonal heterogeneity that emerges when CRCs are treated with anti EGFR antibodies. We propose that MEK inhibitors, in combination with cetuximab or panitumumab, should be evaluated in CRC patients who become refractory to anti-EGFR therapies. A clinical trial (ARES) has been initiated to test this hypothesis.

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