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COLORECTAL CANCER

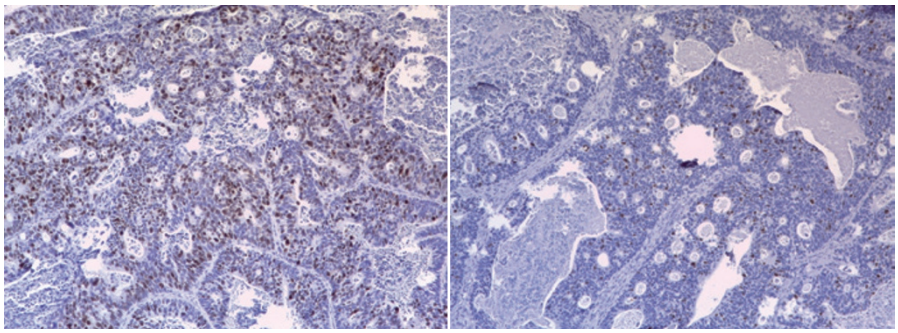
Combining drug therapies to improve treatment efficacy in metastatic colorectal cancer

Combining targeted therapies could be the way forward to improve treatment of chemorefractory metastatic colorectal cancer (mCRC) in selected patients, according to findings from a new study.

A subset of patients with CRC benefits from therapy targeting the epidermal growth factor receptor (EGFR). However, even among these patients, improvements in progression-free survival and overall survival are fairly modest compared with chemotherapy. Part of the problem seems to be that EGFR inhibitors lead to disease stabilization in the majority of patients, rather than massive tumour regressions; "...the impact of EGFR-targeted therapy in mCRC has been incremental rather than transformative," write the authors of the study in *Science Translational Medicine*.

Thus, the research team decided to investigate whether they could identify ways that might increase the number of patients demonstrating marked tumour regression compared with disease stability. "To do this, we harnessed a large series of patient-derived tumour grafts ('xenopatients') from CRC liver metastases, which were systematically profiled for several molecular parameters," explain Livio Trusolino and Andrea Bertotti, corresponding authors. The information gleaned from this step was then used to test rational drug combinations (in concert with cetuximab, an anti-EGFR antibody) in *in vivo* treatment of mouse cohorts. "The methodology is not particularly challenging—the challenging factor is how to deal with the enormous amount of data that accumulates over time!" say Trusolino and Bertotti.

The first stage of the study demonstrated that samples from xenopatients that responded to cetuximab with disease stabilization displayed high levels of EGFR family ligands and receptors. This finding led the researchers to test the combination of cetuximab and lapatinib (a dual EGFR–HER2 small-molecule inhibitor) in cases of stable disease. In 5 of 21 of these cases, this combination caused major regressions of the tumours; these cases were found to have particularly high expression of EGFR and EGFR family members.



No treatment (left panel) and combination treatment with cetuximab and an IGF-1R small-molecule inhibitor (right panel) of a CRC tumour with high expression of IGF-2. Image courtesy of L. Trusolino.

Next, the team decided to investigate other pathways that might affect EGFR inhibition. In particular, a previous study had reported high expression levels of insulin-like growth factor 2 (IGF-2) in 15% of CRC tumours. Interestingly, Trusolino, Bertotti and colleagues found that IGF-2 was strongly overexpressed in some xenopatients that responded to cetuximab with disease stabilization. Similar findings were observed in human patients using information from clinically annotated gene expression databases.

On the basis of these results, the researchers surmised that IGF-2 might have a role in attenuating the effects of EGFR inhibition. Functional studies confirmed that increased expression of IGF-2 blunted response to cetuximab. Furthermore, co-targeting EGFR and IGF-2 signals (with an IGF-1R small-molecule inhibitor) in IGF-2-overexpressing xenopatients led to massive tumour regressions. Notably, several agents targeting the IGF-2 pathway are in development; however, some have shown limited efficacy in clinical trials, potentially owing to a lack of patient stratification.

"We feel our results might provide clinicians with new ways to more proficiently tackle the ill-defined management of stable disease," say Trusolino and Bertotti. "We think that systematic assessment of IGF-2 expression might result in the stratification of a patient subpopulation enriched for patients who will show marginal response to anti-EGFR antibodies but who will probably benefit from a combination therapy with an anti-EGFR antibody and an IGF-1R small-molecule inhibitor."

Francesco Sclafani, an expert in the field who was not involved in the study, broadly agrees with the authors' conclusions. "Identifying new biomarkers for anti-EGFR might lead to the development of novel (combined) treatment strategies that have the potential to overcome the mechanisms of primary and/or required tumour resistance," he says. "However, the results should be considered as hypothesis generating given that they were obtained in xenopatients." More research is clearly needed to continue elucidating the molecular pathogenesis of CRC and thus drive improvements in treatment.

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Original article Zanella, E. R. *et al.* IGF2 is an actionable target that identifies a distinct subpopulation of colorectal cancer patients with marginal response to anti-EGFR therapies. *Sci. Transl. Med.* **7**, 272ra12 (2015)