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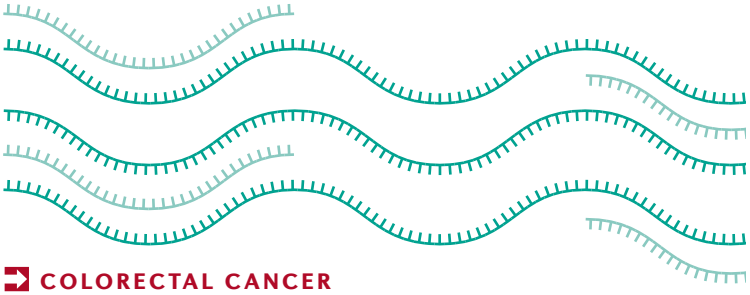

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COLORECTAL CANCER

miR-100 and miR-125b induce cetuximab resistance in CRC

Resistance to cetuximab in colorectal cancer (CRC) can be mediated by upregulation of the microRNAs (miRs) miR-100 and miR-125b, according to a new study published in *Nature Medicine*.

Cetuximab is a monoclonal antibody therapy against epidermal growth factor receptor (EGFR), commonly used in patients with wild-type *KRAS* CRC. However, the development of treatment resistance is frequent, and research since the FDA approval of cetuximab for CRC in 2009 has sought to identify the key pathways involved. The discovery that long non-coding RNAs (lncRNAs) can modulate the expression of key oncogenic or tumour suppressor proteins prompted Yuanyuan Lu and colleagues to investigate the role of these regulatory transcripts in cetuximab resistance.

In 3D-cultured cetuximab-resistant CRC cells (known as cetuximab-resistant cystic colonies, or CC-CRs) derived from the HCA-7 cell line, the researchers first ruled out known causes of cetuximab resistance, including copy number variations, gene fusions and gene mutations reported in prior studies. Relative to cetuximab-sensitive cells, the lncRNA MIR100HG was the most upregulated transcript in CC-CRs. This lncRNA gives rise to three intronic miRs: miR-100, miR-125b and let-7a2; strikingly, miR-100 and miR-125b were the most upregulated miRs in CC-CR cells. Supporting the generalizability of these results, an assessment of 30 other CRC cell lines revealed a close association between degree of cetuximab resistance and expression of MIR100HG and its product miRs.

Decreased levels of the WNT pathway proteins dickkopf-related protein (DKK)3 and DKK1 in CC-CRs compared with cetuximab-sensitive cells suggested that miR-100 and miR-125b could regulate WNT signalling. Using computational target prediction, the researchers identified binding sites for miR-100 and/or miR-125b in mRNAs that encode five WNT regulatory proteins that are downregulated in CC-CR cells: DKK1, DKK3, zinc and ring finger 3, ring finger protein 43 and adenomatous polyposis coli protein 2.

Further supporting a role for WNT signalling in cetuximab resistance, WNT pathway activity (as indicated by nuclear β-catenin levels) was increased in CC-CR cells, and cetuximab treatment of non-resistant CRC cells markedly decreased expression of WNT target genes. On the basis of these results, the investigators administered cetuximab, with or without a WNT–β-catenin inhibitor, to mice with CC-CR cell xenografts. Individually, cetuximab and the inhibitor only slowed tumour growth; however, combined treatment led to tumour regression.

Finally, WNT signalling activity was assessed in paired samples from patients with CRC taken before cetuximab treatment and at the time of tumour progression. The researchers found overexpression of miR-100 and miR-125b in samples from tumours that progressed, in addition to increased levels of nuclear β-catenin.

"In our model, MIR100HG-, miR-100- and miR-125b-mediated WNT activation represents cells adapting to survive under EGFR inhibition by activating compensatory pathways," write the authors. Future trials in patients with wild-type *KRAS*, *NRAS* and *BRAF* CRCs should measure MIR100HG expression, they recommend.

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ORIGINAL ARTICLE Lu, Y. *et al.* lncRNA MIR100HG-derived miR-100 and miR-125b mediate cetuximab resistance via Wnt/β-catenin signaling. *Nat. Med.* http://dx.doi.org/10.1038/nm.4424 (2017)