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Researchers find novel mechanism of resistance to anti-cancer drugs

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The targeted anti-cancer therapies cetuximab and panitumumab are mainstays of treatment for advanced colorectal cancer, the second leading cause of cancer-related deaths in the United States. However, many patients have tumors with genetic mutations that make them resistant to these anti-epidermal growth factor receptor (EGFR) monoclonal antibodies, or the cancers develop resistance during treatment.Researchers seeking to understand mechanisms of intrinsic and acquired resistance have focused on gene mutations, such as activating mutations in the oncogene KRAS.

Now, Vanderbilt investigators have discovered a novel non-genetic cause of resistance to cetuximab. Their findings, reported Oct. 16 in *Nature Medicine*, suggest a strategy for overcoming this resistance.

"It's sort of like we've all been looking under the light post - we look at genes, and we find mutations," said Robert Coffey Jr., M.D., Ingram Professor of Cancer Research and senior author of the current study. "What we found is that there is another form of resistance. It's not due to mutations in genes; it's an epigenetic mode of drug resistance."

Coffey and his colleagues used a 3-D cell culture system they developed to grow colon cancer cells, which were initially sensitive to cetuximab. After four months of cetuximab exposure, colonies of resistant cells grew in the culture system.

The researchers evaluated the cells for gene mutations linked to

cetuximab resistance, but they didn't find any.

"Once we had excluded all known genetic causes of resistance, we figured something interesting was happening, and that led us to dig deeper," said Coffey, who is also professor of Medicine and Cell and Developmental Biology and director of the Epithelial Biology Center.

The investigators found increased expression of a long non-coding RNA called MIR100HG, which houses two microRNAs, miR-100 and miR-125b, that also had increased expression. Long non-coding RNAs and microRNAs are transcribed from the genome just like genes, but they do not encode proteins. Instead, these pieces of RNA coordinate complex epigenetic processes to regulate gene expression.

Coffey and his colleagues discovered that miR-100 and miR-125b collectively suppressed the expression of five different genes that are negative regulators of the Wnt signaling pathway. Removing these "brakes" resulted in increased Wnt signaling, which is known to promote cell proliferation.

When the investigators blocked Wnt signaling using both genetic and pharmacologic inhibitors, they were able to restore responsiveness to cetuximab in cultured colon cancer cells and in colorectal tumors in mice.

The researchers also examined tumor samples from patients with colorectal cancer who received cetuximab therapy and developed resistance to it. They found increased MIR100HG, miR-100 and miR-125b in six out of 10 patients. Tumors from two of the six patients also had genetic mutations."We found that genetic and epigenetic resistance mechanisms can co-occur," Coffey said.

In addition, the same epigenetic mechanisms were present in other colon

cancer cell lines and in head and neck cancer cell lines with both intrinsic and acquired resistance.

The findings suggest that epigenetic regulation to increase Wnt signaling may be a general mechanism cancer cells use to overcome therapeutic blockade of EGFR signaling.

For patients who are eligible for cetuximab (they're not already resistant because of known genetic mutations), it could be worthwhile to evaluate expression of MIR100HG and if it's elevated, to block Wnt signaling, Coffey said.

"Right now there aren't great drugs available to block Wnt signaling, but there are trials underway with a slew of different Wnt inhibitors," he said. "Ultimately, we could imagine giving cetuximab with a drug that would block Wnt - to enhance the activity of cetuximab or to prevent the emergence of resistance."

Coffey and his colleagues are using the 3-D culture system to explore mechanisms of drug resistance in other colon cancer cell lines. They are also developing ways to introduce selective blockers of microRNAs ("antagomiRs"), and their preliminary data suggest this strategy may confer cetuximab sensitivity to colon cancer cell lines with KRAS mutations.

More information: Yuanyuan Lu et al, lncRNA MIR100HG-derived miR-100 and miR-125b mediate cetuximab resistance via Wnt/β-catenin signaling, *Nature Medicine* (2017). DOI: 10.1038/nm.4424

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