MedicalXpress

Study points to strategy for overcoming resistance to targeted cancer drug

September 7 2011

Scientists at Dana-Farber Cancer Institute and colleagues overseas have discovered a pair of backup circuits in cancer cells that enable the cells to dodge the effect of a widely used cancer drug. Jamming those circuits with targeted therapies may heighten or restore the drug's potency, according to a study published in the Sept. 7 issue of *Science Translational Medicine*.

The research focused on the drug cetuximab, an antibody that interferes with cancer cell growth by blocking a structure known as the epidermal growth factor receptor (EGFR). Cetuximab is effective in many patients with colorectal cancer or squamous cell cancer of the head and neck, but the benefits rarely last longer than a year, and some patients receive no benefit from the drug.

Until now, scientists haven't known why cancers that initially respond to cetuximab become resistant to it, or how to overcome such resistance.

In the new study, researchers led by Pasi Janne, MD, PhD, of Dana-Farber and Kimio Yonesaka, MD, PhD, formerly of Dana-Farber and now at Kinki University School of Medicine, in Osaka, Japan, found that in some cetuximab-resistant cancer cells, a protein known as ERBB2 was actively sending "grow" signals, circumventing the "stop growing" signals triggered by cetuximab. The researchers discovered that ERBB2's activity sprang from an oversupply of the protein's parent gene, Her2/neu, or by a related protein, ERBB3, when prompted by high levels of the protein heregulin. In both cases, the new growth messages are

unaffected by cetuximab.

"ERBB2 activates a critical signaling pathway that is not normally blocked by cetuximab, and in this way subverts cetuximab's function," says Janne, the study's co-senior author with Kazuhiko Nakagawa, MD, PhD, of Kinki University. "Because ERBB2 isn't affected by cetuximab, this is an easy way for cancers to become resistant to the drug."

The findings suggest that combining cetuximab with ERBB2-inhibiting drugs could be an effective therapy for cancers that are cetuximab-resistant from the start or for those that become resistant over time, the study authors say. Several such inhibitors have already been approved, while others are undergoing clinical study.

"We hope the findings of our study will inspire the development of clinical trials aimed at overcoming cetuximab resistance," Yonesaka remarks. "We've identified biomarkers that can be used to select cetuximab-resistant patients who may benefit from a combination of cetuximab and ERBB2 inhibitors."

Janne estimates that up to 40 percent of colorectal cancers are cetuximab-resistant when first diagnosed. He notes that although the ERBB2 pathway may be responsible for many cases of cetuximab resistance, there are undoubtedly other pathways, yet to be discovered, that play a similar role. Further research is needed to confirm ERBB2's role in cetuximab resistance and to develop strategies for testing ERBB2 inhibitors and cetuximab in clinical trials.

Provided by Dana-Farber Cancer Institute

resistance-cancer-drug.html