Study may explain why targeted drug doesn't benefit patients with early-stage lung cancer

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The drug erlotinib is highly effective in treating advanced-stage lung cancer patients whose tumors have a particular gene change, but when the same drug is used for patients with early-stage tumors with the same gene change, they actually fare worse than if they took nothing. A study by researchers at The Ohio State University Comprehensive Cancer Center – Arthur G. James Cancer Hospital and Richard J. Solove Research Institute (OSUCCC – James) and at Cincinnati Children's Hospital might show why.

Oncologists use erlotinib to treat lung cancers that have a mutation in a gene called epidermal growth factor receptor (EGFR). The gene mutation causes EGFR to run like it has a stuck accelerator, and erlotinib blocks the overactive molecule. The study shows that while erlotinib effectively causes tumors to shrink – suggesting that the drug is helping – this drug also increases the aggressiveness of the tumor so that growth is accelerated when therapy ends. This study finds that this is due to a secondary and previously unknown effect of inhibiting EGFR.

The researchers found that when erlotinib blocks EGFR, it activates a second signaling molecule called Notch3. Activation of that pathway leads to increased development of cancer stem cells among the surviving tumor cells and to accelerated tumor growth.

"Our findings might explain why erlotinib in clinical trials seems to worsen survival in patients with early-stage lung cancer," says co-corresponding author David Carbone, MD, PhD, professor of medicine,

division of medical oncology at the OSUCCC – James. "They also suggest that combining an EGFR inhibitor with a Notch inhibitor should overcome the effect."

The study was published recently in the journal *Cancer Research*.

Carbone, co-corresponding author Stacey Huppert, of Cincinnati Children's Hospital, and their colleagues conducted the study using several cell lines of non-small-cell lung cancer, the most common form of lung cancer, to learn if inhibiting EGFR enhances the activity of the Notch signaling pathway. "We found that the activated, mutated EGFR directly inhibits Notch signaling, and that inhibiting EGFR with erlotinib removes this restraint and activates Notch signaling," says Carbone, who is the Barbara J. Bonner Chair in Lung Cancer Research. "It suggests that specific dual targeting might overcome this adverse effect."

The study's key technical findings include:

- In two non-small-cell lung cancer cell lines, erlotinib treatment killed 84 percent and 75 percent of cells; of the surviving cells, 23 percent and 70 percent were stem-like cells, respectively (versus 4 percent and 18 percent of control cells);
- Erlotinib treatment increased the potential for growth of surviving lung cancer cells;
- Erlotinib treatment increased the number of stem-like cells through activation of the Notch3 receptor.

More information: cancerres.aacrjournals.org/con … /74/19/5572.abstract

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