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Scientists catch EGFR passing a crucial message to cancer-promoting protein

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Researchers have discovered and mapped the signaling network between two previously unconnected proteins, exposing a link that, if broken, could cut off cancer cell growth at its starting point.

A team led by scientists at The University of Texas MD Anderson Cancer Center reported the tie between epidermal growth factor receptor (EGFR), a well-known cancer drug target, and MCM7, a protein vital to the first step in DNA replication, in the June issue of *Cancer Cell*.

"MCM7 overexpression marks cell proliferation and is associated with glioblastoma and colorectal, ovarian and esophageal cancers, among others. Yet the mechanisms that regulate its function have been unclear," said co-lead author Tzu-Hsuan Huang, Ph.D., formerly of MD Anderson's Department of Molecular and Cellular Biology and now with Amgen, Inc., in Boston.

MCM7 is important to DNA licensing, Huang said, "which is the very first step in DNA replication and, in effect, gives the DNA replication machinery permission to proceed." Its function had not previously been tied to EGFR signaling, which leads to DNA synthesis and cell growth, and is often dysfunctional in human cancers.

EGFR tells Lyn to tell MCM7 to fuel cancer growth

In a series of experiments, Huang, co-lead author Longfei Huo, Ph.D. a

research scientist in Molecular and Cellular Biology, and colleagues tracked the signaling cascade from EGFR activation to activation of another signaling molecule called Lyn to MCM7 ignition.

Both EGFR and Lyn are tyrosine kinases, which activate other proteins by attaching phosphate groups to them. The team found that activated EGFR phosphorylates Lyn, which in turn tags MCM7 with phosphate groups. They found all three actions are correlated in human lung and breast cancer tumors.

Mice with high expression of either Lyn or MCM7 had breast cancer tumor volumes two to three times greater than those with low expression.

Pathway shortens patient survival

"We established that this signaling pathway correlates with EGFR status and poor survival in breast cancer patients," said study senior author Mien-Chie Hung, Ph.D., chair and professor of the department and holder of the Ruth Legett Jones Distinguished Chair.

An analysis of Lyn status in tumors of 125 breast cancer patients and MCM7 status in 120 patients showed substantially higher survival rates for those with low expression of either protein. In both cases, about 60 percent of those with high expression of Lyn or MCM7 survived to 75 months, compared to about 80 percent of those with low levels of the proteins.

Drugs that target EGFR often become less effective over time, Hung noted, so Lyn provides a target downstream from EGFR that might be effective. And the signaling network might be a resistance pathway that overcomes EGFR-inhibiting drugs.

Lyn-inhibiting drugs are under development

Lyn inhibitors have been tested preclinically and in an early stage clinical trial, Huang said. They are not generally available as they're still under development. Combining Lyn and EGFR inhibitors could have a heightened effect on EGFR-driven cancers.

"Lyn overexpression might be indispensable for cancer cells that rely on EGFR signaling to proliferate," Hung noted. Other researchers have shown that knocking out Lyn has less effect on cancer cell lines that are less dependent on EGFR to survive and grow.

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