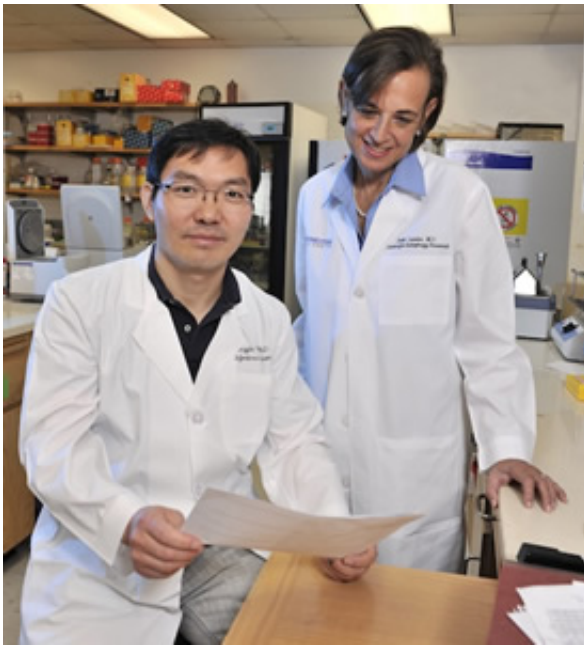


Interference with cellular recycling leads to cancer growth, chemotherapy resistance

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A UT Southwestern study that included Drs. Beth Levine and Yongjie Wei has demonstrated that the protein EGFR can interfere with the body's natural recycling process, leading to cancer growth and chemotherapy resistance. Credit: UT Southwestern Medical Center

Overactivity of a protein that normally cues cells to divide sabotages the body's natural cellular recycling process, leading to heightened cancer growth and chemotherapy resistance, UT Southwestern Medical Center researchers have found.

The [epidermal growth factor receptor](#), or EGFR, is found at abnormally high levels on the surface of many types of [cancer](#) cells. The study, led by Dr. Beth Levine and published Sept. 12 in *Cell*, revealed that EGFR turns off autophagy, a process by which cells recycle unneeded parts, by binding to a protein, Beclin 1, which normally turns on the process. The researchers found that the deactivation of autophagy by EGFR led to more rapid [tumor growth](#) and chemotherapy resistance in mice implanted with non-small lung [carcinoma cells](#).

"The fact that this type of [cell surface receptor](#) can directly interact with Beclin 1 and shut off autophagy provides fundamental insight into how certain oncogenes may cause cancer," said Dr. Levine, director of the Center for Autophagy Research and a Howard Hughes Medical Institute (HHMI) investigator at UT Southwestern. "Our findings suggest that inactivation of autophagy may be a critically important factor in the progression of lung cancer."

Earlier work in the laboratory of Dr. Levine identified beclin 1 as the first mammalian gene shown to function in autophagy. Defects in this gene may contribute not only to cancer, but also to aging, [neurodegenerative diseases](#), and infectious diseases.

While the link between EGFR cell signaling action and [cancer growth](#) was known, with several pharmaceutical inhibitors of EGFR already on the market to combat cancer, exactly how this process worked was a mystery. This latest research uncovers Beclin 1 as one important way in which EGFR may derail the body's cancer-fighting autophagy machinery to increase tumor growth.

A second finding in the new study related to chemotherapy resistance. Several clinical trials are currently ongoing to test inhibitors of autophagy as a means of overcoming the resistance to chemotherapeutic drugs that many tumors develop. Unexpectedly, Dr. Levine's study found

just the opposite: that autophagy inhibition may actually worsen chemotherapy outcomes for patients with specific cancer mutations. The researchers showed that cancer cells with reduced autophagy grew faster and were more resistant to chemotherapy than cancer cells with normal autophagy. Dr. Levine noted that these findings may apply to many different types of cancers, especially those that rely on EGFR (or related signaling molecules) for their rapid growth.

About 10 percent of lung cancer patients have mutations in the EGFR oncogene, according to [Dr. John Minna](#), one of the study authors and Director of the Nancy B. and Jack L. Hamon Center for Therapeutic Oncology Research and the W.A. "Tex" and Deborah Moncrief Jr. Center for Cancer Genetics at UT Southwestern. For those patients in particular, this finding could have significant impact in developing a personalized, targeted therapy.

"The EGFR protein is one of our most important targets for lung cancer therapy—especially in patients whose tumors have certain EGFR gene mutations," Dr. Minna said. "We have oral medications that achieve dramatic clinical benefit and increase survival in this subset of patients, but even these successfully treated patients eventually become resistant to the treatment.

"These new findings are important for two reasons: First, they provide insight into how to extend EGFR-targeted therapy to a much larger group of lung cancer patients, including those whose tumors do not have mutations. Second, they provide a totally new approach to overcoming resistance to EGFR-targeted therapy."

Provided by UT Southwestern Medical Center

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