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EGFR protects cancer cells from starvation via a kinase-independent mechanism

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Scientists have uncovered a previously unrealized mechanism by which the epidermal growth factor receptor (EGFR), a tyrosine kinase, promotes survival of cancer cells through a kinase-independent mechanism. The research, published by Cell Press in the May issue of the journal *Cancer Cell*, provides a rationale for the less than impressive results of recent clinical trials aimed solely at interfering with kinase activity and suggests new directions for potential therapeutic strategies.

The EGFR is closely associated with cell proliferation and survival and excessive expression, and activation of the EGFR is often observed in cancers of epithelial origin. Until now, it was believed that most of EGFR's functions were mediated by its kinase activity, and several compounds that specifically inhibit the kinase activity of the EGFR were developed with the aim of treating these cancers.

However, the clinical experience so far has been that blockade of the EGFR tyrosine kinase activity alone does not elicit significant clinical outcomes in most patients.

"The expression level of EGFR in cancer tissues is correlated with prognosis, but not with responsiveness to EGFR tyrosine kinase inhibitor treatment, suggesting that, independent of its kinase activity, EGFR may contribute to the progression of cancer," explains study author Dr. Isaiah J. Fidler from the Department of Cancer Biology at The University of Texas M.D. Anderson Cancer Center. Dr. Fidler and colleagues designed a series of studies to investigate the kinase-independent prosurvival

function of the EGFR in cancer cells.

The researchers found that the EGFR enables human cancer cells to maintain adequate intracellular glucose levels by stabilizing the sodium/glucose transporter 1 (SGLT1) via a kinase-independent mechanism. Glucose is a major energy substrate for all cells, and without appropriate amounts, cells essentially starve to death through a process called autophagic cell death. Cancer cells are very active metabolically and consume more glucose than normal tissues; moreover, the EGFR overexpression and the associated enhanced stability of SGLT1 allow tumor cells to survive under conditions that would be less than optimal, even for normal cells.

“Our results suggest that EGFR, independent of its kinase activity, maintains the basal intracellular glucose level and thereby prevents cancer cells from succumbing to autophagic death. It is possible that this function of the EGFR may even increase the survival capacity of cancer cells in the presence of chemotherapeutic agents,” offers study author Dr. Mien-Chie Hung. The researchers suggest that inhibition of both EGFR-mediated SGLT1 stabilization and EGFR kinase activity may be necessary for eradication of epithelial tumors.

Source: Cell Press