A Sweet New Role for EGFR in Cancer

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The epidermal growth factor (EGFR) has served as an attractive bull's-eye for targeted cancer therapies. Although the importance of EGFR as an oncogenic tyrosine kinase seems well established, a report by Weihua et al. in this issue of *Cancer Cell* adds a new wrinkle to the role of EGFR in cancer. In this study, the authors demonstrate that EGFR facilitates glucose transport into cells by associating with and stabilizing a sodium/glucose cotransporter (SGLT1). Additionally, they find that this function does not require EGFR kinase activity. These results point to a new kinase-independent role for EGFR in promoting metabolic homeostasis in cancer cells.

Therapies aimed at blocking epidermal growth factor receptor (EGFR) function have been sought since the 1980s, when Mendelsohn and colleagues showed that antibodies targeting this receptor effectively blocked the growth of cancer cells (Kawamoto et al., 1983). Over the past 20 years, these efforts have only continued to grow and accelerate. There are now several antibody and small-molecule inhibitors directed against EGFR that are actively being developed by biotechnology and pharmaceutical companies as cancer therapeutics.

EGFR has historically been an attractive drug target because it is widely expressed in many cancers, and it has well-documented oncogenic activity. Although small-molecule tyrosine kinase inhibitors (TKIs) such as erlotinib (Tarceva) and gefitinib (Iressa) have impressive clinical activity in a small subset of non-small-cell lung cancers (NSCLCs), it is somewhat surprising that they have almost no clinical activity in the majority of cancers that have high expression of EGFR (Eberhard et al., 2008). Thus, many espouse the concept that cancers responding to these inhibitors are "addicted" to EGFR signaling, and EGFR tyrosine kinase is necessary for their survival likely because it is the chief activator of critical downstream survival and growth signals such as p42/44 MAPK and PI3K/AKT pathways (Engelman, 2007; Sharma et al., 2007). Thus, when EGFR signaling is aborted, these pathways are terminated and the cancers undergo massive apoptosis. Although this explanation may be satisfactory, it does not explain why EGFR is highly expressed in so many cancers, and if it has an important role in those cancers.

In this issue of *Cancer Cell*, a study by Weihua et al. (2008) begins to elucidate a novel role for EGFR in cancers. In this study, they observed that EGFR maintains cellular homeostasis in cancers by a mechanism beyond its traditional role as an initiator and transmitter of signal transduction. They find that EGFR physically associates with and stabilizes the sodium/glucose cotransporter (SGLT1) to promote glucose uptake into cancer cells. Their first clue that EGFR impacts cells beyond its tyrosine kinase activity was the finding in PC-3MM2 prostate cancer cells that downregulation of EGFR with siRNA led to substantial cell death, but EGFR kinase inhibition did not. Indeed, the cell death was rescued by expression of either wild-type EGFR or a kinase-dead EGFR mutant. Additionally, the cell death induced by EGFR knockdown had the hallmarks of autophagy, not apoptosis, and was actually associated with an *increase* in AKT and p42/44 MAPK signaling. Thus, this pointed to a critical function for EGFR beyond its kinase activity, and the dependence on EGFR did not mirror the addiction models observed in other cancers such as *EGFR* mutant NSCLCs. The authors demonstrated that the extracellular domain of EGFR associates with the SGLT1, and stable SGLT1 expression required EGFR expression. Indeed, downregulation of EGFR led to loss of SGLT1 expression and lower intracellular glucose levels. In fact, increasing glucose levels in the culture media bathing the cells abrogated the death induced by EGFR knockdown. Thus, these studies suggest that EGFR functions not only as an important instigator of signal transduction cascades, but also as an integral component of an active glucose transport system (Figure 1).

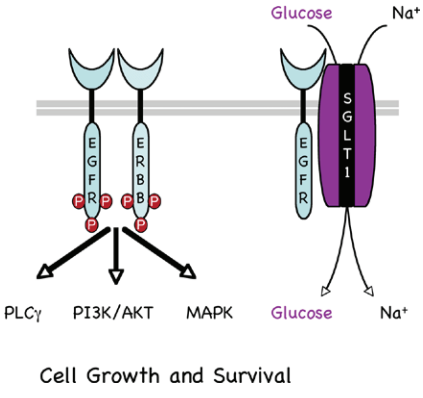

Figure 1. EGFR Facilitates Glucose Transport
This cartoon depicts two functions of EGFR. (Left) EGFR homodimerizes or heterodimerizes with other ERBB family members to promote downstream growth and survival signals. (Right) EGFR binds to SGLT1 and stabilizes its expression to promote glucose uptake.

This study has several important implications that may impact therapeutic approaches to cancer. Do EGFR TKIs and/or antibodies that are clinically effective work, in part, by disrupting the association between EGFR and SGLT1? Although definitive studies have not yet been done, this seems less likely to account for the activity of small-molecule TKIs. Inhibiting EGFR kinase activ-

ity did not block the association of EGFR with SGLT1 or decrease basal intracellular glucose levels. Furthermore, the efficacy of EGFR TKIs appears to be limited to cancers with classic EGFR oncogene addiction in cancers harboring EGFR mutations and/or amplifications that, upon treatment with TKIs, have dramatic down-modulation of downstream cell survival signaling pathways.

In contrast to TKIs, it is less clear how antibodies targeting EGFR function to kill cancer cells. They have been thought to function by disrupting signaling and/or promoting cell-mediated cytotoxicity. However, at this point, one cannot rule out that antibody therapies may work, in part, by disrupting the physical interaction between EGFR and SGLT1, especially since both cetuximab (Erbitux) and SGLT1 appear to interact with the extracellular domain of EGFR. The EGFR antibody cetuximab is most effective in colorectal cancers that express high levels of EGFR ligand and have wild-type *K-Ras* (Khambata-Ford et al., 2007; Lievre et al., 2006). These observations suggest that these cancers have activation of EGFR kinase activity, thereby supporting the classic oncogene addiction model. Indeed, the absence of *K-Ras* mutations also identifies NSCLCs most likely to respond to EGFR TKIs (Pao et al., 2005). However, we do not yet know how the presence of EGFR ligands and potential dimerization partners affects binding between EGFR and SGLT1, and perhaps these biomarkers for cetuximab activity also predict an integral role for EGFR in active glucose transport. There are many potential molecular mechanisms that could describe how the clinical activity of antibody therapies is achieved by perturbing the interaction between EGFR and SGLT1. It will be interesting to learn if cetuximab or other anti-EGFR antibodies affect the ability of EGFR to associate with SGLT1, and if some of their biological activity is achieved by disrupting this interaction.

This study also serves as another example of the intersection between traditional signaling cascades and basic cellular metabolism. It is reminiscent of the findings that intracellular energy and amino acids regulate mTOR signaling (Byfield et al., 2005; Corradetti et al., 2004; Nobukuni et al., 2005; Shaw et al., 2004), and the recent observation that tyrosine phosphorylation signaling affects the activity of the M2 isoform of pyruvate kinase (PKM2) (Christofk et al., 2008). The interaction between EGFR and SGLT1 appears to be another adaptation by eukaryotic cells to coordinate cellular growth and division with nutrient uptake. However, further study is required to understand how signaling and glucose uptake are coupled and regulated by this newly discovered complex. Furthermore, this new dimension of EGFR function seems ripe for therapeutic intervention. Disrupting the association between EGFR and SGLT1 may affect intracellular glucose levels, and this in turn may affect the cancer's ability to withstand stresses (e.g., chemotherapy or radiation therapy). Since this function of EGFR directly impacts glucose uptake, one might expect that PET scans would be a useful biomarker for a therapy aimed toward inhibiting the binding of EGFR to SGLT1. Indeed, combining such a therapy with autophagy inhibitors or other drugs that metabolically stress cancer cells might have impressive clinical activity. It is clear that the findings of this exciting new study will broaden how we develop strategies to target EGFR. Furthermore, when we devise therapies to inhibit EGFR, we will consider its role not only as a kinase, but also as a sweetener.

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