Monitoring Targeted Therapy: Is Fluorodeoxylucose Uptake a Marker of Early Response?

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In this issue, Su et al. (1) present the results of studies of early cellular changes in response to gefitinib, an epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor, in cell lines and a preliminary xenograft model. The EGFR pathway family has been implicated in the pathogenesis of many types of cancer (2–4). EGFR is expressed in almost all normal tissues, with the exception of hematopoietic cells, and is important in a number of normal tissue responses, including tissue repair and morphogenesis (3). Following cell-surface interactions of ligand (such as transforming growth factor or epidermal growth factor) and receptor and between receptors, the pathway is activated through the actions of up to four different membrane proteins (erbB1-erbB4 or HER1-HER4). Of these, erbB1 is often termed EGFR, and erbB2 is frequently referred to as HER2 (or HER2/neu). Heterodimerization or homodimerization of the erbB proteins leads to intrinsic tyrosine phosphorylation and, ultimately, through a complex set of intermediate pathways, to cellular proliferation, angiogenesis, and resistance to apoptosis (see Fig. 1; ref. 4). Aberrant activation of the pathway can occur through overexpression, mutation, and transactivation with other members of the receptor family; all of these mechanisms have been associated with prognosis, sensitivity, and resistance to cancer therapies (5–7).

Given its importance in cancer pathogenesis and progression, the EGFR pathway has attracted much attention as a therapeutic target; two strategies have emerged. Monoclonal antibodies directed at cell-surface proteins, such as cetuximab, interfere with signaling and dimerization and have been effective in combination with chemotherapy and/or concurrent radiation in treating colon cancer and head and neck cancer (reviewed in ref. 2). Alternately, EGFR-targeted tyrosine kinase inhibitors as single agents have shown some efficacy in non–small-cell lung, head and neck, colon, renal cell, and breast carcinoma (2). The attempt to combine oral tyrosine kinase inhibitors with concurrent chemotherapy has led, however, to disappointing results in non–small-cell lung cancer (8). The level of EGFR assayed through tissue immunohistochemistry has provided imperfect prediction of response to agents directed against the EGFR pathway (4, 9, 10). In addition, the optimal therapeutic context (initial, consolidating, salvage) and timing of administration (concurrent, interdigitated, delayed) of directed therapies remains to be determined. Given these challenges and potential gains, a method to detect an early response to anti-EGFR therapy and to identify therapeutic failures could significantly refine therapeutic approaches.

Su et al. (1) found a decline in fluorodeoxylucose (FDG) uptake as early as 2 hours after cell incubation with gefitinib and 24 to 48 hours before changes in cellular proliferation and apoptosis. GLUT transporter expression declined in parallel to FDG uptake, a possible mechanism leading to reduced FDG uptake. These very interesting and significant results suggest a rationale for using FDG positron emission tomography (PET) as an early readout for response to anti-EGFR pathway agents. FDG PET is already in routine clinical use for a number of cancers, such as lung and breast cancer (11, 12), where anti-EGFR therapy is used and could easily be adapted to measure the early clinical efficacy of targeted therapy.

An early and large decline in FDG uptake in response to anti–fibroblast growth factor receptor agents is perhaps not surprising from examination of the EGFR pathway. Intermediates in the EGFR pathway include signal transducers and activators of transcription, AKT, and mitogen-activated protein kinase. AKT is well known to stimulate glycolysis, which may mediate resistance to apoptosis (13). In addition, prior studies have shown that a decline in AKT activation leads to decreased transcription of glycolytic enzymes, including GLUT transporter expression (14). Mitogen-activated protein kinase is a potent mitogen that, when activated, leads to altered cell cycling, for which enhanced glycolysis may be an early event (13, 15). The results of Su suggest that the interruption of a growth factor pathway may lead to changes in glycolysis before downstream effects, such as diminished proliferation and increased cell death, are realized. A similar mechanism may underlie the early changes in FDG uptake seen in response to imatinib therapy in patients with gastrointestinal stromal tumors (16). We have also seen similar changes in early response to neurexin inhibition in an animal model (17). The Su findings raise some important additional questions. What is the time course of decreased FDG uptake beyond 24 to 48 hours? Apoptotic cellular death requires energy and might lead to increased FDG uptake once anti-EGFR therapy leads to apoptosis (18). Does decreased proliferation and increased death always follow a decline in glucose metabolism, or are there scenarios in which glucose metabolism is affected without the downstream changes? It is possible that the EGFR pathway is aberrantly activated in some cancers and that glycolysis and downstream effects are not always linked. It will be important to consider these questions in future preclinical studies and in clinical trials of FDG PET as an early marker of response to anti-EGFR therapy. Carefully designed clinical studies should compare early changes in FDG...
uptake to standard measures of response at later time points and to other outcomes, such as time-to-progression and disease-free survival. It will be interesting to measure the time course and response using multiple PET radiopharmaceuticals, examining combinations of glucose metabolism, proliferation, and apoptosis. PET radiopharmaceuticals to measure proliferation and apoptosis have been developed and tested in patients (19–21). Studies using multiple tracers to study different aspects of cellular biology could help to clarify the relationship between early changes in glucose metabolism and subsequent response.

Su and colleagues postulated that an early decline in GLUT expression was responsible for the decline in FDG uptake. However, their study was not designed to differentiate between transport and loss of phosphorylation by hexokinase as a cause of altered FDG uptake. Because transport is largely reversible, FDG taken up into the cells but not phosphorylated would be unlikely to be retained after cell washing, leaving only phosphorylated FDG (FDG-6P) behind. In vivo, both the reversibly transported unphosphorylated FDG and phosphorylated FDG-6P, metabolically trapped in the cell, contribute to the PET signal (Fig. 2). Prior in vivo studies have suggested that phosphorylation, rather than transport, is the rate-limiting step for FDG uptake and retention in most tissues (22). It is possible, and perhaps likely, that the overall kinetics of glucose metabolism change in response to anticancer therapy, rather than to any single component of the glycolytic pathway. We have shown (e.g., using dynamic FDG PET and kinetic analysis

**Fig. 2.** Diagram of FDG metabolism compared to glucose metabolism.
pre- and post-chemotherapy of breast cancer) that the relationship between FDG transport and phosphorylation changes with treatment, and that this can lead to an overall decrease in FDG uptake measured late after injection (23). Future studies investigating the time course of FDG uptake kinetics could elucidate the mechanism underlying early decreases in FDG with anti-EGFR treatment.

An early decline in FDG uptake has also been found in response to cytotoxic chemotherapy (24–27). However, in this setting, cellular proliferation seems to decline earlier and to a greater extent than glucose metabolism, as seen in both patients (25) and animal models (17). Several factors may contribute to this difference. Most cytotoxic agents have their greatest efficacy in proliferating cells; therefore, a decline in proliferation would be expected as an early change in response. Cellular repair in response to cytotoxic agents requires energy (28) and may contribute to FDG uptake post-therapy. For these reasons, a number of investigators have postulated that cellular proliferation imaging, using PET agents such as [11C]thymidine or [18F]fluorothyminide, may be an earlier and more sensitive marker of response than glucose metabolism imaging by FDG PET. The results of Su et al. and the changes seen in response to imatinib (16) indicate that FDG imaging can be a sensitive and early marker for targeted therapy that interrupts an “upstream” growth factor pathway. It would be interesting to test whether this is also true for other growth factor pathways with existing targeted therapies, such as sex steroid hormone receptor pathways in breast and prostate cancer.

In summary, the results of the preclinical studies by Su provide a rationale for using FDG PET as an early readout for anti-EGFR therapy and suggest the need for further preclinical studies and clinical trials in patients receiving anti-EGFR agents. These very interesting results indicate the ability to provide an early and quantitative assessment of therapeutic efficacy and support the incorporation of imaging using FDG and agents targeting other aspects of cancer biology into preclinical and early clinical testing of new targeted cancer drugs. Biological imaging of targeted therapy can determine which cellular processes are affected by therapy in vivo, and what cellular pathways contribute to resistance, leading to more efficient drug development and testing and to more individualized patient care.

References

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