Blood Flow-Metabolism Mismatch: Good for the Tumor, Bad for the Patient

□□ *Commentary on Komar et al., p. 5511*

David A. Mankoff, Lisa K. Dunnwald, Savannah C. Partridge, and Jennifer M. Specht

Although tightly coupled in most normal tissues, blood flow and metabolism are often not well matched in tumors. A flow-metabolism mismatch, specifically, high metabolism relative to blood flow, can be recognized in tumors by functional and molecular imaging and is associated with poor response to treatment and early relapse or disease progression. (Clin Cancer Res 2009;15(17):5294–6)

In this issue of *Clinical Cancer Research*, Komar and colleagues from Turku University report that malignant pancreatic tumors exhibit decreased blood flow and increased glucose metabolism compared with the normal pancreas (1). This mismatch between tumor blood flow and metabolism was associated with poor survival.

In normal tissues, vascular physiology matches substrate delivery to energy demand. Energy metabolism and blood flow are tightly coupled through a variety of local auto-regulatory mechanisms (2), and under equilibrium conditions, regional rates of metabolism and tissue perfusion are highly correlated. This results in the efficient delivery and use of energy substrates in normal tissues.

Unlike normal tissues, tumors have a highly disordered vascular supply (3). Furthermore, tumor energy metabolism is often aberrant (4). Therefore, in tumors, metabolism and blood flow may not be well matched. The ratio of glucose metabolic rate relative to blood flow can be considerably elevated compared with the tissue of origin for several reasons. The aberrant microvasculature associated with tumors is ineffective at delivering oxygen, leading to inefficient use of energy substrates and higher rates of metabolism of substrates that do not require oxygen, such as glucose (3). Inadequate blood supply that is unable to meet energy demands results in metabolic stress and low oxygen levels, i.e., hypoxia. Hypoxia promotes gene expression via the transcription factor HIF-1, which leads to accelerated glycolysis (5). Even under normoxic conditions, increased glycolysis may be favored as part of a fundamental response to cellular stress, which allows tumor cells to avoid cell death in the face of unregulated growth and meet an extraordinary need for energy and materials to support such growth (4). Accelerated glucose metabolism has been recognized as a hallmark of the malignant phenotype dating back to the early studies of Warburg (6). Through all of these mechanisms, altered metabolism supports tumor cell survival under environmental stresses and can be recognized as an aberrantly high rate of glucose metabolism per unit blood flow, i.e., a flow-metabolism mismatch.

Functional imaging is a unique tool for measuring regional tumor perfusion and metabolism (7). ^{18}F-fluorodexyglucose positron emission tomography (FDG PET) can quantify regional tumor glucose metabolism (Fig. 1) and is widely used in clinical oncology. Several quantitative imaging approaches, such as ^{15}O-water PET, dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI), and dynamic contrast-enhanced computed tomography (CT), can measure regional tissue perfusion. Combinations of FDG PET and perfusion-imaging methods can delineate regional variations in the metabolism-flow ratio. Combined ^{15}O-water-FDG PET is well suited for this task, because both studies can be done in the same imaging session without moving the patient.

Studies combining perfusion and glucose metabolism imaging in a variety of tumors including lung, breast, liver, colon, and head and neck cancers have shown that, unlike normal tissues, tumor blood flow and metabolism are often mismatched (7), especially in more advanced disease. Several studies have shown that a flow-metabolism mismatch, high FDG uptake relative to perfusion, is associated with poor response to systemic therapy and early relapse or disease progression (8, 9). In this issue of *Clinical Cancer Research*, Komar and colleagues show similar findings for pancreatic tumors (1). They found that blood flow in pancreatic lesions was lower than in normal tissue. Malignant lesions, however, had FDG uptake higher than normal tissue, leading to considerably higher FDG-blood flow ratios in tumors versus benign lesions and the normal pancreas. The investigators found a significant association between an elevated FDG-blood flow ratio and poor overall survival, despite a relatively small number of patients. These results suggest that in pancreatic cancer, as in other cancers (7), a flow-metabolism mismatch indicates a more clinically aggressive phenotype. This study provides further evidence that a flow-metabolism mismatch is an identifiable tumor physiology associated with poor survival.

Authors' Affiliation: Departments of Radiology and Medicine, University of Washington and Seattle Cancer Care Alliance, Seattle, Washington
Received 6/22/09; accepted 6/25/09; published OnlineFirst 8/25/09.
Requests for reprints: David A. Mankoff, Seattle Cancer Alliance, Radiology, G2-600, 825 Eastlake Avenue, East, Seattle, WA 98109. Phone: 206-288-2173; Fax: 206-288-6566; E-mail: dam@u.washington.edu.

doi:10.1158/1078-0432.CCR-09-1448

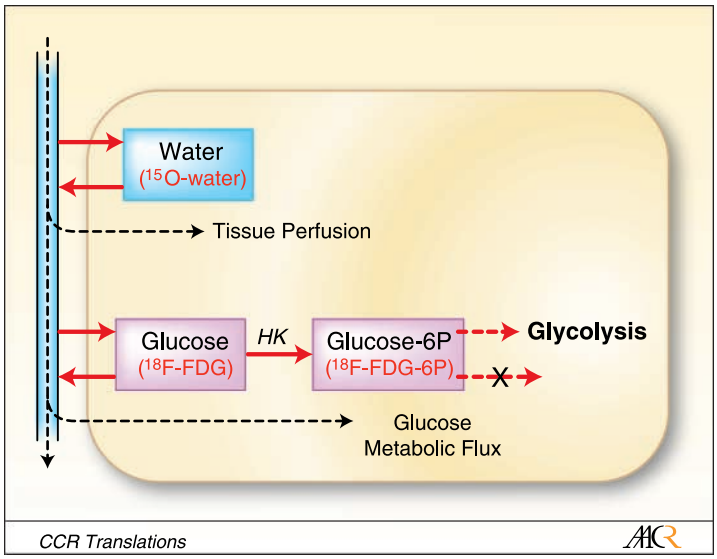

Fig. 1. Diagram of quantitative imaging methods used to measure blood flow and metabolism. Native molecules are shown in black lettering, and administered radiopharmaceuticals are shown in red. The delivery of nutrients and oxygen is dependent upon tissue perfusion or blood flow. ^{15}O-water is a freely diffusible substance whose delivery is limited by blood flow. Dynamic ^{15}O-water captures the time course of tracer uptake and washout in tissue, from which regional tissue perfusion can be estimated. FDG is a glucose analog that traces glycolysis. After delivery by blood flow and transit across capillaries and cellular membranes, FDG is phosphorylated inside the cell by hexokinase (HK), the rate-limiting step in glycolysis; but FDG is not a substrate for downstream steps in glycolysis. FDG, therefore, is "metabolically trapped" as FDG-6P, at a rate proportional to the glucose metabolic flux. Sequential injections of ^{15}O-water ($t_{1/2} \approx 2$ minutes) and ^{18}F-FDG ($t_{1/2} \approx 2$ hours) can yield regional estimates of tissue blood flow and glucose metabolism, and the ratio between flow and metabolism.

This is not an entirely new story. More than 30 years ago, using largely the same imaging methods used in the Komar study, the seminal work of Schelbert and colleagues (10) showed that myocardial flow-metabolism mismatch indicated hibernating but viable tissue in the setting of coronary artery disease. Elevated FDG uptake in regions with poor myocardial perfusion, i.e., a flow-metabolism mismatch, was associated with myocardium that recovered after revascularization. As in the case of cancer cells, accelerated glycolysis is part of the myocardial response to cellular stress, in this case induced by severe coronary insufficiency. The flow-metabolism mismatch indicated preserved cellular viability, and when adequate blood flow was restored by coronary artery bypass surgery, the previously ischemic myocardium recovered functional contractility.

If a flow-metabolism mismatch is a sign of metabolic stress, then why is it associated with poor outcome in cancer patients? One likely reason is its association with cell survival. If a tumor cell can survive the stress of metabolic demands of rapid growth and inadequate delivery of nutrients and oxygen, it may also be able to withstand cancer treatments. This seems to be the case for breast cancer treated by chemotherapy, in which patients whose tumors had flow-metabolism mismatches pretherapy were significantly less likely to achieve a complete response to neo-adjuvant treatment compared with patients with tumors with matched metabolism and perfusion (11). In addition, the response to environmental stress may activate pathways associated with more aggressive and lethal cancers. For example, in addition to accelerated glycolysis, the response to hypoxia through HIF-1 promotes tumor angiogenesis, associated with a more invasive phenotype and greater propensity for spread (5). This is also supported by imaging findings. Nonresponding breast tumors had an average increase in tumor blood flow after chemotherapy (11), suggesting persistent tumor angiogenesis, and preserved tumor perfusion with therapy was associated with poor disease-free and overall survival (8).

Interestingly, despite increases in blood flow, tumors with minimal apparent response to chemotherapy have a small decline in glucose metabolism with treatment (7, 11), moving the metabolic pattern in a direction toward more matched metabolism and perfusion. This pattern may reflect the ability of cancer cells to alter metabolism to adapt to changing environmental conditions, which may be an important component of the cancer phenotype (4, 12). A similar phenomenon occurs in ischemic myocardium. After restoration of blood flow through surgical revascularization, previously ischemic myocardium reverts to a less glycolytic phenotype (10). Altered metabolism indicated by the flow-metabolism mismatch may therefore be yet another example in which cancers can use preprogrammed cellular responses to their selective advantage.

The identification of a flow-metabolism mismatch, uncovered by functional imaging, points toward mechanisms that limit response to therapy and may suggest new avenues for overcoming therapeutic resistance. However, these findings also leave a number of unanswered questions. What is the biology underlying tumor flow-metabolism mismatch? Do cancer cells have molecular features that promote a more resistant and resilient phenotype that is capable of withstanding the stress of rapid tumor growth, leading to a flow-metabolism mismatch, or does a flow-metabolism mismatch induce gene expression that mitigates environmental stresses, leading to a more resistant cancer? What is the natural history of tumors that display flow-metabolism mismatch? Do they "hibernate" as in the case of myocardium, or does the activation of genes involved in the response to metabolic stress lead to a more invasive and aggressive phenotype?

What is an optimal treatment strategy for tumors with flow-metabolism mismatch? Will antivascular therapy normalize

the delivery of oxygen and nutrients to the tumor and possibly render it more sensitive to systemic therapy (3), or will targeting tumor vasculature simply make the imbalance between metabolism and perfusion worse? Can we block the cancer cell's ability to alter energy metabolism in the face of metabolic stress (12) and thus enable cell death? Should we target signaling pathways, such as HIF-1, that link cellular stress to metabolic and vascular responses (5)?

To address these questions, future studies will need to relate quantitative *in vivo* measures from imaging to tumor gene expression. To test possible approaches for treating tumors with flow-metabolism mismatch, quantitative functional imaging can be used to select patients most likely to benefit from chemotherapy and antivascular therapies, and also to measure the effect of therapy on tumor perfusion and metabolism after treatment. The use of functional imaging modalities in combination with tissue-based genomic profiling offers a unique opportunity to elucidate critical pathways of tumor resistance to both antivascular and cytotoxic therapies resulting in true "bench to bedside" innovations. The studies of Komar and colleagues (1) provide further evidence that this is a path worth pursuing.

Disclosure of Potential Conflicts of Interest

Dr. Mankoff is the recipient of research funding from Pfizer.

References

1. Komar G, Kauhanen S, Liukko K, et al. Decreased blood flow with increased metabolic activity: a novel sign of pancreatic tumor aggressiveness. Clin Cancer Res 2009;15:5511–7.
2. Tune JD, Gorman MW, Feigl EO. Matching coronary blood flow to myocardial oxygen consumption. J Appl Physiol 2004;97:404–15.
3. Jain RK. Antiangiogenic therapy for cancer: current and emerging concepts. Oncology 2005;19:7–16.
4. Thompson CB, Bauer DE, Lum JJ, et al. How do cancer cells acquire the fuel needed to support cell growth? Cold Spring Harb Symp Quant Biol 2005;70:357–62.
5. Semenza GL. Targeting HIF-1 for cancer therapy. Nat Rev Cancer 2003;3:721–32.
6. Warburg O. The metabolism of tumors. New York: Richard R. Smith; 1931.
7. Miles KA, Williams RE. Warburg revisited: imaging tumour blood flow and metabolism. Cancer Imaging 2008;8:81–6.
8. Dunnwald LK, Gralow JR, Ellis GK, et al. Tumor metabolism and blood flow changes by positron emission tomography: relation to survival in patients treated with neoadjuvant chemotherapy for locally advanced breast cancer. J Clin Oncol 2008;26:4449–57.
9. Semple SI, Gilbert FJ, Redpath TW, et al. The relationship between vascular and metabolic characteristics of primary breast tumours. Eur Radiol 2004;14:2038–45.
10. Schelbert HR. PET contributions to understanding normal and abnormal cardiac perfusion and metabolism. Ann Biomed Eng 2000;28:922–9.
11. Tseng J, Dunnwald LK, Schubert EK, et al. ^{18}F-FDG kinetics in locally advanced breast cancer: correlation with tumor blood flow and changes in response to neoadjuvant chemotherapy. J Nucl Med 2004;45:1829–37.
12. Morrish F, Neretti N, Sedivy JM, Hockenbery DM. The oncogene c-Myc coordinates regulation of metabolic networks to enable rapid cell cycle entry. Cell Cycle 2008;7:1054–66.