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)
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 do 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

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


Updated version  Access the most recent version of this article at: doi:10.1158/1078-0432.CCR-09-1448

Supplementary Material  Access the most recent supplemental material at: http://clincancerres.aacrjournals.org/content/suppl/2009/09/01/1078-0432.CCR-09-1448.DC1

Cited articles  This article cites 11 articles, 5 of which you can access for free at: http://clincancerres.aacrjournals.org/content/15/17/5294.full#ref-list-1

Citing articles  This article has been cited by 6 HighWire-hosted articles. Access the articles at: http://clincancerres.aacrjournals.org/content/15/17/5294.full#related-urls

E-mail alerts  Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions  To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions  To request permission to re-use all or part of this article, use this link http://clincancerres.aacrjournals.org/content/15/17/5294. Click on "Request Permissions" which will take you to the Copyright Clearance Center's (CCC) Rightslink site.