

Editorial

Positron Emission Tomography-Based Molecular Imaging in Human Cancer: Exploring the Link between Hypoxia and Accelerated Glucose Metabolism

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Molecular imaging in oncology is the noninvasive imaging of the key molecules and molecular-based events that are characteristic of the genotype and phenotype of human cancer. In this issue of *Clinical Cancer Research*, Rajendran *et al.* (1) exploit positron emission tomography (PET)-based molecular imaging to explore a possible link between tumor hypoxia and accelerated glycolysis, two common properties of human tumors. The study design is straightforward. Cancer patients with four common tumors that demonstrate a significant amount of “radiobiological hypoxia” (head and neck tumors, soft tissue sarcoma, glioblastoma multiforme, and breast cancer) undergo PET imaging, with each patient receiving two separate radiotracers: (a) 2-[¹⁸F]fluoro-2-deoxy-D-glucose (FDG), a tracer for glycolysis; and (b) [¹⁸F]fluoromisonidazole, a nitroimidazole that is selectively bound to subcellular proteins at hypoxic tissue O₂ concentrations of <3 mm Hg. The investigators conclude that “Hypoxia is a general factor affecting glucose metabolism; however, some hypoxic tumors can have modest glucose metabolism, whereas some highly metabolic tumors are not hypoxic, showing discordance in tracer uptake that can be tumor type specific.”

Modern imaging technology, especially PET, is opening new doors for the study of the biochemistry of human tumors *in situ*. PET is a commercially available diagnostic imaging technique that provides noninvasive, whole-body, three-dimensional, quantitative images of the distribution of radioactivity in the body. PET imaging is based on the tracer principle to image radioactive forms of key molecules and biochemical processes that are characteristic of cancer (2). Virtually every modern university setting now has PET technology, principally based on its importance in cancer management. The availability of PET provides an important research tool that is capable of exploring multiple facets of the phenotype of human cancer.

When tissues become hypoxic, there is a tendency to switch from Krebs cycle metabolism to glycolysis. This phenomenon has also been shown in cancer cells and results in a 2-fold increase in glycolysis (3). Otto Warburg, working in Germany in the 1920s, discovered that cancer cells have a characteristically increased glycolysis even under aerobic conditions (4). This has been subsequently confirmed by numerous

investigators and is one of the most consistent findings across tumor types. The increased metabolism of tumors for glucose and its analogs, such as FDG, is the basis for the burgeoning role of PET imaging in oncology (5). The magnitude of the Warburg effect in tumors can be very large, with an increase in uptake that may be 10–100-fold greater than the tissue from which the tumor cells arise. It appears that expression levels and enhanced binding to mitochondria of glucose to key enzymes such as hexokinase II are also important in the rate of glucose metabolism by human tumors (6). Thus, hypoxia alone does not appear to be the sole cause for the increase in glucose metabolism that is observed in cancer cells.

It can be shown that the standardized uptake value (SUV_{max}) is proportional to the rate of glucose metabolism (7). Now that PET-FDG is being widely used in clinical oncology, it has become evident that the rate of glycolysis, as captured by the SUV_{max} or related uptake measures, is an important predictor of the biological aggressiveness across multiple tumor types, including brain tumor (8), sarcoma (9), thyroid cancer (10), head and neck cancer (11), non-small cell lung cancer (12, 13), malignant mesothelioma (14), prostate cancer (15), small cell lung cancer (16), esophageal carcinoma, pancreatic tumors (17, 18), and non-Hodgkin’s lymphoma (19). These articles are but examples; there are numerous additional articles showing that the higher the glucose metabolism seen on FDG-PET imaging, the worse the prognosis, especially for untreated tumors [two tumors that may be exceptions (*i.e.*, aggressive tumors with low uptake) are gastric cancer and hepatocellular carcinoma]. Nonetheless, it is clear that a great deal of biological information is contained within the PET-FDG SUV_{max} measure of glycolysis, which correlates strongly with an adverse patient prognosis.

Hypoxia too, is associated with poor prognosis in several common human tumors (20). Physicochemical effects of hypoxia in reducing response to radiation may explain some of these adverse effects. A variety of additional factors transcribed in response to hypoxia-inducible factor 1 α binding with the hypoxia-responsive elements of DNA appear to actually cause the majority of the altered prognostic features of the hypoxic state (21).

In summary, multiple reports provide clear evidence that hypoxia and accelerated glycolysis are common but independent manifestations of the phenotype of human malignancy. Although acute hypoxia can clearly provide a modest stimulus to glycolysis in normal tissues and some tumors, the link to hypoxia does not, in and of itself, appear strong enough for hypoxia to serve as a prime cause for the broad spectrum of accelerated glycolysis that appears to be a property of individual tumors both within and between diverse cancer types. Instead, emerging biological evidence suggests that the expression of hypoxia-inducible factor 1 α , which is itself induced by hypoxia along with a variety of other proproliferative and antiapoptotic

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stimuli action, is the best candidate thus far as the prime mover, behind both the characteristic hypoxia and increased glycolysis that are shared by many common human tumors. As such, hypoxia-inducible factor 1 α would seem to be an excellent therapeutic target in cancer (22, 23), and PET-based molecular imaging of hypoxia and glycolysis is likely to be useful as a marker for the effectiveness of anti-hypoxia-inducible factor 1 α therapy.

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