

Promises and Challenges of Metabolic Imaging: Where Does ^{18}F -FDG Stand in the Immunometabolism Era?

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Since its development in the late 1970s, ^{18}F -FDG has been a major driver of basic science and translational discoveries, which have revolutionized the day-to-day clinical practice of nuclear imaging (1). Initially launched as a tracer for imaging brain metabolism, ^{18}F -FDG rapidly found its major applications in oncologic imaging through detection of cancer-associated enhanced glucose utilization and aerobic glycolysis, referred to as the Warburg effect (1). ^{18}F -FDG PET is now an inseparable imaging modality for the diagnosis, staging, and monitoring of therapeutic response for a variety of cancers. Beyond oncology,

^{18}F -FDG PET has been widely used in a multitude of infectious and inflammatory diseases, including sarcoidosis and vasculitis (2). Despite this widespread clinical use, the biologic basis of ^{18}F -FDG uptake in inflammation has been an evolving concept for nearly 3 decades.

The paper by Kubota et al. in this anniversary issue of *JNM* was a landmark study highlighting the significance of ^{18}F -FDG uptake by tumor macrophages in a mouse xenograft model during the initial years of ^{18}F -FDG biologic validation (3). This study extended the existing knowledge about the accumulation of ^{18}F -FDG in abscesses and other inflamed tissues by elegantly demonstrating that immune cells, and notably macrophages, are a major contributor of ^{18}F -FDG uptake in tumors (3). Through a series of meticulous dual-isotope (^{14}C and ^{18}F) high-resolution autoradiography images, the authors demonstrated that macrophages surrounding the necrotic part of tumors and the inflammatory granulation tissue in the periphery of tumors have a markedly higher uptake of ^{18}F -FDG than do malignant tumor cells (3).

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LABORATORY STUDIES

Intratumoral Distribution of Fluorine-18-Fluorodeoxyglucose In Vivo: High Accumulation in Macrophages and Granulation Tissues Studied by Microautoradiography

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While 2-deoxy-2- ^{18}F fluoro-D-glucose (^{18}F FDG) is a useful tumor imaging agent, its intratumoral distribution has not been described well at the cellular level. In order to demonstrate cellular localization of ^{18}F FDG and 2-deoxy-D- ^3H glucose (^3H -DG) uptake by the tumor in vivo, C3H/He mice transplanted subcutaneously with FM3A tumors were studied 1 hr after intravenous injection of ^{18}F FDG or ^3H -DG using micro- and macro-autoradiography. Fluorine-18-FDG and ^3H -DG showed the same distribution pattern in the tumor with both autoradiographic methods. The newly formed granulation tissue around the tumor and macrophages, which were massively infiltrating the marginal areas surrounding necrotic area of the tumor showed a higher uptake of ^{18}F FDG than the viable tumor cells. A maximum of 29% of the glucose utilization was derived from nontumor tissue in this tumor. The comparison of double-tracer autoradiographic distribution patterns of ^{18}F FDG and [^3H]-thymidine showed the differences and the similarities between glucose utilization and the DNA synthesis. Whole proliferating tissue metabolizes ^{18}F FDG but not vice versa. High accumulation of ^{18}F FDG in the tumor is believed to represent high metabolic activity of the viable tumor cells. Our results showed that one should consider not only the tumor cells proper but also the non-neoplastic cellular elements, which appear in association with

nant tissue is due to the enhanced rate of glucose utilization by neoplastic cells (5–7). Due to increased metabolic demand for glucose, the hexokinase (a key enzyme for glycolysis) activity is increased (8). 2-Deoxyglucose has been shown to be a substrate for hexokinase (9). Therefore, the 2-deoxyglucose analog ^{18}F FDG is a particularly appropriate imaging agent for tumors. Clinical applications using positron emission tomography (PET) have been reported on the correlation of the ^{18}F FDG uptake to: the differentiation of malignant tumor from benign (10); the grade of malignancy (11); and the proliferative activity of tumor cells (12). An autoradiographic study using x-ray films has also reported that ^{18}F -FDG accumulates into areas of malignant growth (13). High ^{18}F FDG accumulation in abscesses (14,15) have also been observed. The influence of radiotherapy on ^{18}F FDG uptake in tumor was reported to be slower than the response of metabolic damage of amino acid and DNA incorporation/synthesis (16). In this study, we report a unique uptake pattern of ^{18}F FDG and 2-deoxy-D- ^3H glucose (^3H -DG) by the complex of heterogeneous cell elements in a malignant tumor model in mice.

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After nearly 3 decades, it is now well recognized that tumor-associated macrophages may constitute a large fraction of tumor mass and are critical players throughout different stages of tumorigenesis, from cancer initiation to local spread and metastasis (4). Moreover, growing immunometabolic discoveries have highlighted the cross talk between cell metabolism and macrophage biology, which may be exploited as novel targets for cancer diagnosis, risk stratification, and therapy (4). However, the field of immunometabolism has been driven largely through ex vivo techniques, such as stable isotope metabolic tracing, which do not accurately reflect the complexities of the natural microenvironment of tumor or inflammatory tissues.

Metabolic imaging is well positioned to address the dire need to define metabolism in vivo. However, major challenges are yet to be overcome, particularly for metabolic assessment of complex and heterogeneous tissues, such as tumors. The spatial resolution of PET does not allow ^{18}F -FDG uptake by malignant cells to be distinguished from uptake by tumor-associated macrophages or other tumor constituents. Therefore, unraveling the biologic significance of ^{18}F -FDG uptake by tumor-associated macrophages and its implications for prognostication of patients (e.g., determining tumor aggressiveness) and monitoring the response to therapy remain an ongoing challenge. Complementing in vivo PET studies by high-resolution microautoradiography (as in Kubota et al. (3)) or state-of-the-art metabolomics techniques (e.g., mass spectrometry imaging (5)) advances our knowledge about the heterogeneity of immune cell metabolism within the tumor microenvironment. The limited specificity of ^{18}F -FDG, which targets a nearly ubiquitous

metabolic process, is another major challenge for the elucidation of immunometabolic links between tumor-associated macrophages and tumor biology by in vivo imaging.

A multipronged approach that includes developing novel tracers with more specific metabolic targets, imaging additional pathways other than glucose uptake, and improving the spatial resolution of PET (e.g., by total-body acquisition), along with careful histologic validations, will be vital to reinforce the role of in vivo imaging in understanding immunometabolism.

DISCLOSURE

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REFERENCES

1. Alavi A, Reivich M. Guest editorial: the conception of FDG-PET imaging. *Semin Nucl Med.* 2002;32:2–5.
2. Jamar F, Buscombe J, Chiti A, et al. EANM/SNMMI guideline for ^{18}F -FDG use in inflammation and infection. *J Nucl Med.* 2013;54:647–658.
3. Kubota R, Yamada S, Kubota K, Ishiwata K, Tamahashi N, Ido T. Intratumoral distribution of fluorine-18-fluorodeoxyglucose in vivo: high accumulation in macrophages and granulation tissues studied by microautoradiography. *J Nucl Med.* 1992;33:1972–1980.
4. O'Sullivan D, Sanin DE, Pearce EJ, Pearce EL. Metabolic interventions in the immune response to cancer. *Nat Rev Immunol.* 2019;19:324–335.
5. Aichler M, Walch A. MALDI imaging mass spectrometry: current frontiers and perspectives in pathology research and practice. *Lab Invest.* 2015;95:422–431.

that higher tumor uptake may reflect not only tumor cell viability and proliferation but also the contribution of secondary inflammatory reaction elements. Further micro-autoradiographic studies with [¹⁸F]FDG will be of help in understanding PET's role in clinical problems.

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REFERENCES

1. Som P, Atkins HL, Bandyopadhyay D, et al. A fluorinated glucose analog, 2-fluoro-2-deoxy-D-glucose (F-18): non-toxic tracer for rapid tumor detection. *J Nucl Med* 1980;21:670-675.
2. Larson SM, Weiden PL, Grunbaum Z, et al. Positron imaging feasibility studies. II. Characteristics of 2-deoxyglucose uptake in rodent and canine neoplasms: concise communication. *J Nucl Med* 1981;22:875-879.
3. Di Chiro G, DeLaPaz RL, Brooks RA, et al. Glucose utilization of cerebral gliomas measured by [¹⁸F]-2-fluoro-deoxyglucose and positron emission tomography. *Neurology* 1982;32:1323-1329.
4. Yonekura Y, Benua RS, Brill AB, et al. Increased accumulation of 2-fluoro-2-(¹⁸F)-deoxy-D-glucose in liver metastases from colon carcinoma. *J Nucl Med* 1982;23:1133-1137.
5. MacKeehan WL. Glycolysis, glutaminolysis and cell proliferation. *Cell Biol Int Rep* 1982;6:635-650.
6. Weber G, Morris HP, Love WC, Ashmore J. Comparative biochemistry of hepatomas. III. Isotope studies of carbohydrate metabolism in Morris hepatoma 5123. *Cancer Res* 1961;21:1406-1411.
7. Weber G. Enzymology of cancer cells. *N Engl J Med* 1977;296:541-551.
8. Monakhov NK, Neistadt EL, Shavlovski MM, Shvartsman AL, Neifakh SA. Physicochemical properties and isoenzyme composition of hexokinase from normal and malignant human tissues. *J Natl Cancer Inst* 1978;61:27-34.
9. Renner ED, Plagemann PGW, Bemlohr RW. Permeation of glucose by simple and facilitated diffusion by Novikoff rat hepatoma cells in suspension culture and its relationship to glucose metabolism. *J Biol Chem* 1972;247:5765-5776.
10. Kubota K, Matsuzawa T, Fujiwara T, et al. Differential diagnosis of lung tumor with positron emission tomography: a prospective study. *J Nucl Med* 1990;31:1927-1933.
11. Di Chiro G. Positron emission tomography using [¹⁸F]-2-fluoro-deoxyglucose in brain tumors, a powerful diagnostic and prognostic tool. *Invest Radiol* 1987;22:360-371.
12. Minn H, Joensuu H, Ahonen A, Klemi P. Fluoro-deoxyglucose imaging: a method to assess the proliferative activity of human cancer in vivo. Comparison with DNA flow cytometry in head and neck tumors. *Cancer* 1988;61:1776-1781.
13. Paul R, Johansson R, Kellokumpu-Lehtinen P-L, Soderstrom K-O, Kangas L. Tumor localization with [¹⁸F]-2-fluoro-2-deoxy-D-glucose: comparative autoradiography, glucose 6-phosphatase histochemistry, and histology of renally implanted sarcoma of the rat. *Res Exp Med* 1985;185:87-94.
14. Tahara T, Ichiya Y, Kuwabara Y, et al. High [¹⁸F]-2-fluoro-deoxyglucose uptake in abdominal abscesses: a PET study. *J Comput Assist Tomogr* 1989;13:829-831.
15. Sasaki M, Ichiya Y, Kuwabara Y, et al. Ringlike uptake of [¹⁸F]FDG in brain abscess: a PET study. *J Comput Assist Tomogr* 1990;14:486-487.
16. Kubota K, Ishiwata K, Kubota R, et al. Tracer feasibility for monitoring of tumor radiotherapy: a quadruple-tracer study with [¹⁸F]-FDG or [¹⁸F]-FdUrd, [¹⁴C]-Met, [³H]-Thd and [⁶⁷Ga]. *J Nucl Med* 1991;32:2118-2123.
17. Kubota K, Kubota R, Matsuzawa T. Dose-responsive growth inhibition by glucocorticoid and its receptors in mouse teratocarcinoma OTT6050 in vivo. *Cancer Res* 1983;43:787-793.
18. Yamada S, Kubota R, Kubota K, Ishiwata K, Ido T. Localization of [¹⁸F]-2-fluoro-deoxyglucose in mouse brain neurons with micro-autoradiography. *Neurosci Letts* 1990;120:191-193.
19. Paul R, Ahonen A, Nordman E. Imaging of hepatoma with [¹⁸F]-2-fluoro-deoxyglucose. *Lancet* 1985;1:50-51.
20. Paul R. Comparison of [¹⁸F]-2-fluoro-deoxyglucose and gallium-67 citrate imaging for detection of lymphoma. *J Nucl Med* 1987;28:288-292.
21. Nolop KB, Rhodes CG, Brudin LH, et al. Glucose utilization in vivo by human pulmonary neoplasms. *Cancer* 1987;60:2682-2689.
22. Haberkorn U, Strauss LG, Dimitrakopoulou A, et al. PET studies of 2-fluoro-deoxyglucose metabolism in patients with recurrent colorectal tumors receiving radiotherapy. *J Nucl Med* 1991;32:1485-1490.
23. Blasberg RG, Shinohara M, Shapiro WR, Patlak CS, Pettigrew KD, Fenstermacher JD. Apparent glucose utilization in Walker 256 metastatic brain tumors. *J Neurooncol* 1986;4:5-16.