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

Sina Tavakoli

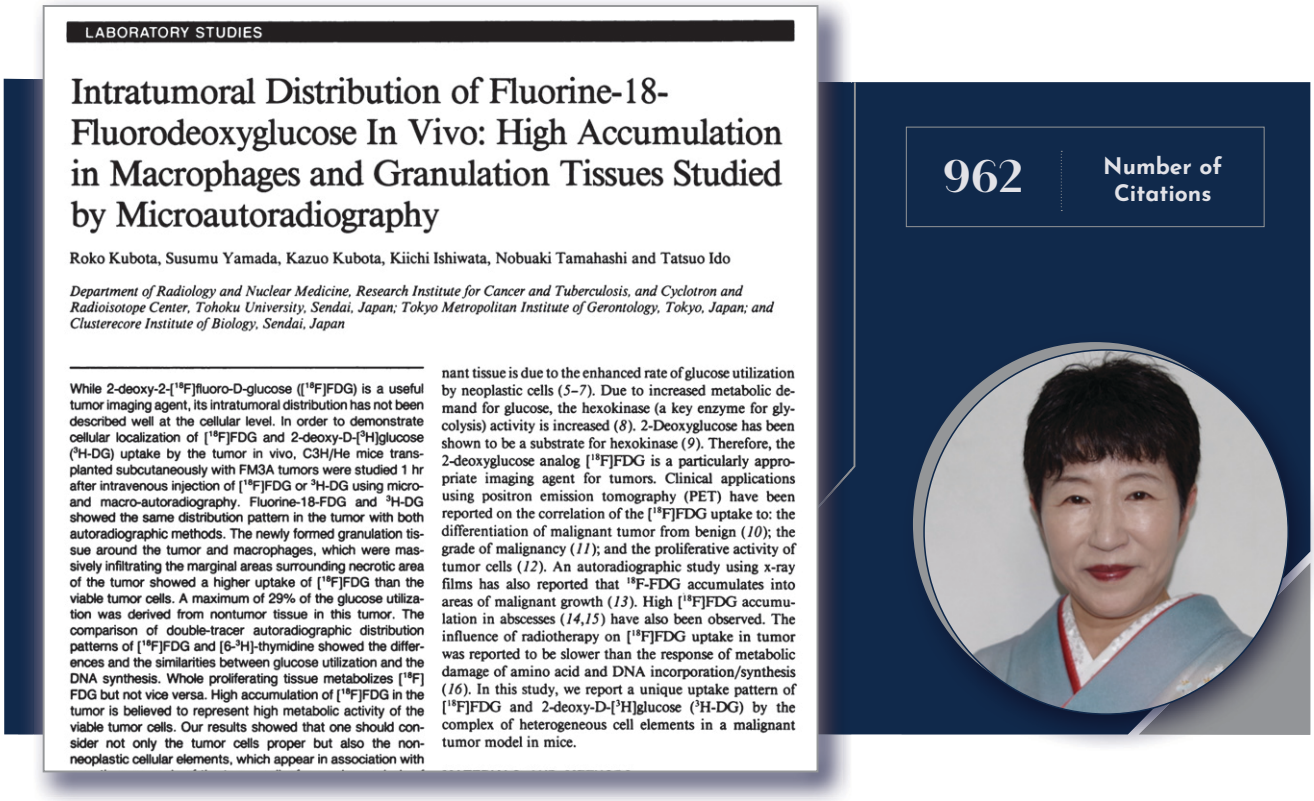
Department of Radiology, University of Pittsburgh, and Heart, Lung, Blood, and Vascular Medicine Institute, UPMC Department of Medicine, Pittsburgh, Pennsylvania

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*).

Received Jun. 16, 2020; revision accepted Jun. 18, 2020.
For correspondence or reprints contact: Sina Tavakoli, UPMC Presbyterian Hospital, 200 Lothrop St., Suite E200, Pittsburgh, PA 15213.
E-mail: sit23@pitt.edu

DOI: 10.2967/jnumed.120.251744



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

The author is supported by the National Institutes of Health (NHLBI K08-HL144911). No other potential conflict of interest relevant to this article was reported.

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 re ect not only tumor cell viability and proliferation but also the contribution of secondary in ammatory reaction elements. Further micro-autoradiographic studies with [^{18}F]FDG will be of help in understanding PET s role in clinical problems.

ACKNOWLEDGMENTS

The authors are grateful to Dr. Prantika Som, Brookhaven National Laboratory, Upton, NY, for advice; to the staffs of the Cyclotron and Radioisotope Center, Tohoku University, for their cooperation; and to Mr. Y. Sugawara for photography. This work was supported by a grant-in-aid for scienti c research (03152018, 03454277 and 04557047) from the Ministry of Education, Science and Culture, Japan.

REFERENCES

1. Som P, Atkins HL, Bandoypadhyay D, et al. A uorinated glucose analog, 2-uoro-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 [^{18}F]- uoro-deoxyglucose and positron emission tomography. Neurology 1982;32:1323 1329.
4. Yonekura Y, Benua RS, Brill AB, et al. Increased accumulation of 2- deoxy-2-(^{18}F) uoro-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. II. 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, Neiufakh 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 [^{18}F] uorodeoxyglucose in brain tumors, a powerful diagnostic and prognostic tool. Invest Radiol 1987;22:360 371.
12. Minn H, Joensuu H, Ahonen A, KJemi P. Fluorodeoxyglucose imaging: a method to assess the proliferative activity of human cancer in vivo. Comparison with DNA ow 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 ^{18}F-2- uoro-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 [^{18}F] uorodeoxyglucose 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 [^{18}F]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 ^{18}F-FDG or ^{18}F-FdUrd, ^{14}C-Met, ^{3}H-Thd and ^{67}Ga. 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 [^{18}F] uorodeoxyglucose in mouse brain neurons with micro-autoradiography. Neurosci Letts 1990; 120:191 -193.
19. Paul R, Ahonen A, Nordman E. Imaging of hepatoma with [^{18}F] uorodeoxyglucose. Lancet 1985;1:50 51.
20. Paul R. Comparison of uorine-18-2- uorodeoxyglucose 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. Haberkom U, Strauss LG, Dimitrakopoulou A, et al. PET studies of uorodeoxyglucose 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.