

## Perspectives on Assessment of Stem Cell Therapy in Stroke by $^{18}\text{F}$ -FDG PET

As many readers are aware, the work by Dr. Shinya Yamanaka concerning induced pluripotent stem cells (iPSCs) received the Nobel Prize in Physiology or Medicine in 2012. Dr. Yamanaka demonstrated that when 4 genes were transferred to skin cells, they could be reprogrammed into iPSCs, which can then be differentiated into all adult cell types including neurons, cardiac cells, and hepatic cells (1,2). This groundbreaking discovery permits the use of stem cells for various medical research and potential medical treatments without the need for embryonic stem cells (ESCs). When these cells are used for medical

by intraventricularly administered ESCs and iPSCs along with increased  $^{18}\text{F}$ -FDG uptake in stroke lesions depicted by small-animal PET and autoradiography. Immunohistochemistry examination at 4 wk after cell transplantation also indicated the presence of neuronal differentiation among injected cells. This study demonstrated similar efficacy by iPSC versus ESC treatment. The application of  $^{18}\text{F}$ -FDG PET to directly compare iPSC and ESC treatments will provide additional evidence of the potential efficacy of future iPSC treatment in stroke.

As is the case with any biomarker, it is important to understand the physiologic or pathophysiologic mechanisms of marker expression. The question is, what does increased  $^{18}\text{F}$ -FDG uptake in the rat stroke treated by stem cells mean? The deoxyglucose method was investigated extensively in the 1970s and 1980s by many investigators, including Sokoloff et al., who pioneered the technology (9,10). Glucose metabolism, an essential pathway in energy metabolism in neurons, became a focus in neuroscience research. This method has also been applied to cancer research, and it is extensively used for clinical evaluations of cancer patients in day-to-day practice in nuclear medicine and radiology. It is important to note that, despite 3 decades of investigations using the deoxyglucose method, the cellular mechanism responsible for glucose consumption in brain tissue is still a matter for debate. Identification of the glucose transporters in the brain and blood-brain barrier of humans in the late 1980s shed mechanistic insights into glucose transport from cerebral capillaries to neurons (11). Pellerin and Magistretti observed the involvement of astrocytes

and glutamate in glucose metabolism and proposed a lactate shuttle model between neurons and astrocytes (12). However, discordant observations have been reported since then, and the exact mechanisms and roles of the molecules involved in the pathway are still under investigation (13). In addition, these observations and hypotheses were made primarily in nondisease conditions, and dynamic changes of such complex systems in disease conditions such as reperfusion stroke are still not understood.

In light of these multiple cellular elements and molecules likely involved in glucose metabolism, we need to cautiously interpret the observed increased  $^{18}\text{F}$ -FDG uptake in stroke lesions treated by stem cells. Does the increased  $^{18}\text{F}$ -FDG uptake in the stroke lesion after stem cell treatment indicate restoration of presumed capillary-astrocyte-neuronal elements and coupling? Do transplanted stem cells themselves accumulate glucose through their transporter expression (14)? Did the stem cells facilitate neovascular growth in the stroke lesion and increase glucose transport through the expression of glucose transporters (15)? Is not only neural but also glial proliferation by stem cell treatment responsible for increased  $^{18}\text{F}$ -FDG uptake (16)? Neuroinflammation in stroke associated with microglial activation and macrophage migration was shown to increase local  $^{18}\text{F}$ -FDG uptake (17) and potentially underestimate neuronal dysfunction (18). Does stem cell therapy somehow modulate neuroinflammation and thus affect  $^{18}\text{F}$ -FDG uptake? Although the exact mechanisms of  $^{18}\text{F}$ -FDG uptake in the stem cell-treated lesions are still in question, the uptake and functional

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treatments, noninvasive evaluation of transplanted cell and organ function becomes essential. Molecular imaging serves a critical role in stem cell research and the development of future stem cell treatments. Various imaging modalities, such as PET (3), MR imaging (4), optical imaging (5), SPECT (6), and multimodal techniques (7), have been used in the field of stem cell research.

The study by Dr. Wang et al. in this issue of *The Journal of Nuclear Medicine* (8) demonstrated functional recovery in a rat stroke model treated

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recovery measured by behavioral testing appear to correlate in this study. Further investigation is needed of whether there are specific, causal mechanisms underlying such a correlation.

Although a further mechanistic investigation of  $^{18}\text{F}$ -FDG uptake in ischemic lesions treated with stem cell therapies is warranted,  $^{18}\text{F}$ -FDG PET and other molecular imaging techniques have been used in human stroke patients who have received cell therapy. Local  $^{18}\text{F}$ -FDG uptake increased at varying degrees approximately 6 mo after cell therapy (19).  $^{99\text{m}}\text{Tc}$ -labeled bone marrow mononuclear cells accumulated in the area of middle cerebral artery stroke demonstrated by  $^{99\text{m}}\text{Tc}$ -ethyl cysteinate dimer 2 h after cell transplantation (20). Similarly,  $^{99\text{m}}\text{Tc}$ -hexamethylpropylene amine oxime-labeled autologous bone marrow mononuclear cells accumulated in the area of stroke within 8 h after cell delivery, whereas whole-body images showed tracer distribution in the liver and spleen (21). Another study used whole-body  $^{18}\text{F}$ -FDG PET to assess potential tumor formation after stem cell therapy (22). If clinical prognostic values of molecular imaging findings can be established, such information may be able to guide personalized stem cell therapy in the future. Stroke stem cell therapy may become an important component of our nuclear medicine and radiology practice similar to our current use of whole-body  $^{18}\text{F}$ -FDG PET evaluation for various cancer patients who have undergone bone marrow transplantation.

## DISCLOSURE

No potential conflict of interest relevant to this article was reported.

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