uPAR as a Glioma Imaging Target
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Gliomas account for 70% of primary brain tumors (1). Among the various types of glioma, glioblastoma is the most aggressive astrocytic tumor, being classified grade IV by the World Health Organization (2). Although CT and MRI are indispensable in providing morphologic information, functional imaging using PET plays an important role in grading tumors, delineating tumor boundaries, monitoring treatment, and discriminating recurrent tumor from treatment-induced changes (3). 18F-FDG is the best-established PET tracer for various malignancies; however, the high glucose metabolism of the brain prevents accurate evaluation of brain neoplasms using 18F-FDG PET. In addition, although higher-grade gliomas metabolize more glucose than lower-grade gliomas, even glioblastomas sometimes show lower uptake than the surrounding brain tissue, making 18F-FDG PET images difficult to interpret—especially in evaluating tumor expansion. In this context, other tracers for brain tumors have been extensively investigated over the past few decades. Among them, amino acid tracers such as 11C-methionine (4,5) and 18F-fluorothymidine (6,7) have been the most successful, followed by hypoxia imaging agents such as 18F-fluoromisonidazole (8) and nucleic acid analogs such as 18F-fluorothymidine (9). Now, urokinase-type plasminogen activator receptor (uPAR) has been added to the array of available tracers for imaging.

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uPAR is a glycosylphosphatidylinositol-anchored receptor that is located on the cell surface and binds the serine protease urokinase-type plasminogen activator (10). uPAR is important in regulating extracellular matrix proteolysis, cell–extracellular matrix interactions, and cell signaling and has limited expression under normal conditions. Some exceptions are keratinocytes during wound healing and brain tissue that has undergone ischemic or traumatic changes (11). Cancer cells also express uPAR. They make use of uPAR because proteolytic degradation of the extracellular matrix is essential for tumor invasion and metastasis. The intensity of uPAR expression is associated with poor prognosis in many malignancies, as demonstrated by nearly 100 papers published between 1990 and 2010 describing uPAR expression in cancers of the bladder, breast, colon and rectum, stomach, blood, liver, lung, pancreas, and prostate (10). Glioblastomas also exhibit increased uPAR expression, with a greater level of expression indicating higher invasiveness and shorter survival. Such characteristics raised the possibility of using uPAR as an imaging agent for glioblastoma.

Ploug’s group contributed greatly to the development of uPAR imaging agents. They developed several peptide-derived antagonists of uPAR and described them in a 2001 article (12). Interestingly, according to that article, these compounds were initially designed for chemotherapy rather than for radionuclide therapy, and some of the data indicated the inhibitory effect of peptide-derived antagonists of uPAR on tumor invasion (12). Based on AE105, which is one of the antagonist products proposed by Ploug’s group, Li et al. (also Ploug’s colleagues) first developed a radioactive uPAR ligand, 64Cu-DOTA-AE105 (13). More recently, the Kjaer group performed a series of important steps to modify and characterize radioactive uPAR ligands. They developed and examined the radioactive uPAR ligands 68Ga-DOTA-AE105-NH2 (14), 68Ga-NODAGA-AE105-NH2 (14), 64Cu-AIF-NOTA-AE105 (15), 64Cu-CB-TE2A-PA-AE105 (16), and 68Ga-DOTA-AE105 (17). In this issue of The Journal of Nuclear Medicine, Persson et al. from the Kjaer group present evidence of the usefulness of two new uPAR PET tracers, 64Cu-NOTA-AE105 and 68Ga-NOTA-AE105, in glioblastoma imaging (18). Three highlights of their study are, first, that an orthotopic glioblastoma model was used to demonstrate strong accumulation of both tracers in the tumor; second, that compared with 18F-fluorothymidine, the new tracers showed lower absolute uptake values but higher tumor-to-background ratios; and third, that autoradiography revealed the intratumoral tracer distribution, which resembled the immunohistochemical staining of uPAR.

In previous investigations by Persson et al., a tumor was implanted in subcutaneous tissue or muscle because that approach is relatively easy and less time-consuming. However, there are always criticisms against such an approach from the viewpoint of the limited similarity between spontaneous cancers and implanted cell lines. In the present study, Persson et al. established cell cultures sampled from a glioblastoma patient and injected the tumor cells into the brain tissue of nude mice. This method is technically demanding but worth establishing. Although this model is still somewhat different from naturally occurring tumors, we consider the present findings to provide more reliable evidence justifying clinical studies of the new tracers. Attention should be paid to the radionuclides used by Persson et al. Whereas the production of 18F, 11C, and 64Cu (half-life, 12.7 h) requires a cyclotron, 68Ga (half-life, 68 min) is produced by a 68Ge/68Ga generator, and thus the preparation of 68Ga-DOTA-AE105 does not require an in-house cyclotron. Conversely, the relatively short half-life of 68Ga may restrict imaging at a late phase. It is important to understand the advantages and disadvantages of different radionuclides when considering them for imaging. In any event, it is good news that both 64Cu and 68Ga can be used to label AE105 peptide.
A few issues are not addressed by Persson et al. in their new report. First, as they admit in the Discussion section, their uPAR ligands have strong species specificity; the ligands bind with 200-fold higher affinity to human uPAR than to mouse uPAR (I9). This may be the significant factor causing the high tumor-to-background ratio in the study (i.e., the tumor is of human origin but the background is of mouse origin). uPAR ligands are also different from analogs of more ubiquitous substrates such as glucose (e.g., 18F-FDG) and amino acids (e.g., 13C-methionine and 18F-fluoroethyltyrosine). Thus, clinical studies using uPAR ligands are expected to result in lower contrast than in the present study. Second, although the autoradiography images were similar to the immunostaining of uPAR, the accumulation was not compared quantitatively. The quantity in the clinical studies using uPAR ligands are expected to result in lower quantitative performance of the tracers. Third, together with previous papers, the new study by Persson et al. presents several uPAR tracer candidates. Comparative studies need to determine the most feasible candidate before clinical studies can take place, and the Kjaer group recently took the first of these uPAR tracers into a human trial (20).

We also hope that future studies will determine whether information obtained from uPAR imaging is an independent factor in determining patient prognosis. After several pilot studies are performed, it will be necessary to conduct studies of large populations with multivariate analyses that did not compare known prognosis factors such as age, glioma grade, and surgical procedure. Comparisons with established tracers such as 18F-FDG, 11C-methionine, 18F-fluoroethyltyrosine, and 18F-fluoromisonidazole are also important. The question of whether the imaging technique can be used for monitoring treatment response is also of interest. The ultimate goal of tumor imaging is, of course, to improve patient outcomes.

Before closing, we would like to mention a uPAR-targeted radionuclide therapeutic agent, 177Lu-DOTA-AE105, which has been tested by Persson et al. using colorectal cancer xenografts (21). This therapy was shown to reduce both tumor size and the rate of uPAR-positive cells without producing significant side effects in the kidneys and other organs. It is greatly beneficial that the same compound can be used for both imaging and therapy, because the imaging technique directly predicts the treatment effects. Preclinical and clinical studies further investigating these agents are eagerly awaited.

DISCUSSION

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

REFERENCES

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