

Molecular Imaging of IGF-1R in Cancer

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Molecular Imaging
Volume 16: 1-7
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DOI: 10.1177/1536012117736648
journals.sagepub.com/home/mix



Abstract

The important role of insulin-like growth factor 1 receptor (IGF-1R) in malignant tumors has been well established. Increased IGF-1R activity promotes cancer cell proliferation, migration, and invasion and is associated with tumor metastasis, treatment resistance, poor prognosis, and shortened survival in patients with cancer. However, while IGF-1R has become a promising target for cancer therapy, IGF-1R-targeted therapy is ineffective in unselected patients. It is therefore essential to evaluate IGF-1R expression before treatment in order to identify responsive patients, monitor therapy efficacy, and estimate prognosis. Insulin-like growth factor 1 receptor molecular imaging is an optimal method for assessing the expression of IGF-1R in vivo accurately and noninvasively. In this review, we will summarize the current status of IGF-1R molecular imaging in cancer, in which 5 major classes of ligands that have been developed for noninvasive IGF-1R molecular imaging will be discussed: natural ligands, monoclonal antibodies, antibody fragments, affibodies, and small molecules. For decades, IGF-1R molecular imaging is studied in full swing and more effort is needed in the future.

Keywords

IGF-1R, target, molecular imaging, cancer

Introduction

The insulin-like growth factor (IGF) signaling pathway is a complex network comprising 2 ligands (IGF-1 and IGF-2), 2 receptors (IGF-1R and IGF-2R), and 6 IGF-binding proteins (IGFBP1-6). Insulin-like growth factor 1 receptor is a key player in several physiological processes such as cell growth, proliferation, differentiation, and apoptosis, and it is well documented that IGF-1R plays a critical role in cancer formation, progression, and metastasis.^{1,2} Preclinical data show that IGF-1R is overexpressed in several malignant tumors including lung cancer,³ breast cancer,⁴ prostate cancer,⁵ glioma,⁶ gastrointestinal cancers,⁷ and so on. Moreover, clinical research demonstrates that IGF-1R has potent antiapoptotic and transforming activities and that increased IGF-1R activity is associated with tumor metastasis, treatment resistance, poor prognosis, and shortened survival.^{3,8-10} Insulin-like growth factor 1 receptor has therefore emerged as a potential and promising diagnostic and therapeutic biomarker in cancers.¹¹

To date, over 10 IGF-1R-targeted drugs have been approved for clinical trials. A wide range of clinical effects were reported in these studies, from minor or no clinical benefits to close to complete response. For instance, in a phase I clinical trial on 4 patients with advanced lung squamous cell carcinoma treated for 7 months with IGF-1R-targeting small-molecule inhibitory drugs (picropodophyllin, PPP, AXL1717), none of the patients

developed new metastases. Moreover, central necrosis was confirmed in these patients with computed tomography (CT) and 18F-Fludeoxyglucose positron emission tomography (PET).¹² However, many studies failed to achieve the desired results. The results of initial phase III studies in unselected patients with anti-IGF-1R monoclonal antibodies were disappointing,^{13,14} thus highlighting the need to develop effective biomarkers to select responsive patients and predict clinical results more accurately.

Tissue biopsy and immunohistochemistry are currently the most commonly used methods for the detection of IGF-1R; however, they present several limitations. First, tissue biopsy is an invasive method poorly accepted by patients and their

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Submitted: 15/07/2017. Revised: 28/08/2017. Accepted: 03/09/2017.

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families. Second, not all lesions can provide pathological data. Finally, tumor heterogeneity may affect the accuracy of biopsy results.¹⁵⁻¹⁷ For instance, different IGF-1R expression levels may be obtained within the same tumor or between the primary tumors and the metastatic lesions. Moreover, IGF-1R expression can change throughout tumor development and also during treatment. There is therefore an urgent need to develop an accurate noninvasive method to detect in vivo IGF-1R expression, in order to screen patients potentially responsive to IGF-1R-targeted treatment, monitor changes in IGF-1R expression levels during treatment, and guide the selection of adequate clinical treatments. In recent years, the development of molecular imaging has allowed the in vivo visualization of cells, molecules, and metabolic processes in real time. Thus, in vivo IGF-1R-targeted imaging could be a valuable tool for determining IGF-1R expression noninvasively.

Insulin-Like Growth Factor 1 Receptor and Cancer

Expression of IGF-1R in tumors. A large number of studies have shown that IGF-1R is upregulated in most malignant tumors and that it plays a crucial role in phenotypic transformation and maintenance. Insulin-like growth factor 1 receptor binding to its natural ligands IGF-1 or IGF-2 activates the PI3K-Akt and Ras-Raf-ERK/MAPK signaling pathways, thereby promoting proliferation, differentiation, migration, and apoptosis inhibition.^{1,18-20} Insulin-like growth factor 1 receptor activation is closely associated with tumor angiogenesis, metastasis, and treatment resistance.^{11,21,22} The mechanism may be related to the following aspects: it can modulate cell mitosis, it is required for tumorigenesis, and it could protect tumor cells from apoptosis.²³

Insulin-like growth factor 1 receptor and oncogenes. Besides having a direct effect on cellular proliferation and survival, IGF-1R is also a key mediator in the biochemical and molecular events driving oncogenic transformation.^{11,20,24} The signaling pathways downstream of IGF-1R have multiple crossing sites with oncogenes such as Ras, c-myc, and c-fos, which can in turn regulate each other, ultimately leading to tumor formation. In addition, these IGF-1R downstream signaling pathways can also interact with the epidermal growth factor receptor (EGFR) and vascular EGFR pathways to regulate cell proliferation and differentiation. Activation of IGF-1R causes upregulation of hypoxia-inducible factor 1 α protein synthesis, which induces expression of VEGF, a central mediator of angiogenesis.²⁵ Insulin-like growth factor 1 receptor is also closely related to breast cancer gene 1 (BRCA1). Indeed, wild-type BRCA1 expression caused a significant decrease in IGF-1R promoter activity and endogenous IGF-1R levels in breast cancer cell lines, whereas mutant BRCA1 expression had no effect on IGF-1R levels.²⁶

The studies discussed earlier are just a small selection among the large body of research demonstrating the essential role of IGF-1R in malignant transformation. Thus, IGF-1R-targeted imaging has strong potential to become an invaluable tool for tumor diagnostics and therapy efficacy monitoring.

Insulin-Like Growth Factor 1 Receptor-Targeted Molecular Imaging

Insulin-like growth factor 1 and analogue molecular imaging. Insulin-like growth factor 1 was labeled with ¹²⁵I and its bio-distribution was evaluated in tumor-bearing mice.²⁷ Insulin-like growth factor 1 (7649 Da) is the natural ligand of IGF-1R, which makes it have a high affinity to IGF-1R, but IGFBPs in the serum may obstruct IGF-1 from binding to target, which greatly reduced its affinity. When coinjected with cold IGF-1, there appeared to be more ¹²⁵I-labeled IGF-1 accumulated in the tumor area and less emerged in normal tissues, maybe due to partial saturation of IGFBPs. However, catabolism occurred rapidly making it not fit for imaging IGF-1R in vivo. The same author²⁸ assessed the feasibility of ¹²⁵I-labeled des(1-3) IGF-1, a truncated analogue of IGF-1, as a probe for molecular imaging. The probe was quickly internalized after binding to IGF-1R and also rapidly catabolized at 37°C with release of breakdown products either. These preliminary results suggested that ¹²⁵I-labeled IGF and ¹²⁵I-labeled des(1-3) IGF-1 had little potential as an imaging probe. Cornelissen et al²⁹ labeled IGF-1 and its analogue IGF-1 (E3R) with ¹¹¹In and showed that IGF-1 (E3R) uptake was strongly correlated with IGF-1R expression. Moreover, human breast cancer cells (MCF-7)/human epidermal growth factor receptor (HER) 2-18 tumors were clearly visible by micro single-photon emission computed tomography (SPECT), thus suggesting that ¹¹¹In-labeled IGF-1(E3K) is a promising molecular imaging tracer.

Insulin-like growth factor 1 receptor monoclonal antibody molecular imaging. R1507 is a fully humanized antibody most commonly used in IGF-1R molecular imaging. R1507 labeled with ¹¹¹In and ¹²⁵I was assessed with SPECT imaging in nude mice bearing breast cancer SUM149.³⁰ In this study, the tumor was clearly visible with ¹¹¹In-R1507, and the tumor to background ratio increased gradually with time. Blocking assays with excess cold R1507 showed that ¹¹¹In-R1507 has high specificity to IGF-1R. Moreover, this probe showed higher tumor uptake than ¹²⁵I-R1507 (20% \pm 6% ID/g vs 8% \pm 1% ID/g, 33% \pm 6% ID/g vs 7% \pm 1% ID/g, 31% \pm 4% ID/g vs 5% \pm 1% ID/g in 1, 3, and 7 days after injection, respectively).

Positron emission tomography imaging has higher sensitivity and provides more accurate quantitative quantifications than SPECT. A new PET imaging tracer, ⁸⁹Zr-N-Succinyl-desferal-human anti-IGF-1R monoclonal antibody R1507 (⁸⁹Zr-R1507), was synthesized successfully and imaging in nude mice bearing breast cancer SUM149 was performed. When compared to ¹¹¹In-R1507 SPECT imaging, the tumor uptake and tumor to blood ratio obtained with ⁸⁹Zr-R1507 PET imaging were similar (22% \pm 3% ID/g vs 20.9% \pm 2.4% ID/g and 3.9% \pm 0.5% ID/g vs 3.8% \pm 0.7% ID/g), but the tumor to liver ratio was slightly lower (4.8% \pm 0.2% ID/g vs 7.5% \pm 1.2% ID/g).^{30,31} These studies suggest that IGF-1R monoclonal antibodies labeled with radionuclides could be valuable probes for IGF-1R molecular imaging.

Fluorescence imaging is among the most widely utilized molecular imaging methods. The IGF-1R monoclonal antibody

AVE-1642, labeled with either small molecular fluorophores or quantum dot (ODs), was assessed in preclinical models of human breast cancer MCF-7.³² Most ODs were detected in normal organs including the liver, spleen, lymph nodes, and bone marrow, rather than on MCF-7 breast tumors expressing IGF-1R. Moreover, ex vivo data showed that this OD accumulation in the tumor regions was unspecific. In contrast, AVE-1642-conjugated Alexa 680 accumulated in tumor areas without obvious nonspecific uptake, suggesting that this probe may be suitable for molecular imaging. Similar results were obtained in a study examining anti-IGF-1R antibodies (clone 24-31) conjugated with 550- to 650-nm fluorophores in molecular imaging of different subcutaneous and orthotopic pancreatic tumors.³³ By further analyzing this fluorescently conjugated IGF-1R antibody in models of subcutaneous colon cancer, in situ colon cancer, and colon cancer liver metastases, the same authors demonstrated that this tracer can identify not only in situ tumor regions but also metastases.³⁴ Together, these studies showed that in situ and metastases tumors may be imaged noninvasively with IGF-1R antibodies conjugated with fluorophores. Fluorescence imaging technology has many advantages such as nonradiation, convenient, and real time, which can accurately reflect changes in disease.³⁵ Although fluorescence imaging had limited depth that restricted its application to deep tumors, fluorescence image-guided surgery is in full swing.^{36,37} A mount of new fluorescence tracers had successfully been tested in animal studies.³⁸⁻⁴⁰ We could expect these preclinical results translating to clinical patients.

In addition, it was demonstrated that monoclonal antibody probes could not only provide a clear imaging of IGF-1R expression in tumors but could also detect IGF-1R expression levels based on probe uptake quantifications. For instance, biodistribution experiments in preclinical models of bone sarcoma tumors with different IGF-1R expression levels (OS-1, EW-5, EW-8, and OS-33) revealed that ¹¹¹In-R1507 had high radioactivity aggregation in OS-1 (IGF-1R overexpression) and EW-5 (IGF-1R moderate expression) tumors (27.5% ± 6.5% ID/g and 14.0% ± 2.8% ID/g, respectively), whereas IGF-1R low-expression tumors (EW-8 and OS-33) showed low radioactive accumulation (6.5% ± 1.5% ID/g and 5.5% ± 0.6% ID/g, respectively).⁴¹ Tumor uptake in these models varied relative to the IGF-1R expression level, with highest uptake in OS-1 and tumor to background ratio gradually increasing with time. As expected, the tumor to blood ratios of OS-1 and EW5 were markedly different. Moreover, probe uptake in different tumors within the same subject was examined in a OS-1/OS-33 tumor-bearing nude mice model. Notably, SPECT imaging revealed that although the OS-1 tumor showed significant radioactive agglomeration, the OS-33 tumor had low tracer uptake. That IGF-1R expression levels could be detected based on probe uptake quantifications was also corroborated by England et al.⁴² In this study, PET imaging with a new IGF-1R tracer (1A2G11) labeled with ⁸⁹Zr was performed on pancreatic tumor models with different IGF-1R expression levels: MIA PaCa-2 (overexpression), BxPC-3 1R (moderate expression), and AsPC-1 (low expression). Maximal uptake of

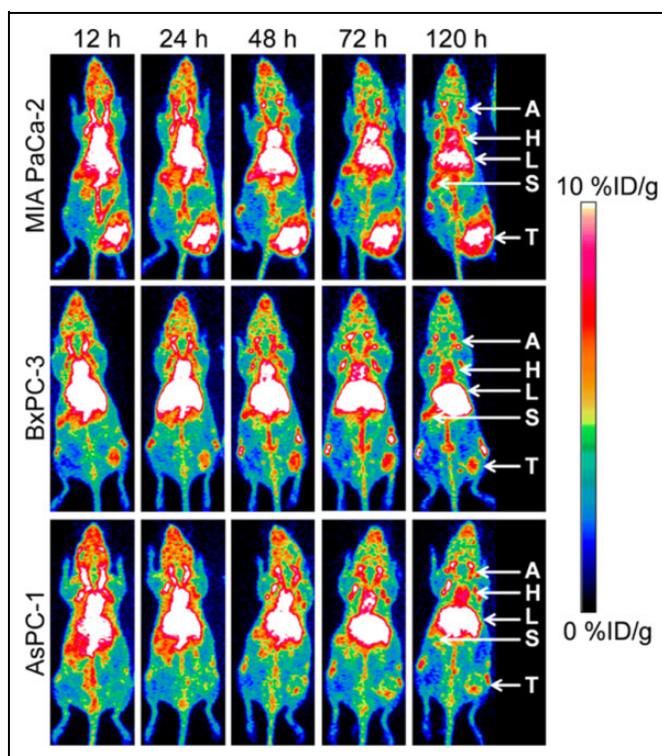


Figure 1. ⁸⁹Zr-Df-1A2G11 positron emission tomography (PET)/computed tomography (CT) imaging was performed in different pancreatic cancer models. MIA PaCa-2 (high insulin-like growth factor I receptor [IGF-1R] expression) tumors showed the highest accumulation followed by BxPC-3 (moderate IGF-1R expression). The lowest tumor accumulation was found in AsPC-1 (low IGF-1R expression) tumors. T indicates tumor; A, carotid artery; H, Heart; L, liver; S, spleen. Adapted and reproduced with permission from England et al.⁴²

⁸⁹Zr-Df-1A2G11 measured 2 hours after injection was detected in MIA PaCa-2 tumors (7.28% ± 1.36% ID/g), followed by BxPC-3 (5.27% ± 0.17% ID/g) and AsPC-1 tumors (2.77% ± 0.12% ID/g). MIA PaCa-2 tumors also showed the highest tracer uptake at 24, 48, 72, and 120 hours (Figure 1). This new tracer is therefore a promising candidate for clinical studies aiming to screen patients who may benefit from IGF-1R therapy.

Insulin-like growth factor I receptor antibody fragment molecular imaging. Despite showing some encouraging results in preclinical studies, monoclonal antibodies present many limitations for molecular imaging. As they have a large molecular volume (150 kDa) and hence slow blood clearance rates, monoclonal antibodies produce high imaging background, low tumor to background ratio, and poor imaging quality, in particular, during the first hours following injection. In addition, the large size of monoclonal antibodies also limits their penetration into the tumor area, which reduces probe access to the molecular target, thereby affecting imaging quality. To overcome these technical challenges, a number of researchers have attempted to use antibody fragments instead of whole antibodies. For instance, ¹¹¹In-F(ab')₂-R1507, an IGF-1R antibody fragment probe

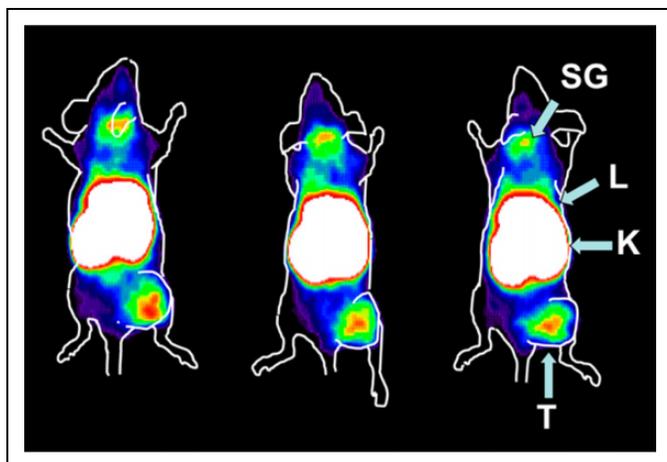


Figure 2. r-Camera imaging was performed by insulin-like growth factor I receptor (IGF-1R) expression DU-145 prostate cancer xenografts 8 hours after ^{111}In -DOTA- $Z_{\text{IGF1R}:4551}$ injection. T indicates tumor; K, kidney; L, liver; SG, salivary gland. Adapted and reproduced with permission from Tolmachev et al.⁴⁷

developed by Fleuren et al,⁴³ showed high tumor uptake in nude mice model of EW5 tumors by SPECT/CT imaging performed at 2, 4, 8, and 24 hours after injection of the imaging agent. Notably, the tumor to blood ratio at 24 hours was significantly higher than that obtained with ^{111}In -R1507. In addition, ^{111}In -F(ab')₂-R1507 showed significant uptake in EW8 tumors, in contrast to ^{111}In -R1507. This important result demonstrates that smaller antibody fragments are superior to whole molecular imaging probes. Another study compared the imaging quality obtained with different antibody fragment probes: ^{111}In -R1507 IgG, ^{111}In -R1507F(ab')₂, and ^{111}In -R1507 Fab.⁴⁴ Interestingly, while ^{111}In -R1507 IgG showed the highest tumor uptake in biodistribution assays, the maximal tumor to blood ratio of ^{111}In -R1507F(ab')₂ was over twice as high as that of ^{111}In -R1507 IgG. ^{111}In -R1507 Fab had the lowest tumor uptake and tumor–blood ratio, and the major fraction of the tumor targeting was nonspecific. Moreover, ^{111}In -R1507F(ab')₂ produced the best SPECT imaging quality in nude mice bearing breast cancer SUM149 when compared to the other probes, in particular at 6 hours after injection of the tracer. ^{111}In -R1507F(ab')₂ accumulated in the tumor area rapidly and was then quickly excreted. The smaller antibody fragment (^{111}In -R1507 Fab) had very low affinity to IGF-1R and hence showed little or no uptake in vivo.

Insulin-like growth factor I receptor affibody molecular imaging. Affibody molecules are nonimmunoglobulin-based scaffold proteins of small size (7 kDa)⁴⁵ that with high affinity and specificity make them have great potential as molecular imaging probes.⁴⁶ Tolmachev et al⁴⁷ first demonstrated the feasibility of using affibody molecules to evaluate IGF-1R expression in vivo by performing DU145 SPECT imaging in prostate cancer models with the newly developed ^{111}In -DOTA- $Z_{\text{IGF1R}:4551}$ affibody molecule (Figure 2). Tumor imaging with the probe was clear. However, radioactive accumulation was

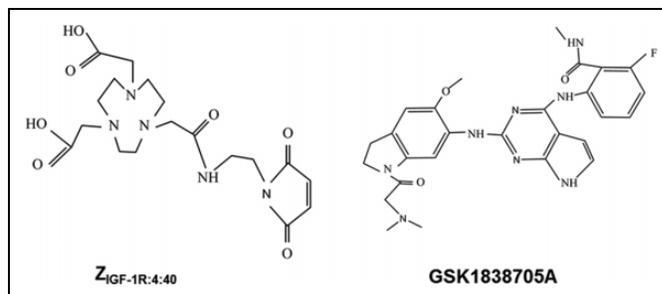


Figure 3. The structure of affibody $Z_{\text{IGF-1R}:4:40}$ and small-molecule GSK1838705A.

also detected in normal organs expressing IGF-1R such as salivary glands, lungs, and stomach.

As ^{111}In has a longer half-life and higher energy than $^{99\text{m}}\text{Tc}$, it is expected that SPECT imaging with $^{99\text{m}}\text{Tc}$ instead of ^{111}In will improve imaging sensitivity and resolution, besides reducing the patient radiation dose. However, SPECT imaging with [$^{99\text{m}}\text{Tc}(\text{CO})_3$]⁺-(HE)₃- $Z_{\text{IGF1R}:4551}$ in prostate cancer DU-145 nude mice showed that this tracer still accumulated in the stomach, lung, and salivary glands.⁴⁸ Nevertheless, significant tumor uptake was detected at 8 hours after probe injection, and the radioactivity accumulation in the liver and spleen was reduced 3.6-fold when compared to ^{111}In -DOTA- $Z_{\text{IGF1R}:4551}$. This study demonstrated that labeling $Z_{\text{IGF1R}:4551}$ with $^{99\text{m}}\text{Tc}$ greatly reduces the probe's liposoluble and background noise, thus improving imaging quality.

Mitran et al⁴⁹ designed a molecular imaging probe by modifying the affinity of the $Z_{\text{IGF1R}:4551}$ affibody molecule. In vitro assays showed that the new probe, $Z_{\text{IGF1R}:4551}$ -GGGC, displayed high specificity and affinity to prostate cancer (DU145) and breast cancer (MCF-7) cell lines which overexpress IGF-1R. Notably, the specificity and affinity of $Z_{\text{IGF1R}:4551}$ -GGGC to IGF-1R was similar to those of its natural ligand, IGF-1. Furthermore, $^{99\text{m}}\text{Tc}$ - $Z_{\text{IGF1R}:4551}$ -GGGC showed excellent tumor to blood ratio in DU145 and MCF-7 tumor models at 4 hours following probe injection. When compared to [$^{99\text{m}}\text{Tc}(\text{CO})_3$]⁺-(HE)₃- $Z_{\text{IGF1R}:4551}$, $^{99\text{m}}\text{Tc}$ - $Z_{\text{IGF1R}:4551}$ -GGGC uptake in the kidneys was decreased nearly 16-fold, but liver uptake was increased by 1.2- to 2-fold, demonstrating that $^{99\text{m}}\text{Tc}$ - $Z_{\text{IGF1R}:4551}$ -GGGC had higher liposoluble than [$^{99\text{m}}\text{Tc}(\text{CO})_3$]⁺-(HE)₃- $Z_{\text{IGF1R}:4551}$. Both these probes present advantages and limitations. Besides producing low radioactivity accumulation in the liver, the HEHEHE tag of [$^{99\text{m}}\text{Tc}(\text{CO})_3$]⁺-(HE)₃- $Z_{\text{IGF1R}:4551}$ can conveniently be used for IMAC purification, thus simplifying the production of the probe. On the other hand, the chelating properties of the GGGC motif causes low radioactivity accumulation in the kidneys, although this tag requires more complicated purification schemes during tracer production.⁵⁰ Follow-up studies should focus on how to reduce the fat solubility of these probes.

In 2010, Li et al⁵¹ screened for new IGF-1R-binding affibody molecules with phage-display technology. A promising candidate, $Z_{4:40}$ (the structure is shown in Figure 3), was shown to specifically and efficiently recognize IGF-1R by different

methods including flow cytometry and fluorescence microscopy. In another study, this affibody was labeled with ^{64}Cu for PET/CT imaging (^{64}Cu -NOTA- $\text{Z}_{\text{IGF-1R}}: 4:40$) and then assessed in a glioma tumor model (U87MG).⁵² The tumor was clearly visible 1 to 24 hours after injection of the probe, and the radioactivity uptake was $5.08\% \pm 1.07\%$ ID/g, with a high tumor to background ratio. Moreover, blocking assays with excess of unlabeled probe showed that ^{64}Cu -NOTA- $\text{Z}_{\text{IGF-1R}}: 4:40$ was highly specific. However, radioactivity uptake in the liver but mostly in the kidneys was high, indicating that the probe had high hydrophilicity and was excreted mostly via the urinary system.

Small molecule-based thymidine kinase receptor inhibitor molecular imaging. Small molecule-based probes could achieve high affinity, selectivity, and adequate lipophilicity, which make them the most potential and vintage molecular tracers. To our knowledge, ^{18}F -BMS-754807 was the first potential small-molecule tracer for cancer IGF-1R imaging.^{53,54} It had been proved by autoradiography studies that ^{18}F -BMS-754807 could bind to IGF-1R of surgically removed human glioblastoma grade IV, breast cancer, and pancreatic tumor with a high affinity. Consecutively, imaging of rat and mice was undergone. The heart and pancreas where IGF-1R is proved to be present showed significant tracer accumulation; however, no notable activity was found in brain, which indicates that it may just potentially be a tumor radiotracer outside the brain. Another molecule tracer, [^{11}C]GSK1838705A⁵⁵ (the structure is shown in Figure 3) was synthesized successfully and showed a higher affinity to U87MG cells in vitro. Micro-PET imaging in C57BL/6 mice indicated that it could enter the brain through blood-brain barrier (BBB), which make it possible to image the intracranial tumors overexpressed IGF-1R in vivo.

Perspectives in IGF-1R Molecular Imaging

As IGF-1R is overexpressed in a variety of tumors, IGF-1R expression could be used to screen patients who may benefit from IGF-1R-targeted therapy as well as to monitor therapeutic efficacy and estimate prognosis. In recent years, there have been a growing number of studies devoted to IGF-1R-targeting molecular imaging research. The author believes that the future directions for the development of IGF-1R-targeted molecular imaging include the following aspects.

Molecular probe. A molecular probe with high stability, high affinity, and high specificity is an important prerequisite for molecular imaging, and the choice of probe determines the imaging feasibility and imaging quality. Because of their large molecular size, antibody and antibody fragment probes display slow tumor accumulation and blood circulation clearance. Affibodies may be superior to antibody due to their relative small size, stable chemical properties, and high affinity to the target. But according to the experience of EGFR-targeted molecular imaging research, small-molecule probes may be the most

promising one because of its small size and high affinity and specificity.

A variety of potential IGF-1R ligands cannot pass through the BBB, which limits their clinical application in brain tumors. It is therefore necessary to develop new IGF-1R-binding probes that can cross the BBB and provide high-quality molecular imaging. Moreover, a lot of probes have high lipophilicity and are excreted via the liver and gallbladder, which make them not the perfect choice to imaging abdominal tumors because of the high background. Thus, hydrophilicity needs to be improved while decreasing lipophilicity in order to reduce nonspecific uptake in organs of the abdomen and improve the imaging quality of abdominal tumors.

Imaging equipment. Single-photon emission computed tomography is more widely used and costs less than PET.⁵⁶ And, the probe of SPECT is more easy to synthesize. However, PET has higher sensitivity, thus providing more accurate quantitative analyses. When combined with specific and efficient tracers, PET can be considered an optimal quantitative metabolic imaging technique. More research is needed for developing new PET targeting molecular imaging probes.

Tumor models. While the various studies discussed in this review mostly used subcutaneous tumor models to assess molecular imaging probes, the microenvironments of orthotopic and subcutaneous tumors differ considerably. Future molecular imaging studies should focus on orthotopic tumor models in order to provide a solid theoretical basis for clinical translation.

Conclusion

Molecular targeted therapy is the future of cancer treatment. Clinical research on IGF-1R targeting therapy shows that modulating IGF-1R expression has significant therapeutic effects. Insulin-like growth factor 1 receptor molecular imaging may provide more accurate information in quantification of IGF-1R expression in vivo, which would provide a reliable basis for screening patients for targeted therapy as well as for evaluating the effects of treatment and estimating prognosis. The development of more high-affinity and high-specific probes would open the way for the clinical translation of IGF-1R molecular imaging. In a future scenario, the replacement of imaging radionuclides with therapeutic radionuclides would allow simultaneous tumor imaging and local radiation therapy. Such a therapeutic strategy could be a breakthrough in cancer treatment, and its added clinical benefits would significantly improve the lives of patients and their families.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: Research was supported by the National Basic Research Program of China

(2015CB931800), National Natural Science Foundation of China (81471724, 31210103913), and the Key Laboratory of Molecular Imaging Foundation (College of Heilongjiang Province).

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