Current Molecular Imaging Positron Emitting Radiotracers in Oncology

Aizhi Zhu · Hyunsuk Shim

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Abstract Molecular imaging is one of the fastest growing areas of medical imaging. Positron emission tomography (PET) has been widely used in the clinical management of patients with cancer. Nuclear imaging provides biological information at the cellular, subcellular, and molecular level in living subjects with non-invasive procedures. In particular, PET imaging takes advantage of traditional diagnostic imaging techniques and introduces positron-emitting probes to determine the expression of indicative molecular targets at different stages of cancer. ^{18}F -fluorodeoxyglucose (^{18}F -FDG), the only FDA approved oncological PET tracer, has been widely utilized in cancer diagnosis, staging, restaging, and even monitoring response to therapy; however, ^{18}F -FDG is not a tumor-specific PET tracer. Over the last decade, many promising tumor-specific PET tracers have been developed and evaluated in preclinical and clinical studies. This review provides an overview of the current non- ^{18}F -FDG PET tracers in oncology that have been developed based on tumor characteristics such as increased metabolism, hyperproliferation, angiogenesis, hypoxia, apoptosis, and tumor-specific antigens and surface receptors.

Keywords Molecular imaging · Oncologic tracer · PET

Introduction

Molecular imaging, particularly positron imaging tomography (PET), plays an important role in cancer management. PET is a noninvasive imaging technique that provides functional or metabolic assessment of normal tissue or disease conditions through detection of tracers administered to patients. The tracers are disease-targeted compounds labeled by different positron emitters. PET is widely used in hospitals and diagnostic clinics, particularly in oncology, for cancer staging, assessing treatment strategies, and monitoring the effects of therapy with appropriate radiotracers.

The potential high sensitivity and specificity of nuclear imaging are due to the high sensitivity of radioisotopes and the special biocharacters of radiotracers, which are labeled by radioactive isotopes, such as radioactive halogens (F-18; Br-76, 77; I-124), carbon-11, and radioactive metals (Ga-68, Cu-64). Radioactive halogens and carbon are widely used to label all kinds of radiopharmaceuticals, but are more appropriate for labeling small molecules than radioactive metals, while the radioactive metals are widely used for labeling bigger molecules such as peptides and antibodies by conjugation of metal chelators, such as 6-hydrazinonicotinic acid (HYNIC), diethylenetriaminepentaacetic acid (DTPA), 1,4,7-triazacyclononane-*N,N',N''*-triacetic acid (NOTA), 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA), and others. The oncological imaging probes have provided insight into physiologic features, extending from glucose consumption (assessed by ^{18}F -FDG) to cell hypoxia (assessed by ^{18}F -fluoromisonidazole). All oncologic imaging tracers are molecularly targeted radiopharmaceuticals and are developed based on the tumor's biocharacters such as increased metabolism, hyperprolif-

A. Zhu · H. Shim (✉)
Department of Radiology, Emory University,
1701 Uppergate Drive, C5008,
Atlanta, GA 30322, USA
e-mail: hshim@emory.edu

H. Shim
Winship Cancer Institute, Emory University School of Medicine,
Atlanta, USA

eration, angiogenesis, hypoxia, apoptosis, and specific tumor biomarkers including tumor specific antigens and tumor-specific receptors. Here, we review the oncologic imaging tracers of various classes. We hope this review could provide useful information for radiochemists in the development of tumor imaging agents and clinicians in the selection of a radiotracer for tumor imaging.

Metabolic Oncologic Tracers

The altered metabolic profiles of tumors, which show elevated uptake of glucose, amino acids, and lipids, have been fully studied and can be monitored by tumor imaging with excellent signal-to-noise ratios. ^{18}F -Fluorodeoxyglucose PET (FDG-PET) is widely used clinically for tumor imaging due to increased glucose metabolism in most types of tumors. FDG is the conventional and most commonly used oncologic PET tracer and the only one approved by the Food and Drug Administration (FDA) for routine clinical use. More than 90% of oncologic PET is performed by FDG-PET. The uptake of FDG is substantially increased in most types of cancers due to the increased metabolism of glucose by tumor cells, as is the case in most lung, colorectal, esophageal, stomach, head and neck, cervical, ovarian, and breast cancers, as well as melanoma and most types of lymphoma [1–3]. The utility of FDG in tumor imaging has been fully reviewed [4–8]. However, increased glucose uptake is not a tumor-specific phenomenon; it is also observed in normal cells, such as brain cells, heart cells, and brown fat [9], as well as in infection and inflammation [10]. In addition to increased glucose uptake, increased protein synthesis in tumors induces higher demand for amino acids. PET imaging using amino acids and amino acid analogs has shown significant potential for tumor detection in organ sites with an undesirable FDG-PET background and in low FDG uptake tumors. Furthermore, choline metabolism is increased for membrane lipid synthesis. Amino acid analogs and choline are more specific to tumor cells than FDG; thus, they play an important role in differentiating cancers from benign conditions and in the diagnosis of cancers with low FDG uptake or high background FDG uptake. The variety of radiolabeled amino acid analogs and choline analogs are shown in Fig. 1.

Radiolabeled Amino Acid Analogs

In addition to FDG, radiolabeled amino acids and their analogs are another class of tumor imaging agents that target increased proliferation requiring active protein synthesis. They are transported across the cell membranes by amino acid transporters, which are upregulated in many

types of tumors. Sodium-independent amino acid transport system L is a major route for providing cells with large neutral amino acids, including branched and aromatic amino acids, such as leucine, isoleucine, valine, phenylalanine, tyrosine, tryptophan, methionine, and histidine [11]. PET imaging with amino acids and their analogs mainly includes natural amino acids and their synthetic analogs.

Radiolabeled Methionine

Most studies of the natural amino acids were performed using C-11-labeled amino acids. The most prominent example is C-11-labeled methionine. PET imaging with L-methyl- ^{11}C -methionine (MET-PET) shows promising results in detection and delineation of viable tumor, especially in low-grade gliomas. MET-PET has been used in clinical management of cerebral gliomas in initial diagnosis, differentiation of tumor recurrence, grading, prognostication, tumor extent delineation, biopsy planning, surgical resection, radiotherapy planning, and assessment of response to therapy [12]. MET-PET is also used clinically to distinguish malignant tissue from normal tissue or benign growths in head and neck cancer, melanoma, ovarian cancer, and other tumors [13–16], but the short physical half-life of C-11 prevents its use in most nuclear medicine departments (i.e., those without an on-site cyclotron).

Synthetic Amino Acids

The synthetic amino acids and analogs, which are non-metabolizable compounds without any efflux of labeled metabolites or with an efflux that is highly restricted, have shown better imaging potential than natural amino acids due to higher accumulation. Therefore, F-18-labeled synthetic amino acids have gained great interest [17, 18]. The radiolabeled synthetic amino acids can be classified into two groups: aromatic amino acids and alicyclic amino acids.

Radiolabeled aromatic amino acids are mostly tyrosine or phenylalanine analogs, and are primarily system L substrates, including 2- ^{18}F -fluoro-L-tyrosine (^{18}F -TYR), L-3- ^{18}F -alpha-methyl tyrosine (^{18}F -FMT), O-(2- ^{18}F -Fluoroethyl)-L-tyrosine (^{18}F -FET), and 6- ^{18}F -fluoro-L-3,4-dihydroxyphenylalanine (^{18}F -FDOPA) [19]. FET and FDOPA have been extensively evaluated in humans. FET-PET has proven valuable in the management of brain tumors. For differentiation of grade III and IV recurrent gliomas from grade I and II recurrences, Popperl and colleagues [20] demonstrated 92% specificity and 92% sensitivity using kinetic analysis. FET demonstrates low uptake in inflammatory tissue compared to FDG and MET, suggesting that FET may be superior for distinguishing neoplasms from inflammatory lesions. FET-PET also has prognostic value in patients with resected glioblastoma multiforme [21–23].

Fig. 1 The chemical structures of some metabolic oncological imaging agents. L-Methyl- ^{11}C -methionine (^{11}C -MET), O-(2- ^{18}F -fluoroethyl)-L-tyrosine (^{18}F -FET), 6- ^{18}F -fluoro-L-3,4-dihydroxyphenylalanine (^{18}F -FDOPA), anti-1-amino-3- ^{18}F -fluorocyclobutane-1-carboxylic acid (anti- ^{18}F -FACBC), ^{11}C -choline (^{11}C -CHO), ^{18}F -fluoromethylcholine (^{18}F -FCH), and ^{18}F -fluoroethylcholine (^{18}F -FEC)

FDOPA-PET has clinical utility in brain tumor imaging [24, 25]. A study comparing FDOPA and FDG for the detection of primary and recurrent brain tumors in 30 patients showed that FDOPA had a sensitivity of 96%, as opposed to 61% for FDG [26]. FDOPA also may have the potential to differentiate low grade from high grade tumors [27]. Additionally, FDOPA has been used to evaluate extracranial neuroendocrine tumors [28].

Alicyclic amino acids, especially 1-amino-cycloalkane-1-carboxylic acids, are a class of α,α -dialkyl amino acids that are not metabolized and incorporated into protein. Radiolabeled alicyclic amino acids, such as ^{11}C -1-amino-cyclopentane-1-carboxylic acid (^{11}C -ACPC), ^{11}C -1-amino-cyclobutane-1-carboxylic acid (^{11}C -ACBC), and its 3-fluoro analogue anti-1-amino-3- ^{18}F -fluorocyclobutane-1-carboxylic acid (anti- ^{18}F -FACBC), which are mainly system L substrates, have been studied for human tumor imaging. Anti- ^{18}F -FACBC is a synthetic L-leucine analog that has shown promising results in patients with glioblastoma multiforme [29]. Comparison study to FDG in glioma patients showed clear tumor margins and a high tumor-to-background ratio. Furthermore, anti- ^{18}F -FACBC also has excellent uptake within primary and metastatic prostate carcinoma with little renal excretion compared to FDG [30]. Anti- ^{18}F -FACBC uptake in patients with newly diagnosed renal masses was examined, and relative amino acid transport compared to the renal cortex was found to be elevated in renal papillary cell carcinoma but not in clear cell carcinoma [31]. Additionally, anti- ^{18}F -FACBC has low urinary excretion, which simplifies the interpretation of genitourinary and pelvic images [32].

Choline

Choline is a precursor of phosphatidylcholine, which is a major constituent of membrane lipids. Membrane lipid synthesis, as well as protein synthesis, is elevated during cell proliferation. Therefore, choline is consumed in large quantities by tumor cells [33]. Carbon-11 choline (^{11}C -CHO) has been introduced as an oncological PET tracer for

the evaluation of a variety of malignant tumors, such as brain tumors, lung cancer, esophageal cancer, colon cancer, bladder cancer, prostate cancer, and many other cancers [34]. ^{11}C -choline uptake is significantly greater in malignant tumors than in benign tumors, correlates well with the degree of FDG accumulation within the lesion, and does not have the disadvantage of high background activity owing to urinary tract excretion, which can interfere with FDG-PET evaluation [35]. Most reports of ^{11}C -choline involve prostate cancer [36–38] and brain tumor [39, 40] imaging. Due to the longer half-life of F-18 than C-11, the F-18-labeled choline derivatives ^{18}F -fluoromethylcholine (^{18}F -FCH) [41] and ^{18}F -fluoroethylcholine (^{18}F -FEC) [34] show advantages in PET imaging. In most organs, high tumor-to-background can be reached within minutes of injection [42]. To date, the majority of studies have focused on FCH-PET to evaluate prostate cancer and metastases. Bone metastases in prostate cancer detected by FCH-PET without any corresponding morphological changes on CT were confirmed by bone marrow involvement in follow-up studies [43]. Due to low physiological uptake in the brain, high-grade gliomas, metastases, and benign lesions can be distinguished on the basis of measured FCH uptake in brain tumor imaging [44]. In other organs, such as the liver, the tumor can be detected despite moderate normal liver tissue uptake. A compared study of FCH-PET and FDG-PET showed that FCH was significantly more sensitive than FDG at detecting hepatocellular carcinoma, particularly in well-differentiated forms; furthermore, FCH was also effective in differentiating hepatocellular adenoma from focal nodular hyperplasia [45]. In summary, FCH is a promising PET tracer for tumor imaging when FDG-PET has a high background uptake.

PET Tracers for Imaging Tumor Cell Proliferation

The proliferative activity of cells is one of the hallmarks of malignant tumors, and the majority of anticancer drugs are designed to inhibit cell proliferation. PET imaging for

proliferation is able to differentiate tumor from inflammation that may cause false-positive results in FDG-PET and recognize changes in tumor proliferation rate induced by various therapeutic interventions. Imaging cellular proliferation has a number of potential advantages over imaging glucose metabolism; it is tumor-specific and occurs early in response to treatment, which is likely to provide earlier and more definitive evidence of response than changes in energy metabolism. Some of the nucleoside radiotracers reporting cell proliferation are shown in Fig. 2.

Thymidine Analogs

Thymidine is a native nucleoside that is incorporated into deoxyribonucleic acid (DNA). It is taken up into cells by the nucleoside transporters located in the cell membrane and trapped intracellularly through phosphorylation to thymidine monophosphate by the cytosolic enzyme thymidine kinase 1 (TK1), which is over-expressed in various tumors and leads to preferential uptake of radiolabeled thymidine by malignant tumors compared with normal tissues. ^{11}C -Thymidine was the first PET radiotracer successfully used to evaluate proliferative activity in various tumors [46]. However, the short 20-min half-life of ^{11}C and its rapid metabolism by thymidine phosphorylase make it difficult to use ^{11}C -thymidine in clinical practice. A series of PET probes that were subsequently developed to address these limitations include the F-18-labeled analogs 3'-deoxy-3'- ^{18}F -fluorothymidine (^{18}F -FLT) and 1-(2'-deoxy-2'- ^{18}F -fluoro-beta-D-arabinofuranosyl)thymine (^{18}F -FMAU) [47].

^{18}F -FLT is taken up by cells and phosphorylated by TK1 with subsequent trapping within the cell [48]. Unlike thymidine, ^{18}F -FLT lacks the 3'-hydroxyl group and cannot be incorporated into DNA; however, being a substrate for TK1, it is still trapped in the cell as ^{18}F -FLT-monophosphate and can serve as an indirect measure of cell proliferation. Several reports have been published describing the use of PET imaging of ^{18}F -FLT uptake as a surrogate marker for early in vivo quantitative imaging of drug-induced changes in cell proliferation. ^{18}F -FLT has been studied and compared with FDG in many different types of tumors including brain tumor [49], colorectal cancer [50], non-small cell lung cancer [51], esophageal cancer [52], breast cancer [53, 54], and lymphoma [55].

Most of the studies showed a higher specificity of FLT than FDG in primary or metastatic tumor imaging. In breast cancer, FLT uptake correlated well with therapy response and could be useful in predicting therapy outcome [54]. However, the high uptake of FLT in bone marrow and human liver limits the detection of lesions in these sites.

^{18}F -FMAU, having a 3'-hydroxyl group, can be incorporated into DNA in the mitochondria. FMAU is a poor substrate for TK1 and regulated by TK2; therefore, it can be used as a biomarker for proliferation via the mitochondrial DNA synthesis pathway [56]. ^{18}F -FMAU PET imaging in normal dogs showed high background uptake in lymph nodes, small intestine, stomach, and marrow due to variations of increased cell proliferation. Because of high levels of thymidine kinase 2, increased activity was also seen in the heart [57]. The first human study showed that tumors in the brain, prostate, thorax, and bone can be clearly visualized with FMAU, whereas visualization in the upper abdomen is limited due to high liver and kidney uptake [58]. ^{18}F -FMAU has higher liver, kidney, and myocardial uptake with a much lower bone marrow uptake, a lower rate of urinary excretion, and a fast blood clearance compared to ^{18}F -FLT. These properties may lead to a superior role for FMAU when measuring bone metastasis or tumors in the pelvic region. In summary, ^{18}F -FMAU-PET imaging may play an important role in the evaluation of cancer therapy response due to its ability to directly measure proliferation through DNA synthesis.

Tumor Angiogenesis PET Imaging

Angiogenesis is a vital component of both normal physiological processes and a number of disease states. It is critical for the growth of primary malignant tumors and for the development of metastases. A number of radiotracers are available to characterize tissue vascularity, e.g., ^{15}O -labeled water and carbon monoxide, which can quantify tissue perfusion and blood volume, respectively [59]. PET angiogenesis imaging could provide medical information at the functional and molecular levels. Several molecular biomarkers, including integrins, VEGF/VEGFR, MMPs, and hypoxia/HIF1 are angiogenesis-related. Various radiotracers targeting these biomarkers have been reported [60].

Fig. 2 Radiolabeled imaging agents for proliferation. Chemical structures of ^{11}C -thymidine, 3'-deoxy-3'- ^{18}F -fluorothymidine (^{18}F -FLT), and 1-(2'-deoxy-2'- ^{18}F -fluoro-beta-D-arabinofuranosyl) thymine (^{18}F -FMAU)

radiolabeled VEGF-A antibody bevacizumab is reported to measure VEGF levels [78–80]. Due to the slow blood clearance of antibody, bevacizumab tracers were labeled by long half-life isotopes as Zr-89, In-111, and Y-86, which is disadvantageous for diagnostic imaging. One of the VEGF-A isomers, VEGF₁₂₁, is labeled by Cu-64 as ⁶⁴Cu-DOTA-VEGF₁₂₁, which has a correlation of tumor uptake and VEGFR expression [81]. Furthermore, VEGF_{DEE}, a mutant of VEGF₁₂₁, is labeled by ⁶⁴Cu as ⁶⁴Cu-DOTA-VEGF_{DEE}, and showed even better VEGFR-2 specificity than the wild-type ⁶⁴Cu-DOTA-VEGF₁₂₁ [82].

Hypoxia PET Imaging

The process of tumor growth and metastasis requires development of new vascularization. Inadequate tumor neovascularization leads to hypoxia, which results in tumors resistant to therapy and the potential for malignancy. Since hypoxia happens when a tumor reaches a certain size, it is not ideal for tumor diagnosis and metastasis evaluation. However, tumor hypoxia imaging can be used to predict therapy responses to traditional chemotherapy and radiotherapy. Highly hypoxic tumors are usually therapy resistant with poor prognosis. When tumors become hypoxic, hypoxia sensitizer should be used in chemotherapy or radiotherapy to increase therapy response. For instance, tirapazamine, an aromatic heterocycle di-*N*-oxide, is reduced to toxic radicals in hypoxic conditions and results in DNA breaks [83]. Many PET tracers have been developed to image tumor hypoxia in vivo [84–88]. Among them, nitroimidazole compounds are promising imaging probes to report severe hypoxia, which become reduced in a hypoxic environment and then covalently bind to intracellular macromolecules (Fig. 4). Quantifying the extent of hypoxia requires that nitroimidazole binding be primarily dependent on oxygen concentration ($PO_2 < 5$ mmHg) as well as nitroreductase levels in the tumor cells [89]. ¹⁸F-FMISO is a well-studied hypoxia marker in humans and animals and widely tested. Many studies showed that ¹⁸F-FMISO tumor uptake has no correlation with ¹⁸F-FDG uptake, as they represent different tumor characteristics [90, 91]. The first clinical studies to image hypoxia using PET were based on halogenated tracers of 2-nitroimidazoles, such as ¹⁸F-FMISO, which showed varied hypoxia in different tumors and different regions in a single tumor [92]. Head and neck cancers with high FMISO uptake treated with cisplatin in combination with tirapazamine have demonstrated a better cure than cisplatin alone, which indicates that FMISO hypoxia imaging is useful in the management of treatment strategies [93]. The images of ¹⁸F-FMISO are of low contrast, but can identify clinically significant regional hypoxia. ¹⁸F-Fluoroazomycin arabino-

side (¹⁸F-FAZA), another ¹⁸F-labeled 2-nitroimidazole derivative, has better pharmacokinetics than ¹⁸F-FMISO with higher tumor-to-background, tumor-to-muscle and tumor-to-blood ratios due to its more rapid clearance from blood and non-target tissues [94, 95]. ¹⁸F-FAZA imaging provides similar hypoxia information to ¹⁸F-FMISO, which may be helpful for therapy planning [96]. In addition, Lehtiö et al. [97] evaluated the use of ¹⁸F-fluoro-erythronitroimidazole (¹⁸F-FETNIM) and tested it as a predictor of radiotherapy outcome. They reported that the data of ¹⁸F-FETNIM were suggestive but inconclusive. Another 2-nitroimidazole, 2-[2-nitro-1*H*-imidazol-1-yl]-*N*-(2,2,3,3,3-pentafluoropropyl)acetamide (EF5), has been successfully used as an immunohistochemical marker of hypoxia in surgical trials. PET images have been obtained with ¹⁸F-EF5 in patients with head and neck cancer [98], and the potential of ¹⁸F-EF5 to detect hypoxia in HNSCC is encouraging. The use of ¹⁸F-EF5 was also reported in cancer animal models such as prostate cancer and others [98–102]. 3-¹⁸F-Fluoro-2-(4-((2-nitro-1*H*-imidazol-1-yl)methyl)-1*H*-1,2,3-triazol-1-yl)propan-1-ol (¹⁸F-HX4), a 2-nitroimidazole nucleoside analogue, was developed as a potential marker and radiosensitizer for hypoxic tumor cells. Due to its better water solubility and faster clearance, ¹⁸F-HX4 may have better pharmacokinetic properties than other nitroimidazole hypoxia markers such as ¹⁸F-FMISO. Currently, it is in clinical trial phase II [103, 104].

Cu(II)-ATSM, a neutral lipophilic molecule, is another alternative PET probe for hypoxia imaging based on a metal complex of radioactive copper with ATSM, diacetyl-bis(*N*4-methylthiosemicarbazone), which is highly membrane permeable. In hypoxic cells, it will be reduced to [Cu(I)-ATSM][−] and entrapped in cells. ⁶⁰Cu-ATSM imaging showed therapy responders had lower tumor-to-normal tissue compared to FDG imaging, while non-responders showed high tumor-to-normal tissue ratios in both [105]. Studies comparing ⁶⁴Cu-ATSM with ¹⁸F-FMISO and ¹⁸F-FDG in vivo are also reported. The regional distribution of ¹⁸F-FMISO at 2 h correlates well with the distribution of ⁶⁴Cu-ATSM at 10 min or 24 h in 9 L gliosarcoma tumors, whereas a poor correlation existed between ⁶⁴Cu-ATSM and ¹⁸F-FDG at 10 min [106]. Lewis et al. [107] reported that studies of ⁶⁴Cu-ATSM in ten cervical cancer patients obtained high quality images of tumor hypoxia. ⁶⁴Cu-ATSM reveals unique information about tumor oxygenation that is predictive of tumor response to therapy, which makes it a promising hypoxia imaging agent.

Apoptosis PET Imaging for Cancer Therapy Response

Apoptosis is the process of programmed cell death, which is the early response to cancer chemotherapy; thus, imaging apoptosis could be an effective measure of evaluating

Fig. 4 Radiolabeled hypoxia imaging agents. Chemical structures of 3- ^{18}F -fluoro-2-(4-((2-nitro-1*H*-imidazol-1-yl) methyl)-1*H*-1, 2, 3-triazol-1-yl)propan-1-ol (^{18}F -HX4), ^{18}F -fluoroazomycin arabinoside (^{18}F -FAZA), ^{18}F -fluoroerythronitroimidazole (^{18}F -FETNIM), 1- ^{18}F -fluoro-3-(2-nitro-1*H*-imidazol-1-yl)propan-2-ol (^{18}F -FMISO), 2- ^{18}F -2-[2-nitro-1*H*-imidazol-1-yl]-*N*-(2,2,3,3,3-pentafluoropropyl)acetamide (^{18}F -EF5), and Cu-diacetyl-bis (*N*4-methylthiosemicarbazone) (Cu-ATSM)

therapy response. Annexin V is useful in detecting apoptotic cells by binding to phosphatidylserine (PS), which is exposed on the outer surface of the cell membrane during apoptosis. ^{18}F -labeled annexin V is a PET tracer for apoptosis imaging through labeling of wild-type annexin V with *N*-succinimidyl-4- ^{18}F -fluorobenzoate [108]. ^{18}F -labeled annexin V was applied to evaluate myocardial ischemia in a rat model, and accumulation in the left ventricle was examined [109]. Rat liver apoptosis induced by cycloheximide was evaluated by ^{18}F -labeled annexin V and resulted in a 3- to 9-fold increase in uptake of ^{18}F -annexin V in the liver apoptosis group at 2 h, compared with controls, which is consistent with histological analysis [110]. ^{124}I -Annexin V is also reported in animal liver apoptosis imaging [111]. Tumor apoptosis after photodynamic therapy was visualized by PET using ^{64}Cu -labeled streptavidin, following pre-targeting of apoptotic cells with biotinylated annexin V [112]. ^{64}Cu -DOTA-streptavidin was administered 4 h after biotinylated annexin, and the PET images delineated apoptosis in a tumor-bearing mouse apoptosis model as early as 30 min after ^{64}Cu -DOTA-streptavidin administration, with tumor-to-background ratios reaching a maximum at 3 h post-injection, and no radioactivity uptake detected in the reference tumor.

Recently, two major classes of small molecular compounds inducing apoptosis have been developed as potential anticancer agents, including the caspase-inhibiting isatin derivatives [113–115] and the apoptosis-inducing 4-aryl-4*H*-chromens, which inhibit tubulin polymerization and bind at the colchicine binding site [115–117]. Several articles have reported the synthesis and biological evaluation of radiolabeled isatin derivatives for imaging of apoptosis using PET [114, 118–123]. ^{18}F -ICMT-11 (Fig. 5), as a caspase-3-specific PET imaging radiotracer with a subnanomolar affinity for activated capsase-3, has the potential to monitor early responses to therapy [118]. Another radiolabeled isatin sulfonamide, the caspase-3 inhibitor WC-II-89, was labeled by F-18 or C-11 and reported as a potential PET tracer for

noninvasive imaging of apoptosis (Fig. 5) [122]. The synthesis of apoptosis inducers carbon-11-labeled 4-aryl-4*H*-chromens as new PET agents for imaging of apoptosis in cancer are also reported [124]. Until now, all apoptosis PET imaging probes have remained in the preclinical phase [98].

Radiotracers Targeting Specific Tumor Biomarkers

During the growth of a tumor, tumor cells overexpress some specific receptors, antigens, and proteins for self-development, for example, epidermal growth factor receptors (EGFR) and somatostatin receptors for fast growth, and chemokine receptor type 4 (CXCR4) for metastasis. These specific biomarkers are excellent targets for cancer treatment and imaging.

PET Probes for Imaging Epidermal Growth Factor Receptors (EGFR)

EGFR, a receptor tyrosine kinase, is activated by binding of its specific ligands, including EGF and transforming growth factor α (TGF α). EGFR, overexpressed in many types of cancers, has been shown to correlate with aggressiveness of tumors and poor survival of patients [125]. Radiolabeled EGF, EGFR antibodies, and small molecule EGFR inhibitors are available as radiotracers to image EGFR expression [126].

As a natural EGFR ligand, human EGF (hEGF) has been labeled for tumor imaging [127]. One limitation of hEGF is that it has 5 tyrosine residues; one *N*-terminal and two lysine side chain amino groups may produce a mixture of radiotracers during labeling. Furthermore, mutated EGFR may lose the binding affinity to EGF [128]. Therefore, EGFR mAb shows better specificity than EGF. In particular, cetuximab, a chimeric (mouse/human) mAb clinically used to treat metastatic colorectal cancer and head and neck cancer, is labeled by radioisotopes for tumor imaging; the

Fig. 5 Radiolabeled apoptosis imaging agents. Chemical structures of 5-(2-((2,4-difluorophenoxy)methyl)pyrrolidin-1-ylsulfonyl)-1-((1-(2- ^{18}F -fluoroethyl)-1*H*-1,2,3-triazol-4-yl)methyl)indoline-2,3-dione

(^{18}F -ICMT-11), 1-(4-(2- ^{18}F -fluoroethoxy)benzyl)-5-(2-(phenoxy-methyl)pyrrolidin-1-ylsulfonyl)indoline-2,3-dione (^{18}F -WC-II-89)

use of ^{64}Cu -labeled DOTA-cetuximab conjugate (^{64}Cu -DOTA-cetuximab) in xenograft tumor mouse models has been reported [129]. Tumor uptake determined by PET imaging showed a good correlation with EGFR expression levels as measured by Western blot analysis. Cetuximab has provided the most encouraging results by exhibiting high specificity and high accumulation in tumor; however, its slow serum or blood clearance results in limited imaging contrast at early time points post-injection. Recently, radiolabeled affibodies targeting EGFR have earned attention and shown promising results [130–133]. Therefore, the labeling of smaller antibody fragments may have a promising role in EGFR imaging. Furthermore, EGFR tyrosine kinase inhibitor PD153035 (Fig. 6), a small molecule compound, has been labeled by C-11 and tested in humans, and shown low background in the chest, whereas intense tracer uptake was observed in the liver, gallbladder, urinary bladder, and kidneys. Therefore, it may be a promising agent for cancers in the chest [134].

PET Probes for Imaging Somatostatin Receptors

A majority of malignant tumors, such as neuroendocrine tumor (NET), small cell lung cancer, breast tumor, and malignant lymphoma, overexpress multiple somatostatin receptor subtypes, of which the somatostatin receptor 2 (sst2) subtype is predominantly expressed [135]. Octreotide (OC), an eight amino acid analog of somatostatin, has a longer plasma half-life of 1.7 h and higher metabolic stability than somatostatin [136]. It has been conjugated with various metal chelators and holoforms, such as ^{64}Cu , ^{68}Ga , and ^{18}F , to evaluate somatostatin receptor-positive tumors in rodent models and humans [137]. ^{64}Cu - or ^{68}Ga -

DOTA-conjugated OC showed greater imaging potential than ^{111}In or $^{99\text{m}}\text{Tc}$ -labeled OC [138]. F-18-labeled OCs have also been reported, including (2- ^{18}F -fluoropropionyl-(D)phe¹)-octreotide and N^α-(1-deoxy-D-fructosyl)-N^ε-(2-[^{18}F]fluoropropionyl)-Lys⁰-Tyr³-octreotate (Gluc-Lys([^{18}F]FP)-TOCA). Gluc-Lys([^{18}F]FP)-TOCA has been applied in patients to evaluate correlation of tracer uptake, lesion size, and arterial perfusion in patients [138]. Recently, a facile F-18 octreotide-labeling method has been reported through chelation of ^{18}F -aluminum fluoride (Al^{18}F) by NOTA-OC, which had similar biodistribution to ^{68}Ga -NOTA-OC, but the ideal half-life of F-18 is more promising [139]. Furthermore, a high selective and binding affinity sst2 peptidic antagonist, sst2-ANT, was conjugated with the ultrastable ^{64}Cu chelator 4,11-bis(carboxymethyl)-1,4,8,11-tetraazabicyclo[6.6.2]hexadecane (CB-TE2A) and tested in rats, and demonstrated a nanomolar binding affinity and excellent tumor-to-background contrast at 4 h after intravenous injection [140]. Taken together, OC PET showed great sensitivity and accuracy for imaging neuroendocrine tumors, especially in detecting metastatic tumors (lymph node, bone, and liver), thus permitting more accurate disease staging.

Radioligands for Imaging the Sigma-2 (σ_2) Receptor

σ_2 receptors as a biomarker of proliferation in solid tumors were reported 10 years ago [141], and became a target for tumor diagnosis and treatment [142]. σ_2 receptors are expressed in proliferating tumor cells at a level about ten times higher than in quiescent tumor cells [141, 143]. In pursuing imaging proliferation, benzamide radioligands with σ_2 receptor specificity were reported as PET tracers.

Fig. 6 Radiotracers targeting specific tumor markers. Chemical structures of ^{11}C -N-(3-bromophenyl)-6,7-dimethoxyquinazolin-3(4*H*)-amine (^{11}C -PD153035), 4-(6,7-dimethoxy-3,4-dihydroisoquino-

lin-2(1*H*)-yl)-N-(2-(2- ^{18}F -fluoroethoxy)-5-methylbenzyl)butan-1-amine (^{18}F -ISO-1), and ^{64}Cu -1,4-bis((1,4,8,11-tetraazacyclotetradecan-1-yl)methyl)benzene (^{64}Cu -AMD3100)

Two of the compounds showed good biodistribution kinetics and tumor-to-normal tissue ratios, and the microPET scan showed clear tumor images [144]. The follow-up studies showed one of the compounds, 4-(6,7-dimethoxy-3,4-dihydroisoquinolin-2(1*H*)-yl)-*N*-(2-(2-¹⁸F-fluoroethoxy)-5-methylbenzyl)butan-1-amine (¹⁸F-ISO-1) (Fig. 6), with binding affinity at the nanomolar level at 2.8 nM, and the tumor-to-normal tissue ratio fell between 2 to 6 at 5 mins to 60 mins, which is suitable to develop into a radiotracer in clinical trials [145, 146]. Therefore, these benzamide σ_2 receptor imaging agents may have potential for highly proliferative tumor imaging.

Imaging Agents Targeting Chemokine Receptor

Chemokine receptor CXCR4 and its ligand CXCL12 are responsible for leukocyte trafficking and homing. Tumor cell migration and metastasis are regulated by CXCR4/CXCL12 interaction in various tumors [147–149]. Kang et al. [150] and Yoon et al. [151] have shown that CXCR4 is a required factor for metastatic progression in breast and head and neck cancer, respectively. Therefore, imaging CXCR4 is a great gauge to predict whether the tumor cells could successfully found a metastasis at distant organ sites. Attempts to image CXCR4 have been made by labeling peptides, mAbs, CXCL12, and anti-CXCR4 compounds [152–155]. Most of these are unsuitable for in vivo imaging due to the low stability and slow blood clearance of peptides and antibodies. Currently, a bicyclam CXCR4 compound, AMD3100, is the only clinical agent to target CXCR4, which can be efficiently labeled by metals, such as Cu-64, through cyclam chelation [156, 157] (Fig. 6). It remains to be determined whether ⁶⁴Cu-AMD3100 will have sufficient sensitivity and pharmacokinetics to be an effective diagnostic PET tracer to predict the metastatic potential of small foci. An F-18-labeled small non-cyclam molecule ¹⁸F-M508F, reported at the recent Radiological Society of North America Annual Meeting, may have much better potential to be a CXCR4 PET tracer with fast blood clearance, better sensitivity, and higher potency, which would be convenient for patients with a shorter waiting period between injection of radiotracer and imaging session [158].

Conclusion

During the last decade, various non-FDG oncological PET imaging agents have been developed, and some of them have been advanced in clinical trials. ¹⁸F-FDOPA has demonstrated excellent imaging results in brain tumor and extracranial neuroendocrine tumors; ¹⁸F-FACBC has shown great potential in imaging brain tumor and prostate cancer

with high FDG background. ¹⁸F-FLT, as a proliferation indicator, has the potential to become the next FDA-approved PET radiotracer because of its great potential in prediction of early therapy response. In addition, ¹⁸F-galacto-c(RGDfK) for angiogenesis, ⁶⁴Cu-ATSM and ¹⁸F-FMISO for hypoxia, and ¹⁸F-ISO-1 for σ_2 receptor imaging are all in clinical trials with promising oncological imaging potential. However, there are great unmet clinical needs for successful PET tracers targeting specific cancer biomarkers. With the discovery of oncologic biomarkers, the development of novel PET tracers with high specificity in targeting those will be an important research endeavor. Current oncologic therapy has moved forward from cytotoxic treatment to personalized therapy targeting specific molecular biomarkers, which can be aided by PET. With the development of highly specific PET tracers, PET will play a major and integral role in the diagnosis and monitoring of cancer.

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Conflict of Interest The authors declare that they have no conflict of interest.

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