Integrin α6 targeted cancer imaging and therapy

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Abstract – Integrins represent ideal targets for molecular imaging and targeted therapy of cancer and their role in cancer has been reviewed extensively elsewhere. Except for αVβ3 and αVβ5, the remaining integrins were not systematically considered and tested as potential therapeutic targets. In recent years, the studies on integrin α6 as a cancer imaging and therapeutic target are increasing, due to their highly expressed in several cancers, and their expression has been associated with poor survival. Integrin α6 appears to be a particularly attractive target for cancer imaging and therapy, and therefore we have developed a wide array of integrin α6-targeted molecular probes for molecular imaging and targeted therapy of different cancers. Despite the studies on integrin α6 as a cancer imaging and therapeutic target increasing in recent years, most of them were derived from preclinical mouse models, revealing that much more can be done in the future. The development of integrin α6 drugs may now be at an important point, with opportunities to learn from previous research, to explore new approaches. In this review, we will briefly introduce integrin α6 and highlighted the recent advances in integrin α6 targeted imaging and therapeutics in cancer.

Key words: Integrin α6, Imaging, Therapy, Cancer, Extracellular matrix.

Introduction

Integrins are a family of αβ heterodimeric transmembrane receptors involved in cell-extracellular matrix (ECM) and cell-cell adhesion [1]. So far, 18 α and 8 β subunits are known in mammals to associate non-covalently forming 24 distinct integrin heterodimers [2]. Among them, integrins can be broadly divided into four subfamilies, depending on whether they bind to leukocyte-specific receptors (αLβ2, αMβ2, αXβ2, αDβ2, αEβ7, α4β7, α9β1, and α4β1), arginine–glycine–aspartate (RGD) receptors (α5β1, α3β1, α8β1,αβ3, αlβ3, αVβ5, αVβ6, and αVβ8), collagen receptors (α1β1, α2β1, α10β1, and α11β1) or laminin receptors (α3β1, α6β1, α7β1, and α6β4) [3, 4]. Under physiological states, integrin-mediated cell adhesion plays an essential role in the formation and remodeling of tissues and organs in multicellular organisms [5]. In the pathologic state, integrin plays an important role in the inflammatory response, thrombosis, invasion, and metastasis of malignant tumors and angiogenesis [6]. As the majority of solid tumors originate from epithelial cells that are conferred with the ability to resist apoptosis, migrate, and disseminate through the epithelial-mesenchymal transition (EMT) [7], the integrins expressed by epithelial cells are retained in the tumor [8]. Integrins α6β4, α6β1, αVβ5, α2β1, and α3β1, regulate the adhesion of epithelial cells to the basement membrane, however, in tumor cells their levels and physiologic functions may be altered to involve and contribute to cell migration, proliferation, and survival [9]. In fact, the expression level of integrin subunits (including α3, α5, α6, αV, β1, β3, and β4) in different types of cancer cells has been related to their invasive and metastatic potential [10].

As a transmembrane protein, integrins have large extracellular regions and are easily conjugation with various targeting drugs. Moreover, integrin expression is altered in cancer compared to the corresponding healthy tissue, and this altered expression was correlated with outcomes [11, 12], and therefore represents ideal targets for molecular imaging and targeted therapy of cancer [13]. The integrins, especially integrin αvβ3 (binding to RGD sequence), have been extensively investigated as imaging and therapy targets for more than 25 years due to their key roles in angiogenesis, leukocytes function, and tumor development and their easy accessibility as cell surface receptors interacting with extracellular ligands [14–16]. So far, more than 100 clinical studies using more than 20 RGD-based imaging agents have been reported [3, 15, 17–19]. The role of integrins in cancer imaging and therapy has been reviewed.
extensively elsewhere about a decade ago [14]. Most of the 24 known integrins are implicated in cancer progression [20, 21], however, in addition to αVβ3 and αVβ5, the remainder of the integrins were not systematically considered and tested as potential therapeutic targets [22]. Although molecules that target αVβ3/αVβ5 and αβ integrins generally have an acceptable safety profile, interest in using them to tackle cancer has waned, mainly owing to a lack of clinical benefits and no inhibitors has been registered as an anti-cancer drug [22]. Recently, the focus of interest is now moving away from αβ integrin and angiogenesis towards other integrin subtypes which are involved in a large variety of tumorigenic pathways. The laminin receptors αβ and αβ have arguably the largest potential next to RGD receptors, because they are expressed by several cancers, while their expression has been linked to poor survival [23], studies in integrin αβ as cancer imaging and therapeutic target are on the increase in recent years [3].

In this review, we briefly overviewed integrin αβ and highlighted the recent advances in integrin αβ targeted imaging and therapeutics in cancer. We apologize for may not be able to cite all published work on the topic due to the specific focus of the review and space limitations.

Overview of the integrin αβ

Integrin αβ subunit (140 kDa) [24], also known as CD49f [25], is encoded by the ITGA6 gene and heterodimerized with either integrin β1 or β4 to form integrin αβ1 and αβ4 [26, 27], which binding specifically to extracellular matrix laminin [28]. Integrin αβ1 was first identified in 1998 as a stem cell marker of keratinocyte stem cells [29] and further identified as the only biomarker commonly found in more than 30 different populations of stem cells, including pluripotent and multipotent stem cells, and cancer stem cells (CSCs) [30]. In particular, integrin αβ1 is expressed in a wide variety of cancers, including breast, prostate, colorectal, brain, and non-small cell lung cancers [22]. Integrin αβ1 is subject to alternative splicing to generate two different cytoplasmic variants call αβ6A and αβ6B, having distinct cytoplasmic domains but no difference in laminin specificity [31, 32]. In addition to the cytoplasmic variants, human integrin αβ6 has two extracellular domain variants called αβ6X1 and αβ6X2 [33], which appear no difference in ligand specificity and affinity [34]. Moreover, a smaller structural variant of integrin αβ6 called αβ6p (70 kDa) has been identified in human prostate, colon, and epithelial cancer cell lines [35]. The αβ6p is believed to function as an inactive receptor for cell adhesion to the extracellular ligand due to the lack of the entire β-propeller domain associated with ligand binding, but it remains bound to its β integrin partner [35].

Integrin αβ1 and αβ4 are well-known “classical” laminin receptors, of which integrin αβ1 binds laminin-1, -2, and -4, while integrin αβ4 binds laminin-1 and -5 [32]. Integrin αβ4 is a receptor for laminin and is expressed by a variety of epithelial tissues and cell types [36]. Integrin αβ4 is exclusively expressed on the basal surface of basal cells, where it is found in specialized adhesion structures called hemidesmosomes [37]. Integrin αβ4 has been reported to promote tumor invasion by activating the PI3K/AKT, Ras, and NF-κB signaling pathway [38, 39]. Integrin αβ4 may also promote tumor angiogenesis by activating NF-κB and ERK signaling pathways [40], and promote the origin of breast cancer by amplifying ErbB2 signaling [41]. Integrin αβ1 is expressed at high levels in capillary endothelial cells and mediated VEGF-induced angiogenesis [42]. Integrin αβ1 has also been shown to contribute to maintaining tumor stemness in glioblastoma stem cells and triple-negative breast cancer [43, 44]. Studies indicated that ITGA6 expression is regulated by hypoxia-inducible factor-1 (HIF-1) [26]. According to the GEPIA database (http://gepia.cancer-pku.cn/) [45], ITGA6 was significantly overexpressed in 13 types of cancers, including colon adenocarcinoma, esophageal carcinoma, glioblastoma multiforme, head and neck squamous cell carcinoma, kidney chromophobe, acute myeloid leukemia, brain lower grade glioma, liver hepatocellular carcinoma, lung squamous cell carcinoma, pancreatic adenocarcinoma, rectum adenocarcinoma, stomach adenocarcinoma, and thymoma [46]. It is currently known that integrin αβ6 is overexpressed in 14 cancer types including head and neck squamous cell carcinomas, lung cancer, breast cancer, liver cancer, colorectal cancer, prostate cancer, cervical cancer, gastric carcinoma, human epidermal neoplasia, pancreatic cancer, glioblastoma, esophageal squamous cell carcinoma, acute lymphoblastic leukemia, and nasopharyngeal carcinoma [46]. In addition, integrin αβ6 was present abundantly in lung-tropic exosomes and mediate exosomes homing to the lung [47]. The abnormally high expression of integrin αβ6 has been correlated with cancer progression and poor prognosis of multiple tumor types [48]. This resulted in integrin αβ6 being an attractive target for cancer imaging and therapy. To study the potential of integrin αβ6 for molecular imaging and therapy, we have developed a series of target probes for molecular imaging and targeted therapy of a diverse array of cancers. Below, we mainly summarized our study as well as others’ studies about integrin αβ6 targeted cancer imaging and therapy.

Integrin αβ targeted radionuclide imaging

Radionuclide imaging, including positron emission tomography (PET) and single-photon emission computed tomography (SPECT), uses radiation emitted by radioisotopes for imaging and has the advantages of high sensitivity and specificity, precise quantification and virtually no tissue penetration limit [49, 50]. Radionuclide imaging can determine the concentration of specific molecules down to the pico-molar level in the body [50], thus providing sufficient sensitivity to visualize most interactions between physiological targets and receptor ligands [51]. Biomacromolecules like peptides and antibodies can serve as targeting agents in multiple drug delivery platforms [52], many of them have been labeled with diagnostic radionuclides and used successfully to imaging tumors [51]. We first reported the 18F-labeled derivative of the peptide sequence CRWYDENAC (abbreviated as RWY) as an integrin αβ6 targeted PET tracer 18F-ALF-NOTA-RWY (abbreviated as 18F-RWY) and preclinically characterized in mouse models of hepatocellular cancer (HCC) [53]. The RWY peptide was initially discovered in our laboratory with phage display on nasopharyngeal carcinoma (NPC) S18 cells and was confirmed to have high specificity and affinity for integrin αβ6 in NPC [54]. 18F-RWY can produce higher sensitivities and tumor-to-liver
ratios than integrin αvβ3-targeted 18F-3PRGD2 and clinical 18F-FDG. Furthermore, 18F-RWY is able to visualize small HCC lesions of approximately 0.2 cm in diameter that are difficult to be distinguished from surrounding hepatic vascular by enhanced magnetic resonance imaging (MRI) with hepatobiliary MR contrast agent gadoxetate disodium Gd-EOB-DTPA. Video 1 demonstrates a visual representative dynamic PET video in an H11NL-Myc genetically engineered HCC mouse after injection with 18F-RWY.

To further assess the performance of 18F-RWY for PET imaging applications in tumors with high expression of integrin αv6, we investigated the applicability of this tracer for colorectal cancer (CRC) imaging [55]. In PET imaging, 18F-RWY produced high PET signals in subcutaneous, chemically induced, and genetically engineered CRC mice, which suggests its potential clinical translation in CRC. On the basis of its excellent tumor-targeting properties and safety in preclinical models, we further labeled the RWY peptide with radionuclide 99mTc to prepare a radiotracer 99mTc-RWY, which was able to clearly show tumor lesions in two breast cancer patients (Fig. 1) [56]. It was the first-in-human study of an integrin αv6-targeted radiotracer for SPECT imaging of breast cancer and this work was performed in collaboration with the laboratory of Prof. Wang.

Although RWY-based radionuclide imaging exhibited favorable imaging capability, the binding affinity between the current integrin αv6-targeted RWY peptide and integrin αv6 (micromole affinity) is relatively low compared to the well-developed RGD peptides and integrin αvβ3 (nanomole affinities). To increase the affinity of RWY to integrin αv6, we used the alanine scanning mutagenesis to modify the RWY peptide by alanine substitution of E and obtained a peptide CRWYDA- (abbreviated as cKiE). The cKiE2 was synthesized by coupling two cKiE monomers through a glutamic acid residue and two triglycine (G3) linkers and further labeled with radionuclide 99mTc to prepare a radiotracer 99mTc-cKiE2. In vitro experiments have proved that the integrin αv6-binding affinity of cKiE2 (IC50: 252.8 nM) was about four times higher than that of RWY (IC50: 1081.8 nM) [57]. In vivo experiments showed that the tumor uptake of 99mTc-cKiE2 related closely with the integrin αv6 expression level. Importantly, in SPECT/CT imaging in orthotopic HCC xenograft mouse experiments demonstrated that 99mTc-cKiE2 is superior to 99mTc-3PRGD2 in terms of both tumor uptake and tumor-to-liver ratio.

**Integrin αv6 targeted MR imaging**

MR imaging is a widely used non-invasive clinical imaging modality that offers high spatial and temporal resolutions, unlimited tissue penetration, and tomographic capabilities [64]. Due to its excellent soft tissue contrast [65], MR imaging is widely accepted as a premier imaging modality for brain tumors [66], HCC [67], NPC [68], breast cancer [69], gynecologic cancer [70–72], rectal cancer and prostate cancer [73, 74]. Compared with PET and SPECT, MR imaging offers better anatomical resolution without the use of ionizing radiation or radiotracers and therefore appears to be the most appropriate for molecular imaging [75], however, its success in molecular imaging is limited by its intrinsic insensitivity [76]. This is
Figure 1. 99mTc-RWY SPECT/CT imaging of a 52-year-old woman with clinical stage II breast cancer in the left breast and the expression level of integrin α6 in breast cancer. (a, b) Transverse, (c, d) coronal, and (e, f) sagittal plane CT and SPECT/CT. SPECT/CT images of the chest obtained 0.5 h p.i. displayed intense 99mTc-RWY accumulation in the cancer tissue in the left breast (white arrow). (g) Hematoxylin–eosin (HE) staining confirmed the presence of tumor cells in the section indicated by the white arrow. Scale bar, 100 μm. (h) Immunohistochemical staining indicated high integrin α6 expression in the area with high radioactivity accumulation. The figure and legend are modified and reproduced with permission from [56] under the terms of the Creative Commons CC BY license.

Video 2. Representative dynamic PET/MR video in a genetically engineered KPC mouse with spontaneously developed PDAC after injection with 18F-S5. In this mouse, representative dynamic PET/MR video showed high tumor uptake of 18F-S5. https://vcm.edpsciences.org/10.1051/vcm/2022007#V2.

Video 3. Representative dynamic PET/MR video in a genetically engineered KC mouse with spontaneously developed PanIN (precancerous lesion of PDAC) after injection with 18F-S5. In this mouse, representative dynamic PET/MR video showed a high accumulation of 18F-S5 in the possible lesion site. https://vcm.edpsciences.org/10.1051/vcm/2022007#V3.
due to causing a detectable signal change requiring micromolar concentrations (0.01–0.1 mM) of molecular agents, while many molecules are present at much lower concentrations (in the nano- or picomolar range) [77]. To overcome the intrinsic insensitivity of MR imaging, it is necessary to design and development of targeted probes, to provide or enhance image contrast by active targeting [78]. Gadolinium (III) is particularly well-suited for use as an MRI contrast agent [79]. For Gd-based agents, high sensitivities can be attained by coupling with Gd (III) chelates and targeting ligands such as small molecules, peptides, proteins, antibodies, and cells [80]. Compared to antibodies, peptide-based systems have several major advantages, including their small size, sufficient capillary permeability, low immunogenicity, short biological half-time, rapid clearance from non-target tissues, ease of manufacture, and being readily labeled with specific nuclides [80–82]. Gd(III) chelates can be directly conjugated to targeting agents but with a lower detection signal and larger steric hindrance [83]. Gd(III) chelates are often loaded on various carriers (including polymers, dendrimers, liposomes, and micelles) to increase the concentration around the targeted. As a structurally simple and nontoxic water-soluble polymer [84], polyethylene glycol (PEG) is commonly used as a linker to space the contrast agents from the targeting agents, thus enhancing the effective binding of the targeting groups to the target sites [83]. To our knowledge, besides our laboratory, there are no reports on MR imaging probes targeting integrin α6 so far.

Based on the integrin α6-targeted RWY peptide, we developed an MR contrast agent RWY-dL-(Gd-DOTA)4 for the MR imaging of HCC [67]. The chemical structure of RWY-dL-(Gd-DOTA)4 is shown in Figure 2A. RWY-dL-(Gd-DOTA)4 contains four different domains, including Gd-DOTA monoamide, RWY peptide domain, PEG4 spacer, and lysine dendrimer. Four Gd-DOTA monoamide chelates for MR signal enhancement and one integrin α6-targeted peptide for tumor targeting. Lysine dendrimer was used to increase the molar ratio of Gd-DOTA monoamide to the peptide for effective targeted contrast enhancement and PEG4 spacer was used to avoid steric hindrance of Gd-DOTA monoamide for tumor targeting binding. In the MR imaging, RWY-dL-(Gd-DOTA)4 generated significant signal enhancement in HCC-LM3 subcutaneous liver tumors, quantitative signal analysis revealed that RWY-dL-(Gd-DOTA)4 resulted in approximately threefold more signal enhancement than control agent (Ctrl-dL-(Gd-DOTA)4) within the first 5 min post-injection and about fourfold more signal enhancement at 50 min post-injection. For DEN-induced HCC mice, RWY-dL-(Gd-DOTA)4 enabled the detection of some HCC lesions that are hardly distinguished by Gd-EOB-DTPA. In addition, RWY-dL-(Gd-DOTA)4 readily penetrated the tumor tissue through the vascular endothelium and excreted in urine via kidneys.

Even though RWY-dL-(Gd-DOTA)4 had demonstrated the efficiency for MR imaging of HCC in subcutaneous and chemical-induced HCC mouse models, its safety and contrast enhancement still need to be improved. The S5 peptide with higher affinity provides a critical raw material for the development of the second-generation integrin α6-targeted MR probe. The optimized integrin α6-targeted peptide S5 was further conjugated with Gd(III) chelates to develop integrin α6-targeted MR contrast agent DOTA(Gd)-ANADYWR (abbreviated as Gd-S5) [48]. The chemical structure of Gd-S5 is shown in Figure 2B. We optimized the synthetic procedure of Gd-S5 via direct condensation reaction between carboxyl groups in DOTA and amine groups in the reverse S5, thereby rendering the reaction step simpler and the product yields higher. It should be noted that the peptide used for 18F-S5 was a cyclic peptide, and for Gd-S5 peptide was a straight peptide based on the convenience and requirements of the synthesis process. The microscale thermophoresis (MST) experiments have confirmed that the binding affinity of straight S5 was as strong as that of cyclic S5. In MR imaging, Gd-S5 can generate more significant signal enhancement in the HCC lesions than nonspecific clinical agent gadoteridol and detect small HCC lesions (approximately 1 mm) which is hardly detected by the clinically available Gd-EOB-DTPA.

In view of the promising MR imaging of HCC in mice, we further studied the imaging efficacy of Gd-S5 in CNS-L with high expression of integrin α6. CNS-L refers to the central nervous system involvement of acute lymphoblastic leukemia (ALL), which is difficult to accurately diagnose and leads to delayed or excessive treatment [59]. Unlike solid tumors, CNS-L rarely forms solid lesions and results in a great challenge for conventional imaging methods [85, 86]. Moreover, 18F-FDG has poor contrast in intracranial lesions due to the high uptake of glucose in normal brain tissue [87]. MR imaging in NALM6-Luciferase tumor-bearing mice showed that Gd-S5 generated superior signal enhancement at the site of meninges located between the skull bone and brain parenchyma. Relatively, Gd-DTPA did not generate the distinguishable MR signal in the same head regions. This study suggests the potential application of integrin α6-targeted MR imaging probe Gd-S5 for the accurate detection of CNS-L. To our knowledge, this is the first application of the MR imaging probe to CNS-L imaging.

### Integrin α6 targeted therapeutics

The integrins exert their functions through activation, ligand binding, focal adhesion formation, and cytoskeletal contacts. Blocking either one of these processes inhibits integrin-regulated functions [88]. In addition, integrin contains a larger N-terminal extracellular domain, which is more amenable to binding antagonists. Therefore, integrins emerge as ideal pharmacological targets [89, 90]. Several integrins, including αvβ3, αvβ5, and αβ3, have been studied for more than 25 years as potential therapeutic targets for various cancers [16]. Integrin-targeted therapeutics have been shown to give benefits in the delivery of chemotherapeutics, oncolytic viruses, proapoptotic peptides, and radionucleotides to both tumor cells and the supporting vasculature [8]. Various integrin antagonists, such as low molecular weight inhibitors, peptidomimetics, or monoclonal antibodies, are in various stages of development for anti-cancer therapy [91]. Integrin α6β1 and α6β4 are subtypes of integrins that have the potential to be an attractive therapeutic target for cancer therapy, due to their highly expressed in several cancers and their expression has been associated with poor survival [3, 54]. To our knowledge, only a few integrin
α6-targeted therapeutic approaches have been developed for cancer therapy to date.

Landowski et al. reported the first use of function-blocking antibody called J8H which targeted intracellular integrin α6 for the inhibition of osteolytic progression of metastatic prostate in mice [92]. J8H is a mouse mAb created by Hogervorst et al. [93]. J8H can recognize an extracellular epitope of α6 resulting in block integrin α6 converting to α6p, but not integrin α6 dependent adhesion [28]. In a xenograft human prostate cancer mouse model, J8H not only retarded pre-existing cancer lesions progression in bone, but also improved survival. Interestingly, the proportion of bone lesions displaying a sclerotic rim of new bone formation increased in mice that received J8H, which demonstrated that the J8H treatment can reduce osteolytic tumor activity and induce a sclerotic reaction in bone lesions [92].

We have reported an NPC-targeted nanomedicine RWY-NP/Pt(IV), which was developed by encapsulating a cisplatin prodrug Pt(IV) with RWY-grafted polymeric nanoparticles [54]. In vitro controlled release assay showed that the RWY-NP/Pt(IV) displayed a 100-fold increase in cytotoxicity towards integrin α6-overexpressing NPC compared to free cisplatin. Growth inhibition was about 78% for RWY-NP/Pt(IV).
treatment, but only 44% for free cisplatin. Importantly, RWY-NP/Pt(IV) not only enhances the efficacy of cisplatin treatment but also reduces potential side effects.

In association with Prof. Sadler, we have further developed a photoactive platinum(IV) complex trans- [Pt(N3)2(py)2(OH)(succinate)] (Pt-cP), a conjugate of a photoactive trans-diazido platinum(IV) complex with RWY [94]. The chemical structure of Pt-cP is shown in Figure 2C. Pt-cP exhibited good dark stability and photocytotoxicity towards cancer cells, including ovarian A2780, lung A549, and prostate PC3 human cancer cells upon irradiation with blue light. Conjugation with cancer-cell-targeting peptide RWY enhances the photo-cytotoxicity and photo-accumulation of photoactive platinum(IV) complexes and their photo-selectivity towards cancer cells without reducing their dark stability.

Additional agents targeting integrin α6 have also shown some anti-cancer effects in some studies results to be developed as anti-cancer agents. It has been shown that siRNA oligonucleotides targeting either subunit of the integrin α6β4 reduced the cell surface expression of this integrin and led to the reduced invasion of breast cancer cells [95]. In ALL xenografts mouse model, PI3Kδ inhibitor (which decreased integrin α6 expression on ALL cells) or specific α6 integrin-neutralizing antibodies can lead to a significant reduction in ALL transit along bridging vessels, blast counts in the cerebrospinal fluid and CNS disease symptoms despite a slight reduction in bone marrow disease burden [96]. HYD-1 (peptide sequence: KIKMVISWKG) peptides that blocked integrin α6β4 markedly decreased exosome uptake, as well as lung metastasis [47].

Summary and prospects

This review summarizes recent research development of integrin α6 targeted imaging and therapeutics in cancer. The studies reviewed here have provided support for integrin α6 as an attractive target for both cancer imaging and therapy. Overall, integrin α6 target cancer imaging and therapy have some potential strengths, which can be summarized as follows. First, as is highly expressed in 14 tumors, integrin α6 has a potential application in the imaging and therapy of these tumors. Second, integrin α6 target imaging exhibits great potential for early detection of HCC and PDAC, which are difficult early imaging clinically. Third, integrin α6 target imaging allows for imaging of CNS-L, thus offering a unique non-invasive method to evaluate the non-solid tumor. Four, integrin α6 target therapy contributes to CSC killing, as integrin α6 is a CSC maker in several types of cancers. Five, integrin α6 can promote cancer distant metastasis and is found expressed in several metastases, and therefore it can serve as an imaging and therapy target for these metastases.

Similarly, current integrin α6 target cancer imaging and therapy also face some challenges. First, integrin α6β4 is an essential component of the basement membranes and its knock-out is embryonically lethal in mice. This indicates that integrin α6 target therapy may have notable adverse effects. Second, when compared to a wealth of study on molecular imaging, there is a relative paucity of work on integrin α6-targeted therapy, further studies are warranted to reveal the effects and adverse effects. Third, there has been no report of integrin α6-humanized antibodies, although a few generations of specific antibodies have been reported. Four, despite the studies on integrin α6 as a cancer imaging and therapeutic target, are increasing in recent years, most of them were derived from preclinical mouse models. Future research should address these challenges. Increasing the affinity of integrin α6 binding peptides seems to be a feasible method. In fact, we have obtained a new integrin α6-targeting peptide whose affinity is more than 300 times higher than RWY in our recent research, which provides a critical raw material for integrin α6 target cancer imaging and therapy. In sum, we optimistically envisage that integrin α6 will become a rising star in tumor imaging and therapy in the future.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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