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Invited Article

Development of Drugs and Technology for Radiation Theragnosis

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ABSTRACT

Personalized medicine is tailored medical treatment that targets the individual characteristics of each patient. Theragnosis, combining diagnosis and therapy, plays an important role in selecting appropriate patients. Noninvasive *in vivo* imaging can trace small molecules, antibodies, peptides, nanoparticles, and cells in the body. Recently, imaging methods have been able to reveal molecular events in cells and tissues. Molecular imaging is useful not only for clinical studies but also for developing new drugs and new treatment modalities. Preclinical and early clinical molecular imaging shows biodistribution, pharmacokinetics, mechanisms of action, and efficacy. When therapeutic materials are labeled using radioisotopes, nuclear imaging with positron emission tomography or gamma camera can be used to treat diseases and monitor therapy simultaneously. Such nuclear medicine technology is defined as radiation theragnosis. We review the current development of drugs and technology for radiation theragnosis using peptides, albumin, nanoparticles, and cells.

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1. Introduction

Personalized therapy is a tailored medical treatment targeting the individual characteristics of each patient. Theragnosis, combining diagnosis and therapy, plays an important role in selecting appropriate patients. Pharmacogenomics or gene panel studies are actively getting into the clinical process to predict patients' the responses to drugs. However, biopsy-driven examinations are based on only a small sample of tissue that is removed from a part of the body. These cannot predict the response of each lesion, especially in cancer patients. After radionuclide therapy using ^{131}I for thyroid cancer, whole-body scans are generally performed to evaluate uptakes and distribution in the body. Lesions can now be more accurately localized and characterized using single photon emission computed tomography/computed tomography (SPECT/CT). SPECT/CT is a hybrid imaging system that colocalizes radionuclide accumulations on CT-based anatomical structures. We suggest defining a new term, theragnosis. Combining therapy and *in vivo* imaging, theragnosis simultaneously localizes therapeutic drugs, peptides, genes, or cells through labeling with radionuclides, fluorescent dye, contrast agents, etc. In this review, we will focus on current development drugs and technologies for radiation theragnosis in nuclear medicine.

2. Theragnosis using peptides

A variety of nuclear imaging probes led to the development of molecular imaging using SPECT and positron emission tomography (PET). Nuclear imaging techniques, which are based on the radiolabeling of specific molecular probes using radioisotopes, can provide insights into the phenotypic functional changes of the disease and the specific biochemical processes of probes. Using different isotopes labeling directly or by bifunctional chelators, recently peptide-based radiopharmaceuticals have been developed and used as biological tools for tumor receptor imaging as well as targeted radionuclide therapy. The typical peptide used as nuclear imaging probes consist of a relatively small number of amino acids (up to 30) with comparably favorable properties, including high receptor binding affinity, selective *in vivo* biological activity, and rapid pharmacokinetics, but usually do not have immunogenic features. The most widely used radioisotopes for peptide labeling for diagnostic and radiotherapy purposes are listed in Table 1.

The first clinical study of ^{123}I-labeled somatostatin derivative (^{123}I-labeled tyr-3-octreotide) in cancer patients was reported by Krenning *et al.* [1] in 1989. Subsequently, ^{111}In-labeled octreotide (^{111}In-Octreoscan, ^{111}In-pentetreotide) was developed and approved by the U.S. Food and Drug Administration (FDA) as the imaging agent for somatostatin receptor-positive cancer, such as neuroendocrine tumors, mammary cancer, and small cell lung cancer [2]. In addition, ^{99m}Tc-labeled somatostatin analogs were successfully developed by the preconjugation of the HYNIC ligand to the peptide and used in humans [3]. Owing to the development of macrocyclic chelators such as DOTA, DOTAOC, DOTATOC, DOTAVAP, DOTATATE, and lanreotide DOTALAN, somatostatin analogs are thus promising theragnosis for peptide receptor imaging (^{111}In or ^{68}Ga) and radionuclide therapy (^{90}Yo or ^{177}Lu for β emitters; ^{213}Bi or ^{225}Ac for α emitters) [4–10].

The above results also promote the development of other peptide radiopharmaceuticals, such as bombesin, neurotensin (NT), cholecystokinin (CCK)/gastrin, exendin, RGD, and substance P (Table 2).

Bombesin and gastrin-releasing peptide (GRP) share a highly conserved seven-amino acid C-terminal sequence (Trp-Ala-Val-Gly-His-Leu-Met-NH_2) and also play an important role in the growth of different type of cancers [11]. Therefore, ^{68}Ga-labeled Pan-bombesin analog (^{68}Ga-BZH_3) was developed and used to evaluate the impact of peptide receptors scintigraphy on the diagnosis and the potential therapy [12]. Consistently, new radiolabeled bombesin analogs have been developed, and their encouraging preclinical results are applied to clinical oncology [13–17].

NT is a tridecapeptide found in several human cancers including Ewing sarcoma, meningioma, astrocytoma, and pancreatic carcinomas [11]. An example for radiolabeled NT, reported by Franz Buchegger, is the synthesis of ^{99m}Tc-NT-XI containing tricarbonyl ^{99m}Tc moiety [18–20]. Despite the favorable preclinical animal studies of ^{99m}Tc-NT-XI, the initial clinical findings are not promising because of the high nonspecific uptake of radioactivity in the kidneys.

Based on receptor autoradiographic studies in humans, CCK and gastrin, which are highly expressed in the intestines and brain, are highly expressed in 90% of medullary thyroid carcinomas and in a high percentage of other tumors such as stromal ovarian cancers, small cell lung cancer, astrocytoma, gastroenteropancreatic neuroendocrine tumors, and gastrointestinal stromal tumors [11,21].

In a comparison of three promising CCK-2 receptor-binding peptides [^{99m}Tc-N_4-Gly-D-Glu-$(Glu)_5$-Ala-Tyr-Gly-Asp Trp-Met-Asp-Phe-NH_2 (^{99m}Tc-demogastrin 2), ^{111}In-DOTA-D-Asp-Tyr-Nle-Gly-Trp-Nle-Asp-Phe-NH_2 (^{111}In-DOTA-CCK), and ^{111}In-DOTA-D-Glu-Ala-Tyr-Gly-Trp-Met-Asp-Phe-NH_2 (^{111}In-DOTA-MG11)], ^{99m}Tc-demogastrin 2 showed better detectability and was able to visualize tumor regions in human medullary thyroid cancer patients better than ^{111}In-DOTA-CCK and ^{111}In-DOTA-MG11 [22].

The glucagon-like peptide receptor (GLP-1R) is a member of the G-protein-coupled receptor family, and was found to be overexpressed in insulinomas, gastrinomas, and medullary thyroid carcinomas. Exendin-4 consists of 39 amino acids with metabolic resistance and shares an approximately 50% homology with the human GLP-1. For diagnosis and internal radiotherapy, ^{111}In labeled exendin-4 was developed and evaluated for its therapeutic efficiency. In particular, ^{111}In labeled [Lys^{40}(Ahx-DTPA)-NH_2]-exendin-4 was able to distinguish between benign and malignant insulinomas. Moreover, ^{111}In labeled [Lys^{40}(Ahx-DOTA)-NH_2]-exendin-4 is a very promising peptide radiopharmaceutical for visualizing insulinomas and clinically detects pancreatic and ectopic insulinomas [23–25].

One of the most frequently studied peptides are cyclic RGD (Arg–Gly–Asp) peptides, which have been evaluated for imaging integrin $\alpha_v\beta_3$ expressed tumors. The vitronectin receptor, integrin $\alpha_v\beta_3$ receptor, is known to play an important role in tumor-induced angiogenesis and tumor metastasis. A