Advanced Drug Delivery Reviews 110–111 (2017) 38–51

Contents lists available at ScienceDirect

Advanced Drug Delivery Reviews

journal homepage: www.elsevier.com/locate/addr

Peptide-based imaging agents for cancer detection☆

Xiaolian Sun [a,*], Yesen Li [a], Ting Liu [a], Zijing Li [a], Xianzhong Zhang [a,*], Xiaoyuan Chen [b,*]

[a] Center for Molecular Imaging and Translational Medicine, State Key Laboratory of Molecular Vaccinology and Molecular Diagnostics, School of Public Health, Xiamen University, Xiamen 361102, China
[b] Laboratory of Molecular Imaging and Nanomedicine (LOMIN), National Institute of Biomedical Imaging and Bioengineering (NIBIB), National Institutes of Health, Bethesda, MD 20892, United States

ARTICLE INFO

Article history:
Received 17 March 2016
Received in revised form 10 June 2016
Accepted 11 June 2016
Available online 18 June 2016

Keywords:
Peptide
Molecular imaging
Chemical modification
Clinical experience

ABSTRACT

Selective receptor-targeting peptide based agents have attracted considerable attention in molecular imaging of tumor cells that overexpress corresponding peptide receptors due to their unique properties such as rapid clearance from circulation as well as high affinities and specificities for their targets. The rapid growth of chemistry modification techniques has enabled the design and development of various peptide-based imaging agents with enhanced metabolic stability, favorable pharmacokinetics, improved binding affinity and selectivity, better imaging ability as well as biosafety. Among them, many radiolabeled peptides have already been translated into the clinic with impressive diagnostic accuracy and sensitivity. This review summarizes the current status in the development of peptide-based imaging agents with an emphasis on the consideration of probe design including the identification of suitable peptides, the chemical modification of probes and the criteria for clinical translation. Specific examples in clinical trials have been provided as well with respect to their diagnostic capability compared with other FDA approved imaging agents.

Contents

☆ This review is part of the *Advanced Drug Delivery Reviews* theme issue on "Peptides and peptide conjugates in medicine".

* Corresponding authors.
E-mail addresses: xiaolian-sun@xmu.edu.cn (X. Sun), zhangxz@xmu.eu.cn (X. Zhang), shawn.chen@nih.gov (X. Chen).

http://dx.doi.org/10.1016/j.addr.2016.06.007
0169-409X/

1. Introduction

Molecular imaging visualizes and measures biological processes at the cellular and subcellular levels within living systems. Targeted molecular imaging, which can quantify the target expression, is an indispensable tool in diagnosing and managing diseases [1–3]. A targeted imaging probe is generally composed of a targeting ligand (such as peptide, aptamer, protein or antibody), an imaging moiety (such as radioisotope for positron emission tomography (PET) or single photon emission computed tomography (SPECT), magnetic nanoparticle for magnetic resonance imaging (MRI) and organic fluorescent dye for optical imaging) and a linker to connect these two [4–6]. An ideal imaging probe should have high binding affinity and specificity for the particular receptor, and can be rapidly cleared from non-targets in order to ensure an adequate target-to-background ratio. In addition, high stability and integrity under physiological condition, low immunogenicity and toxicity for human exposure as well as easy production are all necessary for clinical translation.

With the help of sophisticated molecular biology, a great number of disease targets and corresponding target ligands have been discovered [7–9]. Given their unique advantages, peptides have attracted much attention for targeted imaging [10–12]. Peptides play important roles in cellular functions and intercellular communication. They are composed of amino acid monomers connected by amide bonds and typically have a low molecular weight (less than 100 amino acid residues according to the United States Food and Drug Administration (FDA) definition) which enables fast clearance from the blood as well as non-target tissue. Selected peptides generally have high affinities and specificities for their receptors and are active at concentration down to nanomolar level, therefore, resulting in desirable target-to-non-target ratios. An increasing number of peptides, such as somatostatin (SST) peptide, vasoactive intestinal peptide (VIP), Arg-Gly-Asp (RGD) peptide, and bombesin/gastrin-releasing peptide (BBN/GRP), have been successfully characterized for tumor receptor imaging [13–17].

The FDA typically handles peptides as conventional drugs instead of biological products with a focus on their compound structure [18]. Peptides normally are susceptible to chemical modification. After determining the amino acid residues for specific targeting, chemical modifications (such as cyclization, PEGylation, introduction of unnatural amino acid) are utilized to engineer the peptides for enhanced metabolic stabilities and favorable pharmacokinetics. Imaging labels are directly or indirectly conjugated to the peptides for in vivo imaging application. Accompanied by the structure modification is the possibility to lose the binding affinity and biological activity of peptides. Thus, design of chemical structure (such as insertion of appropriate linker) is explored to minimize the interaction between active binding site and unnatural modification.

In general, construction of peptide-based imaging probes involves three steps: (1) identification of the receptor and its targeting peptide; (2) design and preparation of the peptide analogs with the aim to optimize the biological activity and metabolic behavior; and (3) chemical conjugation of an imaging functionality to the peptide. Despite the great progress made in the development of peptide-based probes, their application in diagnostic imaging and monitoring therapeutic efficacy is still in its infancy. The clinical application of peptide-based agents will greatly rely on the evaluation of in vivo selectivity (whether the probe can specifically bind to its target and not to the non-target tissues); the in vivo stability (whether the probe can reach the target in an intact state); the pharmacokinetic profile (the rate and extent of the probes clears from the body) and the toxicological studies. In this review, we make a summary of the major progress in the development of peptide-based imaging agents for disease detection with a focus on demonstrating the design concept for improving the performance of imaging probes.

2. Peptides targeting receptors overexpressed in specific cancers

Targeting peptide sequences can be selected mainly in three different ways: (1) derivatization from natural proteins [19]; (2) chemical synthesis and structure-based rational engineering [20,21]; and (3) screening of peptide libraries [22]. Each method has its own strength and weakness, and is a review within itself. Among them, phage display technology is a conventional but most widely used method with many advantages such as ease of handling and large number of different peptides can be screened effectively [23].

2.1. Peptide selection/identification by phage display

Phage display technology is based on the principle of screening for specific peptides that bind to the desired target from a library of phage particles. It was introduced by George P. Smith in 1985 [24]. Since then, thousands of peptides have been screened out via phage display. In a typical in vitro phage display process, the phage surface is exposed to the foreign peptide libraries composed of small peptides varying from 5 to 45 amino acids to allow the peptides to incorporate into the phage [25,26]. Every phage clone displays one single peptide while the whole library can display up to 10^9 peptides in total. The phage display library is passed through the targeting molecules. The unbound phage is then washed off and those with desired binding activity is captured and later recovered by competitive elution. A variety of affinity selection methods have been reported to increase the chance to obtain peptides binding to the targeting molecules with good affinity. Usually, at least four rounds of iterative selection are needed to enrich phage with desired binding ability [23]. For in vivo phage display, library phages are injected into animals. Unbound phages are removed via vascular perfusion as well as additional ex vivo washing. The phages with binding activity are rescued from target organs, amplified and purified [27]. Potential candidates obtained via this identification step will be further subjected to chemical and biological evaluations for in vivo molecular imaging.

2.2. Representative peptides for in vivo imaging

The biological activities of peptides are regulated through binding with corresponding receptors. Those with receptors overexpressed on tumor cells rather than on normal cells are excellent candidates for in vivo tumor imaging. To date, many peptides and their analogs have been identified and used for disease detection (Table 1). Some representative ones are discussed below.

2.2.1. Arg-Gly-Asp (RGD) peptide

The tripeptide RGD is specifically binding to integrin receptors [60]. Integrins constitute two subunits (α and β subunits). The integrin family, especially $\alpha_v\beta_3$, is significant for tumor angiogenesis and metastasis. They are overexpressed on endothelial cells during angiogenesis, but