

Radiolabeled Peptides as Imaging Probes for Cancer Diagnosis

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Cancer is one of the main causes of morbidity and mortality worldwide. The most frequent types of this disorder are lung, breast, colorectal, prostate, stomach and liver cancers. In 2012, approximately 14.1 million new cases of the disease were registered, resulting in about 8.2 million of deaths [1]. Most of these deaths could be avoided if an early diagnosis is achieved. As a result, many efforts have been made to develop new methods for an early and accurate cancer diagnosis. It would allow less aggressive and mutilating treatments of patients, leading to better prognostics with greater chances of cure. Besides that, it would result in a reduction of cancer treatment costs at advanced stages and metastasis.

In this sense, nuclear medicine offers a possibility for early cancer diagnosis by means of radiotracer-based imaging either using single-photon emission computed tomography (SPECT) or positron-emission tomography (PET) [2]. These imaging techniques are based on physiological and biochemical changes of the organ or tissue in analyses, and are defined as visualization, characterization and measurement of biological processes at molecular and cellular level [3]. Actually, nuclear medicine contributes with two different strategies for cancer imaging, termed as ‘catch-all’ and ‘catch-one’ approaches. The former employs high sensitive but low specific radiotracers, such as methylene diphosphonate radiolabeled with technetium-99m (^{99m}Tc -MDP), which is used for bone scan and accumulates in any part of the bone tissue where there is damage, such as metastasis, inflammation, granuloma, and infection. Bone scintigraphic image with ^{99m}Tc -MDP is highly sensitive, but its specificity depends on the clinical context. On the other hand, the ‘catch-one’ approach employs radiotracers designed specifically for the disease process, remaining the high sensitivity [4,5]. In this context, we highlight radiolabeled peptides, since there is over-expression of peptide receptors on cancer cells surface compared to normal cells [6]. So, the up-regulation on the expression of peptide receptors can be used to distinguish tumor and normal tissues, enabling the use of peptides for the identification of tumors by means of SPECT and PET, if radiolabeled with a gamma-emitter or a positron-emitter radioisotope, respectively.

Peptides present suitable features for their use as a radiotracer, including low antigenicity and low molecular weight (<50 amino acids). Additionally, peptides can easily penetrate into tumor tissue and they are, typically, cleared very fast from the bloodstream, allowing for good contrast and images in high quality. Moreover, peptides exhibit metabolic stability and tolerance to changes in their structures, which is very common in the radiolabeling process [6,7]. A variety of peptide receptors has been identified as over-expressed on cancer cells surface, such as vasoactive intestinal peptide receptor, cholecystokinin-B/gastrin receptor, epidermal growth factor receptor, $\alpha_v\beta_3$ integrin receptor, somatostatin receptor (SSTr) and gastrin releasing peptide receptor (GRPr). Therefore, over the last years, many studies have been reported in order to describe novel radiolabeled peptides for molecular-based imaging of cancer in the nuclear medicine field, especially those for SSTr and GRPr [8,9].

The expression of GRPr is up-regulated in prostate, breast, lung,

gastric, colorectal and pancreas cancer cells. Therefore, gastrin releasing peptide (GRP) analogs have been radiolabeled and investigated as imaging probes for those tumors [10]. Bombesin is a tetradecapeptide analog to GRP and its derivatives are the most extensively evaluated as radiotracers for GRPr over-expressing tumors in pre-clinical and clinical studies. Bombesin $_{(7-14)}$, a truncated sequence containing the eight carboxy-terminal residues of bombesin, has been radiolabeled with technetium-99m (^{99m}Tc -HYNIC- β Ala-Bombesin $_{(7-14)}$) and injected into prostate (PC3 and LNCaP cells) [11,12], colon (HT-29 cells) [13] and breast (Ehrlich and MDA-MB-231 cells) [14,15] tumor-bearing mice. Authors have related radio peptide uptake in the kidneys, bladder and tumor sites, after biodistribution and imaging studies. In a clinical trial, RM2, a derivative of the bombesin, was radiolabeled with gallium-68 (^{68}Ga -RM2) and injected into 14 prostate cancer patients [16]. PET/computed tomography (CT) images were performed and results showed high radiopeptide specificity for prostate cancer, since its uptake by tumor tissue was higher than that by benign tissue. In another clinical study, demobesin 4, a derivative of bombesin, was radiolabeled with technetium-99m (^{99m}Tc -Demobesin 4) and administered into 8 prostate cancer patients [17]. SPECT/CT images were obtained and the researchers found out that in patients who had undergone hormone therapy, the radiopeptide was not effective in detect metastasis. On the other hand, the radiotracer was effective in detect primary prostate cancer in newly diagnosed patients. To the best of our knowledge, up to date, no bombesin analog has been approved for current use in cancer diagnosis.

The up-regulation of SSTr expression has been related for neuroendocrine, lung, gastro enteropancreatic, non-Hodgkin's lymphoma, paragangliomas, melanoma and breast cancer cells. Thereby, radiolabeled somatostatin (SST) analogs have been extensively evaluated for the identification of those tumors [18]. Actually, only SST derivatives have been approved for clinical use in humans, such as Octreo Scan[®], a truncated sequence of STT containing eight amino acid residues radiolabeled with indium-111 (^{111}In -DTPA-Octreotide). This radiolabeled SST conjugate has been used for the identification of primary and metastatic neuroendocrine tumors by SPECT/CT [19].

Finally, it is important to mention an emerging approach of peptides for cancer targeting. Peptides have been anchored onto the surface of nanocarriers, such as liposomes, micelles and nanoparticles [20,21]. This strategy aims to drive nanosystems toward cancer cells surface, where peptide receptors are over-expressed. Nanostructures

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may contain a therapeutic agent, an imaging probe or, as recently described, both substances, which is termed as 'theranostics', leading to advantages over single strategies [18,22]. The purpose of theranostic agents is to diagnose and to treat cancer at the earliest stage, when the disease is more likely curable.

In conclusion, peptides possess suitable features for a radiopharmaceutical and the expression of a variety of peptide receptors is up-regulated on cancer cells surface. Despite of the intense research in order to attain radiolabeled peptides for cancer diagnosis, only one radiolabeled SST analog (¹¹¹In-DTPA-Octreotide) is extensively under clinical use. However, we strongly believe that in the next few years radiolabeled peptides will have major impact for cancer diagnosis in the nuclear medicine field. Beyond that, we also believe that the use of peptides as nanocarriers guiders will have a great influence in the nanomedicine field in the near future.

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