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Total solid-phase synthesis of DOTA-Functionalized tumor targeting peptides for PET imaging and therapy

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Objective: The convenient synthesis of metal chelating agents couple with tumor targeting peptides is needed to accelerate the research and clinical translation in molecular imaging. DOTA has been one of the most widely used macrocyclic ligands for the development of new metal based imaging and therapeutic agents owing to its ability to form stable and inert complexes under physiological conditions making these radiopharmaceuticals useful for imaging and therapy. DOTA-tris-t-butyl ester is commercially available, but it is expensive and contain impurities of both the di-alkylated and tetra-alkylated cyclen. There is a need to explore new methods for preparation of DOTA-tri-tert-butyl ester, which are less expensive and provides a high purity DOTA product. The aim of this study was to develop a convenient and cost effective synthetic approach for the preparation of DOTA peptides directly on solid support for tumor imaging and therapy.
Methods: The tumor targeting peptide (i.e. bombesin 7-14) was synthesized by Fmoc-based solid-phase peptide synthesis. For coupling with DOTA, bromoacetic acid after activation with HOBt/DIC was coupled to free amino group of peptide resin. This was followed by the monoalkylation of bromoacetylated peptide resin with cyclen (tetraazacyclododecane). The cyclen peptide was then alkylated with tert-butylbromoacetate to afford the desired DOTA peptide. Additionally, the same peptide was prepared from commercially available tris-tert-butyl-DOTA for comparison. Theses peptides after labeling with 68Ga were evaluated for their ability to bind bombesin receptors overexpressed on human breast and prostate cancer cells. In vivo tumor targeting was examined in nude mice implanted with MDA-MB-231 xenografts.
Results: The identity and purity of DOTA peptides was confirmed by mass spectrometry and HPLC. The peptides radiolabeled efficiently with 68Ga (>90%) and exhibited high binding affinity to BN positive MDA-MB-231 and PC3 cancer cell lines (kd=<20 nM). In nude mice with MDA-MB-231 xenografts, 68Ga-labeled peptides displayed efficient clearance from the blood and uptake/retention in all the major organs was found to be low to moderate (below 5%ID/g). The accumulation in the BN positive tumors was ~2% ID/g at 1 h p.i., with good tumor to blood and muscle ratios. The main route of excretion was renal pathway. Both peptides displayed comparable in vitro and in vivo behavior.
Conclusion: We have described the preparation and in vitro and in vivo activity of two DOTA coupled peptides. The synthesized peptides hold good tumor affinity and tumor targeting potential. This successful and economical synthetic strategy can be applied to the facile synthesis of various tumor targeting peptides which ultimately can be translated into clinical settings.

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