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Endothelial targeting of polymeric nanoparticles stably labeled with the PET imaging radioisotope iodine-124

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ABSTRACT

Targeting of therapeutics or imaging agents to the endothelium has the potential to improve specificity and effectiveness of treatment for many diseases. One strategy to achieve this goal is the use of nanoparticles (NPs) targeted to the endothelium by ligands of protein determinants present on this tissue, including cell adhesion molecules, peptidases, and cell receptors. However, detachment of the radiolabel probes from NPs poses a significant problem. In this study, we devised polymeric NPs directly labeled with radioiodine isotopes including the positron emission tomography (PET) isotope ^{124}I, and characterized their targeting to specific endothelial determinants. This approach provided sizable, targetable probes for specific detection of endothelial surface determinants non-invasively in live animals. Direct conjugation of radiolabel to NPs allowed for stable longitudinal tracking of tissue distribution without label detachment even in an aggressive proteolytic environment. Further, this approach permits tracking of NP pharmacokinetics in real-time and non-invasive imaging of the lung in mice using micro-PET imaging. The use of this strategy will considerably improve investigation of NP interactions with target cells and PET imaging in small animals, which ultimately can aid in the optimization of targeted drug delivery.

1. Introduction

Molecules on the surface of endothelial cells lining the lumen of blood vessels are involved in a plethora of physiological and pathological processes and can be used as targets for drug delivery and medical imaging [1–4]. The luminal location of some of these surface determinants may serve as molecular signatures of physiological or pathological changes in vascular phenotype [5,6]. Nuclear imaging modalities, such as gamma-scintigraphy [7], single photon emission computed tomography (SPECT) [8,9], and positron emission tomography (PET) [10] have been used to non-invasively visualize vascular binding of isotope-labeled imaging probes. Vascular imaging probes have traditionally consisted of radiolabeled ligands of endothelial surface determinants, including cell adhesion molecules [11–13] and ecto-enzymes [9,14]. Targeted nanoparticles (NPs) (e.g., polymeric carriers with diameter ranging from 20 to 500 nm) may further improve this approach to vascular imaging [6,15]. First, multivalent binding of ligand-coupled NPs improves targeting [16–18]. Second, with a notable exception of fully PEG-coated polymersomes [19] and filomicelles [20], NPs are generally cleared from circulation faster than proteins. This helps to increase the target/blood ratio, a parameter critically important for imaging highly perfused organs. Third, NPs can carry substantially higher isotope loads without affecting the avidity to the target, providing enhanced image sensitivity.

A variety of NP probes carrying radioactive isotopes have been devised and studied *in vivo* [21–32]. However, detachment of the radionuclide bound (covalently or chelated) to the NP represents a significant problem. This can occur, for example, due to disassembly of kinetically unstable radiometal-chelate systems [33], or degradation of radiohalogen bonds that are metabolically labile such as radiolabeled peptides and proteins [34–36]. Direct conjugation of tracers to stable NP components is advantageous in this context [27,37]. However, this approach has not been tested yet with targeted NPs. Our goal was to bridge this gap of knowledge by

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