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Targeted nanotechnology for cancer imaging ☆

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ABSTRACT

Targeted nanoparticle imaging agents provide many benefits and new opportunities to facilitate accurate diagnosis of cancer and significantly impact patient outcome. Due to the highly engineerable nature of nanotechnology, targeted nanoparticles exhibit significant advantages including increased contrast sensitivity, binding avidity and targeting specificity. Considering the various nanoparticle designs and their adjustable ability to target a specific site and generate detectable signals, nanoparticles can be optimally designed in terms of biophysical interactions (*i.e.*, intravascular and interstitial transport) and biochemical interactions (*i.e.*, targeting avidity towards cancer-related biomarkers) for site-specific detection of very distinct microenvironments. This review seeks to illustrate that the design of a nanoparticle dictates its *in vivo* journey and targeting of hard-to-reach cancer sites, facilitating early and accurate diagnosis and interrogation of the most aggressive forms of cancer. We will report various targeted nanoparticles for cancer imaging using X-ray computed tomography, ultrasound, magnetic resonance imaging, nuclear imaging and optical imaging. Finally, to realize the full potential of targeted nanotechnology for cancer imaging, we will describe the challenges and opportunities for the clinical translation and widespread adaptation of targeted nanoparticles imaging agents.

Contents

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1. Introduction

Due to the unique material properties that appear at the nanoscale, nanoparticles provide many benefits and new opportunities to address the complexity of cancer. Historically, attempts to improve nanoparticle homing to tumors have relied on the enhanced permeability and retention (EPR) effect to direct imaging and therapeutic agents to the primary site [1–10]. This stemmed from the success of liposomal anthracyclines, which were among the first, and to date the most extensively utilized, nano-therapeutics to be approved for clinical use. By exploiting the leaky vasculature of the tumor microenvironment [6], it was universally accepted that a 100-nm liposomes with polyethylene glycol (PEG) coating offered improved delivery of therapeutics to tumors while reducing off-target delivery [7–9]. Following the success stories of nanotherapeutics, nanoparticle contrast agents have been developed for a wide range of imaging modalities, which include Computed Tomography (CT), Magnetic Resonance Imaging (MRI), Positron Emission Tomography (PET), ultrasound and optical imaging.

However, current practice indicates that the benefit of nanoparticle imaging agents in a variety of targeting contexts has not yet reached its ultimate potential for translating to the clinic. This is related to the fact that nanoscientists initially adapted the nanoparticle-based therapeutic strategies for imaging applications. Shared advantages for nanoparticle-based therapeutic and imaging agents initially included prolonged blood circulation and the ability to load high concentrations of molecular agents. This was beneficial for the first generation nanoparticle imaging agents, which were primarily designed as blood pool agents. On the other hand, targeted nanoparticles and molecular imaging require different design strategies. First, many recent publications, have started pointing out that the impact of the EPR effect is more heterogeneous than it was initially thought [11]. Second, the EPR effect is a prerequisite for receptor-mediated targeting of a nanoparticle to cancer cells in the deep interstitial space. However, in this case, the signal of the event (*i.e.* targeting of the cancer biomarker) will be difficult to discriminate from the non-specific signal generated due to the EPR-driven accumulation of the nanoparticle in cancerous tissues. Third, while prolonged blood residence of a nanoparticle may be advantageous for EPR-driven therapeutic strategies, it may be detrimental for targeted imaging applications. Since accurate detection requires sufficient signal difference between the lumen of the blood vessels and the targeting site, imaging may need to be delayed for days after injection to allow the agent to clear from the bloodstream.

Furthermore, to date, the preclinical development of nanoparticle systems has mainly focused on targeting primary tumors of relatively large sizes. These results obtained from mouse studies, however, are somewhat disconnected from clinical practice. A clinician would prefer to detect small lesions at an early stage, when therapeutic interventions are most effective. While the EPR effect may be effective in well-vascularized tumors of several millimeters in diameter [2], it is ineffective in the early development of primary tumors or micrometastatic disease, which presents small clusters of malignant cells within variable tissue types [12,13]. For example, meta-analysis has shown that current clinical modalities (*e.g.* CT, MRI, FDG PET) can detect large metastatic tumors (>1 cm) with high accuracy [14–16]. However, by the time metastatic disease becomes clinically evident, long-term patient outcomes are not favorable [17]. Unfortunately, current imaging rarely detects the early stages of cancer development at the primary or metastatic site (*i.e.* the early spread of tumor cells) [18], which prohibits early and effective interventions [19]. Apparently, targeting an occult lesion hidden within a large population of normal cells presents a unique challenge.

However, in the last decade, nanoscientists have recognized that nanoparticle technology exhibits a highly engineerable nature, which is governed by its own distinctive principles in terms of targeting interactions with cells and intravascular, transvascular and interstitial transport. While conventional small molecular agents are rapidly distributed within cancer and healthy tissues in a non-specific manner, targeted nanoparticles can be optimally designed in terms of biophysical interactions (*i.e.* intravascular and interstitial transport) and biochemical interactions (*i.e.* targeting avidity towards cancer-related biomarkers) for site-specific navigation within a very distinctive microenvironment. Once one considers the various nanoparticle designs and their adjustable ability to target a specific site and generate detectable signals, many questions arise. What should be the nanoparticle's material, size, shape and polymer coating? How long should the nanoparticle circulate? Which types of targeting ligands and how many of them should a nanoparticle have? What is the safe dose of the agent and how is that compared to the dose required to accomplish detection? How will detection of a specific cancer microenvironment impact the decision-making process of the oncologist?

This review illustrates that the design of a nanoparticle dictates its *in vivo* journey and ultimately targeting of hard-to-reach cancer sites, which facilitates the early and accurate diagnosis and interrogation of the most aggressive forms of cancer. In the proceeding sections, we will discuss how the design of nanoparticles should be tailored to improve targeting, examine targeted nanoparticles under preclinical development, and evaluate how we can expedite the translation of nanoparticle imaging agents. First, the physiological obstacles to nanoparticle targeting will be discussed. Next, we will evaluate how a nanoparticle's size, shape, and surface chemistry can be selected to increase targeting to tumors. More specifically, we will discuss how to design nanoparticles both for deep interstitial targeting and vascular targeting. After this discussion, we will review nanoparticle imaging agents designed for X-ray computed tomography (CT), ultrasound, magnetic resonance imaging (MRI), positron emission tomography (PET), single photon emission computed tomography (SPECT) and optical imaging. We will conclude by describing challenges and opportunities for the clinical translation of targeted nanotechnology for imaging.

2. Obstacles to the widespread use of nanoparticle imaging agents for cancer

While abundant in preclinical development, nanoparticles are rarely used in the clinic. Since an unmet clinical need today is the detection of early tumor development at primary and metastatic sites, nanoparticles can be widely adopted in the clinic due to their potential of targeting accuracy to tumors. Certainly, the design of imaging methodologies that could detect tumors earlier would significantly improve patient outcomes. For example, the early detection of breast cancer has been shown to improve 5-year survival from 23% for distant-stage breast cancer to 84% for regional stage breast cancer [20]. Historically, the primary mode of targeting nanoparticles to tumors is the EPR effect. In essence, this mechanism is the passive extravasation of nanoparticles from the tumor microcirculation to the tumor interstitial space [21–23]. Unlike healthy vasculature, tumor neovasculature is characterized by a discontinuous vascular endothelium. The rate of tumor angiogenesis results in the formation of gaps, ranging between 100 and 1000 nm in width (depending on tumor type) between pericytes and smooth muscle cells,