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Vascular targeting of nanoparticles for molecular imaging of diseased endothelium☆

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ABSTRACT

This review seeks to highlight the enormous potential of targeted nanoparticles for molecular imaging applications. Being the closest point-of-contact, circulating nanoparticles can gain direct access to targetable molecular markers of disease that appear on the endothelium. Further, nanoparticles are ideally suitable to vascular targeting due to geometrically enhanced multivalent attachment on the vascular target. This natural synergy between nanoparticles, vascular targeting and molecular imaging can provide new avenues for diagnosis and prognosis of disease with quantitative precision. In addition to the obvious applications of targeting molecular signatures of vascular diseases (*e.g.*, atherosclerosis), deep-tissue diseases often manifest themselves by continuously altering and remodeling their neighboring blood vessels (*e.g.*, cancer). Thus, the remodeled endothelium provides a wide range of targets for nanoparticles and molecular imaging. To demonstrate the potential of molecular imaging, we present a variety of nanoparticles designed for molecular imaging of cancer or atherosclerosis using different imaging modalities.

Contents

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1. Introduction

Historically, nanoparticles have been engineered predominantly for applications that require them to target tissues beyond the vascular endothelium. In this review, we refer to this strategy as 'deep-tissue targeting'. This comes with no surprise considering that the first success story of nanoparticles was based on exploiting the intratumoral accumulation of particles *via* passive means through the leaky vasculature of tumors due to the enhanced permeability and retention (EPR) effect [1–13]. However, an increasing number of publications indicate that the impact of the EPR effect in deep-tissue targeting is inconsistent, resulting in a patchy, near-perivascular accumulation of nanoparticles in tumors [14–16]. To further increase specificity, targeting ligands have also been employed to direct nanoparticles to upregulated receptors on cells at sites of disease. Precise targeting of cells in diseased tissue (deep-tissue targeting) requires that the nanoparticle has to successfully overcome a series of biobarriers including evasion of the immune system (intravascular transport), extravasation across the endothelium (transvascular transport), navigation through the extracellular space (interstitial transport) and finally meaningful interactions with the intended cell-surface receptors on the target cells. Thus, it is nearly impossible to identify a single design for a nanoparticle that takes under consideration each and every biobarrier. This typically leads to nanoparticles capable of successfully tackling only a subset of the biobarriers, compromising the overall effectiveness of targeting.

Here, we review the rationale and applications of targeting nanoparticles to the endothelium for molecular imaging of biomarkers associated with disease. Besides blood components and plasma proteins, the vascular endothelium is the closest point-of-contact for circulating nanoparticles. By having direct access to the vascular bed, one can envision that nanoparticles can continuously scavenge the endothelium for biomarkers of disease. Thus, considering elimination of two challenging biobarriers (*i.e.*, transvascular and interstitial transport), vascular targeting may be more effective than deep-tissue targeting in many occasions.

While conventional agents of small molecular weight are rapidly distributed within diseased and healthy tissues in a non-specific manner due to the enhanced diffusion of small molecules, we suggest that nanoparticles are highly suitable for vascular targeting due to enhanced targeting avidity as a result of geometrically enhanced multivalent attachment to the vascular target. In fact, the size and the multivalent avidity, due to formation of multiple receptor-ligand bonds, make nanoparticles ideal for targeting of vascular-associated pathologies. However, even if the targeting scheme appears to be simplified than deep-tissue targeting scenarios, one still has to consider the enormous availability of different nanoparticle designs in terms of size, shape and composition, which directly govern the particle's ability to target a specific vascular site and generate detectable signals using various imaging modalities. Further, depending on the exact diagnostic requirements of a disease, the design of the nanoparticle has to be mindful of the clinical deployment and radiological imaging. For example, a clinical problem may significantly benefit from the high sensitivity of positron emission tomography (PET) compared to the higher resolution or soft tissue information provided by magnetic resonance imaging (MRI) or X-ray computed tomography (CT). While these considerations may appear overwhelming at first, one of the principle features of nanotechnology is its engineerable nature, which provides multiple degrees of freedom facilitating the fabrication of nanoparticles with the distinct properties required by a specific application.

This review also seeks to illustrate that the objective of molecular imaging of diseased endothelium using nanoparticles is not just to take 'pretty pictures' but rather provide new and useful information to physicians and impact their decision-making process. To demonstrate the potential of molecular imaging, we will present applications on two representative diseases, cancer and atherosclerosis. Obviously there are applications of molecular imaging and targeted nanoparticles on many diseases, we selected cancer and atherosclerosis because the field has significantly focused on them. We will first briefly introduce the pathobiology of the two diseases and their characteristics that are related to vascular targeting and molecular imaging (*e.g.*, targetable upregulated biomarkers). For more details about the pathogenesis and development of the two diseases, we guide the reader to comprehensive reviews. In the proceeding sections, we will then discuss design criteria of nanoparticles that dictate their vascular targeting effectiveness. After this discussion, we will review a variety of nanoparticles designed for molecular imaging of cancer or atherosclerosis using nuclear imaging, optical imaging, CT, MRI, ultrasound and multimodal imaging.

2. Disease pathobiology and its influence on the endothelium

2.1. Cancer

Tumor growth often occurs by the successful hijacking of an existing blood supply and the local angiogenesis that follows *de novo* to mediate nourishment of the fast proliferating tumor mass [17]. Largely due to its rapid growth, the tumor microenvironment is strikingly different from healthy tissue [18–22]. The vasculature feeding a tumor is often convoluted and disordered, and blood flow is significantly slowed, transiently stagnant, or even reversed (Fig. 1) [22–24]. There are also a large number of vascular shunts that shuttle blood directly from an arteriole to a venule. Early studies showed that the tumor vasculature is inherently 'leaky', where the tight cell-cell junctions between endothelial cells that normally serve to maintain tissue integrity are compromised. In a developing tumor, endothelial cells of angiogenic vessels are often further apart (up to 400–600 nm between cells) [25]. This finding in the early 1980's, termed the enhanced permeability and retention (EPR) effect, jump-started a burgeoning field where a large spectrum of untargeted imaging and therapeutic agents were delivered *via* the circulation in the hopes that a significant proportion of the dose would be passively retained by the tumor mass [1,26–31]. Certainly there has been some success with EPR delivery of nanoparticles for imaging and therapy. However, this strategy also has serious shortcomings, namely achieving tumor-specific targeting within short timescales, achieving efficient tumor penetration necessary for therapeutic efficacy, and targeting small tumors such as metastases that may not be well vascularized. Further and importantly, there is a high interstitial pressure barrier within a tumor mass that may be difficult for nanoparticles to overcome to penetrate deeper tissue. As such, in the decades following, efforts to drive efficient, active vascular targeting of nano-agents have gained much attention. Compared to achieving the deep-tissue penetration necessary to target the tumor cells themselves, efforts to preferentially target the tumor-associated vascular endothelium are arguably simpler and intuitively more promising in their increased homing efficacy. Besides applications in molecular imaging, from a therapeutic perspective, methods to mechanically or chemically trigger release of drug cargoes from nanoparticles homing to the tumor-associated vascular bed can serve to deliver therapeutic payloads to deeper tissue as necessary, if vascular delivery is not adequate. From a