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Nanoparticle design considerations for molecular imaging of apoptosis: Diagnostic, prognostic, and therapeutic value☆,☆☆

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ABSTRACT

The present review analyzes various approaches for the design and synthesis of different nanoparticles for imaging and therapy. Nanoparticles for computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET) and optical imaging are discussed. The influence of nanoparticle size, shape, surface charge, composition, surface functionalization, active targeting and other factors on imaging and therapeutic efficacy is analyzed. Cyto- and genotoxicity of nanoparticles are also discussed. Special attention in the review is paid to the imaging of apoptotic tissues and cells in different diseases.

Contents

Abbreviations: CNS, central nervous system; C-SNAM, caspase-3 sensitive nanoaggregation MRI probe; CT, computed tomography; DISC, death-inducing signaling complex; DOPE, 1,2-dioleoyl-sn-glycero-3-phosphatidyl ethanolamine; DOTA, 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid; EPR effect, enhanced permeation and retention effect; FADD, Fas-associated death-domain protein; GRAS, generally recognized as safe; IMM, inner mitochondrial membrane; MASI, matrix associated stem cell implant; MRI, magnetic resonance imaging; NIR, near infrared; OMM, outer mitochondrial membrane; PEG, poly-ethylene glycol; PET, positron emission tomography; PLGA, poly(lactic-co-glycolic acid); PUMA, p53 upregulated modulator of apoptosis; QDs, quantum dots; QTPP, quality target product profile; ROS, reactive oxygen species; SPECT, single-photon emission computed tomography; SPIONs, superparamagentic iron oxide nanoparticles; T-PESCIS, targeted plasmonically enhanced single-cell imaging spectroscopy; TUNEL, terminal deoxynucleotidyl transferase dUTP nick end labeling; VSSA, volumetric specific surface area.

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1. Introduction

Oncologic, cardiovascular, and neurological diseases are the most common causes of death in the developed world. It is well established, especially for cancer that early diagnosis results in more favorable outcomes. Although various diagnostic tests are available, imaging tests remain an important part of the diagnostic arsenal. Whereas blood tests can inform of the presence of a disease, imaging procedures allow for locating and visualizing the diseased areas. In addition, these imaging procedures can allow for monitoring treatment response.

Radiographic angiography, magnetic resonance imaging (MRI), positron emission tomography (PET), and ultrasound are common procedures used in the diagnosis of cardiovascular events and are mainstays in the cancer-imaging realm as well [1]. These different imaging modalities reveal different aspects of disease. Dense tissues such as bones can be imaged using X-rays and soft tissues are visualized using MRI. The selection of an appropriate imaging modality requires evaluation of factors such as spatial resolution, sensitivity, temporal resolution, and tissue type and depth (Table 1) [1]. When these imaging modalities are used in conjunction, a more thorough understanding of the disease can be attained.

The different imaging modalities are not highly sensitive when used alone for most purposes. Therefore, it may be necessary to administer a contrast agent that increases sensitivity of the procedure. The majority of contrast agents are small molecules or chelates [2]. However, these small molecule contrast agents do not accumulate in optimal concentrations at disease sites because they usually have short half-lives and in most cases are not targeted to a site of the disease. They also are renally excreted and may cause toxicity concerns in patients with renal dysfunction [3,4]. In addition, some imaging agents can be toxic themselves.

Nanoparticles may possess inherent contrast capabilities or encapsulate imaging agents. Different strategies include attaching imaging chelates on nanoparticle surfaces, encapsulating fluorescent dyes within the nanoparticle matrix, combination of encapsulation and surface conjugation, and hybrids of multiple imaging modalities (Fig. 1).

Because of the tunable characteristic such as size, shape, surface functionalization, and composition, nanoparticles can be designed to fit the imaging purpose (Fig. 2) [5]. In addition, imaging nanoparticles can be targeted to the site of a disease. In case of cancer, nanoparticle-bound imaging dyes can detect not only primary tumors but also spread metastases. They likewise can improve pharmacokinetics of the encapsulated agent, limit its toxicity and allow the contrast substance to penetrate into a diseased organ, tissue or cell.

Disturbance of normal apoptosis plays a central role in many diseases. Apoptosis is classically known as programmed cell death [6–10].The significance of apoptosis ranges from normal cell turnover in homeostasis to pathogenic cell death. Proliferative tissues undergo apoptosis to renew and maintain proper functioning. Apoptosis allows for death of older cells in a controllable manner without causing damage or injury to surrounding tissues. Whereas it is a driver of pathogenesis in ischemic cardiovascular injuries and neuronal loss, the lack of apoptosis seen in cancer. Many chemotherapeutic agents as well as radiation and photothermal therapy are designed to induce iatrogenic apoptosis [11].

Apoptosis is one of the most well studied cellular processes and there are numerous *in vitro* assays for the detection for apoptosis using gel electrophoresis, flow cytometry, and microscopy [10]. However, the clinical usefulness of these assays is limited not only by their *in vitro* or *ex vivo* nature, but also by their inability for real time monitoring. Because of its role in many processes and therapeutics, research in developing an *in vivo* apoptosis imaging agent is gaining interest as a diagnostic and prognostic tool. Such *in vivo* apoptotic imaging agent can help in decision-making and lead to better outcomes.

The present review summarizes recent advantages in nanoparticle-based contrast agents including molecular probes for apoptosis detection and analyzes the influence of nanoparticle parameters on the efficiency, specificity and safety of imaging procedures.

2. Nanoparticles for MRI

Unlike optical imaging, MR signal is not directly the result of contrast agents, but rather the magnetization of water protons in the immediate environment [12]. When exposed to an external magnetic field, the nuclear spins of the protons will equilibrate with a frequency determined by the strength of the magnetic field. An applied radiofrequency pulse will flip the proton spin from being parallel to the external field to being transverse. Removal of the pulse will allow for the proton spin to revert back to equilibrium. Along with the spin–lattice/longitudinal relaxation (T1) and spin–spin/transverse (T2) relaxation, the proton density and instrument parameters determine the contrast in a magnetic resonance image.

Table 1
Summary of different imaging modalities (modified from [1]).

Modality	Temporal resolution	Spatial resolution	Penetration depth	Sensitivity	Safety	Clinical use
Computed tomography	Minutes	0.5–1 mm	Limitless	Not known	Radiation	Yes
Magnetic resonance imaging	Minutes–hours	~1 mm	Limitless	10^{-3} to 10^{-5} M		Yes
Positron emission tomography	Seconds–minutes	5–7 mm	Limitless	10^{-11} to 10^{-12} M	Radiation	Yes
Optical fluorescence	Seconds–minutes	2–3 mm	<1 cm	10^{-9} to 10^{-12} M	Depends on fluorophore	Emerging