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MR imaging techniques for nano-pathophysiology ☆

Kevin M. Bennett [a], Jun-ichiro Jo [b], Horacio Cabral [c], Bakalova Rumiana [b], Ichio Aoki [b,*]

[a] The University of Hawaii at Manoa, Department of Biology, College of Natural Sciences, 2540 Campus Rd., Honolulu, HI 96822 USA
[b] Molecular Imaging Center, National Institute of Radiological Sciences, Anagawa 4-9-1, Inage, Chiba City, Chiba 263-8555, Japan
[c] Department of Bioengineering, Graduate School of Engineering, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8656, Japan

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ABSTRACT

The advent of nanoparticle DDSs (drug delivery systems, nano-DDSs) is opening new pathways to understanding physiology and pathophysiology at the nanometer scale. A nano-DDS can be used to deliver higher local concentrations of drugs to a target region and magnify therapeutic effects. However, interstitial cells in intractable tumors, as occurs in pancreatic or scirrhous stomach cancer, tend to impede nanoparticle delivery. Thus, it is critical to optimize the type and size of nanoparticles to reach the target. High-resolution 3D imaging provides a means of "seeing" the nanoparticle distribution and therapeutic effects. We introduce the concept of "nano-pathophysiological imaging" as a strategy for theranostics. The strategy consists of selecting an appropriate nano-DDS and rapidly evaluating drug effects *in vivo* to guide the next round of therapy. In this article we classify nano-DDSs by component carrier materials and present an overview of the significance of nano-pathophysiological MRI.

Contents

Abbreviations: 3D, three dimensional; C_{60}, fullerene; CEST, chemical exchange saturation transfer; CNT, carbon nanotube; cRGD, cyclic peptide containing an arginine–glycine–aspartic acid sequence; CT, computed tomography; DACHPt, (1,2-diaminocyclohexane)platinum(II); DDS, drug delivery system; DOTA, 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid; DTPA, diethylentriaminepentaacetic acid; EFTEM, energy-filtering transmission electron microscopy; EPR, enhanced permeability and retention; FRET, Förster resonance energy transfer (Fluorescence resonance energy transfer); Gd-DOTA, gadolinium 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid; Gd-DTPA, gadolinium diethylene triamine pentaacetic acid; Gd-DTPA-PE, Gd-DTPA-phosphatidylethanolamine; HIFU, high-intensity focused ultrasound; MRI, magnetic resonance imaging; Nano-DDS, nanoparticle drug delivery system; NIR, near infrared; NODA, 2,2′-(7-(4-((2-aminoethyl)amino)-1-carboxy-4-oxobutyl)-1,4,7-triazonane-1,4-diyl)diacetic acid; PARACEST, paramagnetic chemical exchange saturation transfer; PDT, photodynamic therapy; PEG, polyethylene glycol; PEG-b-P(Asp), PEG-b-poly(α,β-aspartic acid); PEG-b-PAsp(DET, poly(ethylene glycol)-b-poly [N-[N′-(2-aminoethyl)-2-aminoethyl] aspartamide]; PET, positron emission tomography; PICsome, polyion complex vesicles; PLGA, poly(lactide-co-glycolide); PLL, poly-L-lysine; QDs, quantum dots; ROS, reactive oxygen species; scFv, single chain variable fragments; SDT, sonodynamic therapy; SPECT, single photon emission computed tomography; SPIO, superparamagnetic iron oxide; SWCNT, single-walled carbon nanotube; T_1, longitudinal relaxation time; T_2 and T_2^*, transverse relaxation time.

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* Corresponding author. Tel.: +81 43 206 3272.
E-mail address: aoki@nirs.go.jp (I. Aoki).

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1. Introduction

As noted in previous chapters, the advent of nanoparticle drug delivery systems (DDS) is opening new pathways to understanding physiology and pathophysiology at the nanometer scale. One of these pathways lies in the merger of DDS with high-resolution, 3D magnetic resonance imaging (MRI). In this chapter, we review the pioneering concepts and research that have been brought about by this merger, and predict the changes it may bring to medicine.

MRI is based on the resonance between radio waves of a specific frequency and the magnetic moments of protons in water molecules in living tissue. This resonance is observed in the presence of a large, static magnetic field. MRI is widely used in clinical diagnosis. Unlike X-ray computed tomography (CT), it involves no exposure to ionizing radiation and provides high contrast in soft tissue. Moreover, unlike nuclear imaging methods such as positron emission tomography (PET) or single photon emission computed tomography (SPECT), MRI enables morphological imaging in 3D with high spatial resolution and can be used to measure blood flow, water diffusion, and many other functional parameters, co-registered with high-resolution anatomical images. In recent years the development of high-sensitivity receiving coils, particularly cryogenically cooled coils, and the use of higher magnetic field strengths, have enabled practical micro-imaging in spatial resolutions of 20–50 μm for small animals, bringing the resolution of MRI into the same range as that of low-magnification light microscopy in brain [1] or in tumors (Fig. 1).

Nanoparticle-based DDS (Nano-DDS) is defined as the delivery of drugs to organs, tissues or cells using nanoparticles. However, most nanoparticles accumulate in the liver following intravenous injection and do not accumulate in the target tissue in sufficient concentrations for diagnostic or therapeutic purposes. To avoid accumulation in the liver and thereby prolong their residence time in circulation, nanoparticles are often covalently attached to polyethylene glycol (PEG) polymer chains on the surface through "PEGylation". PEGylation increases the opportunity for nanoparticles to accumulate at the target. In "passive targeting" of tumors, for example, PEGylated nanoparticles of approximately 30–150 nm can accumulate in the tumor through enhanced permeability and retention (EPR) due to increased tumor vasculature permeability, prolonging retention of the nanoparticles in the tumor [2]. In "active targeting", nanoparticles with antibody, peptide, or protein coatings can bind specifically to the surfaces of tumor cells or to neovascular endothelial cells, despite having a lower blood half-life.

With targeted drugs, nano-DDS can be used to deliver higher local concentrations in the target region than with small-molecule drugs, and nano-DDS holds promise for delivery that magnifies therapeutic effects and reduces side effects of the delivered drug. However, certain challenges remain, as shown by the limited performance of the first clinically approved PEGylated liposome (Doxil™) [3]. In immunodeficient animal models the liposome exhibited marked antitumor effects. However, in clinical applications the liposomes exhibited efficacy against only a limited number of tumors, such as Kaposi's sarcoma. This can be attributed to the complexity of tumor morphology during the successive stages of inflammation, fibrillization, hemorrhage, and repair that occur repeatedly in the process of tumor formation and growth in humans. In intractable tumors, such as those of pancreatic or scirrhous stomach cancer, interstitial cells tend to proliferate and impede nanoparticle delivery. Nanoparticle delivery can be improved in these cases by the concurrent use of TGF-β blockers [4]. In pancreatic cancer models, only polymeric nano-micelles with a diameter of 30 nm, but not with a diameter of 100 nm, can be delivered [5]. This illustrates

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