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Macromolecular MRI contrast agents: Structures, properties and applications

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ABSTRACT

Stable gadolinium chelates are widely used as the contrast agents (CAs) for magnetic resonance imaging (MRI). Conjugation of the chelates onto macromolecular carriers forms macromolecular CAs (mCAs). Compared with small molecule MRI CAs, mCAs have advantages of high relaxivity and prolonged retention in blood circulation. Variants of mCAs have been synthesized and tested using animal models, showing their great potential applications in angiography, cancer imaging, kidney imaging, liver imaging, lymphatic imaging, and noninvasive visualization of drug delivery. Herein, the state of the art of mCAs, including their structures, properties, and applications is reviewed and future directions for developing mCAs are suggested.

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Contents

1. Introduction 00
2. Macromolecular effects on MRI CAs 00
   2.1. Enhancing relaxivity (r_1) 00
   2.2. Extending retention in blood circulation 00
3. Structures and properties 00
   3.1. Block mCAs 00
   3.2. Graft mCAs 00
   3.3. Dendritic mCAs 00
   3.4. Micellar MRI CAs 00
4. Clearance and pharmacokinetics 00
   4.1. Size 00
   4.2. Hydrophilicity 00
   4.3. Surface modification 00
   4.4. Shape 00
   4.5. Flexibility 00
5. Clinical applications 00

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5.1. Blood pool imaging 00
5.2. Cancer imaging 00
5.3. Liver imaging 00
5.4. Kidney imaging 00
5.5. Lymphatic imaging 00
5.6. Visible drug delivery system (visible DDS) 00
6. Summary 00
Acknowledgements 00
References 00

1. Introduction

Magnetic resonance imaging (MRI) is a widely used medical imaging technique to visualize the structure and function of the body. Compared with other imaging techniques, such as computed tomography (CT), MRI has no radiation harm and provides great contrast between different soft tissues, making it widely used in neurological, musculoskeletal, cardiovascular, and oncological imaging [1]. To further improve the contrast of the imaging, MRI contrast agents (CAs) are generally needed to enhance the image contrast between normal and diseased tissues, and to indicate the status of organ function or blood flow. Currently, nearly half of all MRI studies are contrast enhanced, and the degree of contrast utilization is expected to increase in the future [2]. In 2006, contrast media (all imaging types) accounted for a total of $1.57 billion in revenue in the United States alone, $364 million (23%) of which was from sales of MRI CAs [2]. The development of novel MRI CAs remains an active area of research, with many new CAs currently in preclinical developments or in clinical trials [3].

Paramagnetic transition metal ion chelates (mainly gadolinium (Gd) chelates) and superparamagnetic iron oxide nanoparticles are the most widely studied and used MRI CAs. Paramagnetic transition metal ion chelates increase the signal intensity by decreasing the longitudinal (or spin-lattice) relaxation time (T_1) of H_2O. Many acyclic and macrocylic polyaminocarboxylate-Gd^{3+} chelates with various structures, shown in Fig. 1, have been clinically used [3]. In addition to them, a variety of chelates with different structures and functions have been reported as MRI CAs for various applications. The design, structure, theory, dynamics, and applications of small molecule MRI CAs with different ligands and transition metal ions can be found in recently published, high-quality reviews [1,4–7].

In contrast, the superparamagnetic nanoparticles that consist of specific iron oxide cores coated with macromolecular materials including dextran, carboxydextran, chitosan, starch, heparin, albumin and polystyrene, decrease the signal intensity by shortening transverse relaxation time of H_2O (T_2) [8]. Three iron oxide nanoparticle CAs including Feridex, Endorem, and Resovist have been approved for clinical use as liver-specific CAs. A detailed introduction of iron oxide nanoparticle CAs is available in recent reviews [9–11].

Currently, the development of MRI CAs is mainly focused on searching for CAs with high relaxivity, low toxicity, and tissue- or tumor-targeting capabilities. MRI CAs, i.e., Gd^{3+} chelates, conjugated with macromolecules, referred to as macromolecular CAs (mCAs), have shown great potential in improving contrast efficiency, providing tissue- or tumor-targeting capability, as well as conferring new functions for MRI. An increasing number of reports on the synthesis, structures, properties and applications of mCAs have been published [12–17], and several mCAs are undergoing clinical trials. The goal of this review is to summarize the research in this field and discuss the prospective directions for MRI mCAs.

2. Macromolecular effects on MRI CAs

2.1. Enhancing relaxivity (r_1)

Gd-based CAs play a role in MRI by increasing the longitudinal (or spin-lattice) relaxation rate ($1/T_1$) of H_2O protons, which is linearly dependant on the concentration of Gd chelates [Gd]. The capability of increasing the $1/T_1$ of H_2O protons for a CA is expressed in terms of relaxivity, r_1, which is defined as the slope of this dependence in a unit of $mM^{-1}\,s^{-1}$ (Eq. (1)). The r_1 is determined by both the nature of the CAs and the condition of the measurement [6].

$$\left(\frac{1}{T_1}\right)_{\text{obsd}} = \left(\frac{1}{T_1}\right)_{\text{d}} + r_1[\text{Gd}] \quad (1)$$

The origin of paramagnetic relaxation enhancement is generally divided into two parts, inner-sphere and outer-sphere (Eq. (2)). The inner-sphere relaxation refers to the relaxation enhancement of H_2O directly coordinated to the transition metal, the outer-sphere relaxation refers to relaxation enhancement of H_2O in the second coordination sphere and beyond (i.e., bulk H_2O) [3,6].

$$\left(\frac{1}{T_1}\right)_{\text{p}} = \left(\frac{1}{T_1}\right)_{\text{inner sphere}} + \left(\frac{1}{T_1}\right)_{\text{outer sphere}} \quad (2)$$

The longitudinal relaxation contribution from the inner-sphere mechanism is determined by the number of H_2O molecules coordinated on Gd^{3+}, the exchange rate of H_2O molecules between the coordinated H_2O and bulk H_2O, and the relaxation time of the bound H_2O, as shown in Eq. (3) [3,6].

$$\left(\frac{1}{T_1}\right)_{\text{inner sphere}} = \frac{P_M q}{T_{1M} + \tau_M} \quad (3)$$

where P_M is the mole fraction of Gd^{3+}, T_{1M} is the relaxation time of the coordinated H_2O on Gd^{3+}, τ_M is the residence lifetime of the coordinated H_2O. The T_{1M} is given by the Solomon–Bloembergen equations, which represent

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