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Magnetic resonance molecular imaging for non-invasive precision cancer diagnosis

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Abstract

Magnetic resonance imaging (MRI) is a non-invasive clinical imaging modality for high-resolution imaging of soft tissues. Magnetic resonance molecular imaging (MRMI) has the potential to provide high-resolution delineation of cancer for precision medicine. However, its clinical application is hampered by the low sensitivity of contrast enhanced MRI and the lack of safe and effective targeted MRI contrast agents. Significant progress has recently been made in the design and development of novel clinically translatable targeted MRI contrast agents for MRMI of cancer. The challenges and strategies for designing the safe and effective targeted MRI contrast agents are discussed here. Some of the recent progresses in MRMI are also highlighted. These progresses provide a new paradigm for the design and development of safe and effective MRI contrast agents for clinical translation and pave the way for clinical application of MRMI in precision management of cancer.

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Introduction

Precision medicine offers the promise to tailor personalized therapies to improve healthcare of cancer patients. Precision medicine requires accurate cancer detection and characterization of tumor aggressiveness. Molecular imaging provides non-invasive measurement of cancer biomarkers for accurate cancer detection and characterization. Magnetic resonance imaging (MRI) is routinely used for three-dimensional visualization of soft tissues in high-resolution and for cancer detection and diagnosis. Although MRI is advantageous over other clinical imaging modalities, including nuclear medicine and computed tomography (CT), for high-resolution imaging of cancer biomarkers, its potential is limited by its low sensitivity. Nevertheless, the recent decade has witnessed several groundbreaking advancements in MR molecular imaging (MRMI) of cancer. Novel targeted contrast agents with better safety profiles have been designed and developed to overcome previous limitations for effective MR molecular imaging of cancer [1,2]. Indeed, high spatial resolution of molecular MRI with newer targeted contrast agents can now facilitate early detection of tumors as small as a few hundred cells, a few hundred microns in size, and risk-stratification of aggressive tumors. This article summarizes the concepts, principles, and recent progress of molecular MRI in cancer imaging.

Current imaging technologies in cancer diagnosis

Early and accurate detection of malignant tumors is a vital step in initiating early effective treatment of the disease. Medical imaging is routinely used for non-invasive cancer detection, monitoring disease progression, and timely assessment of therapeutic efficacy to assist physicians in tailoring better therapies to achieve the best possible therapeutic outcome. Imaging modalities, including mammography, ultrasound, X-ray CT, and MRI, which provide anatomical images of the tissues of interest, are used for cancer detection and localization based on morphological changes. High-resolution anatomical imaging with these modalities is also used for assessing disease progression, therapeutic response, and image-guided interventions. Positron emission tomography (PET) and single-photon emission computed tomography (SPECT) constitute the most commonly used clinical molecular imaging modalities. To visualize biomarkers in cancer, PET or SPECT require imaging probes prepared from radioisotopes emitting positrons or gamma-rays. Both these modalities are highly sensitive for quantitative detection and measurement of cancer markers and are commonly used in the clinical management of cancer. However, they suffer from various drawbacks for cancer imaging and cannot suffice for early accurate detection and characterization of malignant tumors for precision medicine. Dual imaging modalities of PET-CT/MRI and SPECT-CT/MRI have been developed to combine the advantages of sensitive and quantitative molecular imaging of PET and SPECT and high-resolution anatomical

imaging by CTand MRI to improve the accuracy of cancer diagnosis [3–5].

The principle of MR molecular imaging

MR molecular imaging has the potential to provide high-resolution, sensitive, and quantitative molecular imaging of cancer markers as a single imaging modality. MRI measures the longitudinal (T_1) and transverse (T_2) relaxation rates of protons (mainly water protons) in the body to produce high-resolution images of soft tissues. Contrast agents based on paramagnetic materials are often used to enhance the image contrast between tumors and the surrounding normal tissues [6,7]. MRI is used for both high-resolution anatomical imaging and functional imaging of cancer. T_1-weighted MRI contrast enhanced with gadolinium-based contrast agents provides brighter tumor contrast enhancement and is commonly used in cancer imaging. Contrast enhanced MRI is often used in clinical practice for the characterization of primary tumors, assessment of treatment response, and detection of local recurrence in patients. High-resolution molecular MRI can be achieved to improve accurate detection and differential diagnosis if safe and effective contrast agents specific to cancer markers are available for clinical use. The expression levels of cancer markers can be quantitatively determined with T_1-mapping and the targeted contrast agents.

Effective molecular MRI requires targeted contrast agents to specifically bind to cancer biomarkers to generate detectable signal enhancement by MRI scanners. Currently, the two main classes of MRI contrast agents, including stable paramagnetic Gd(III) chelates [8] and superparamagnetic iron oxide nanoparticles, have been extensively explored for molecular MRI. Gd-based contrast agents (GBCAs) generate bright signal enhancement in T_1-weighted imaging, and are most commonly used in clinical practice. Superparamagnetic iron oxide nanoparticles are mainly T_2-weighted contrast agents and provide dark enhancement. Targeted MRI contrast agents have been designed and prepared by incorporating targeting moieties, which bind to cancer biomarkers, into Gd(III) based MRI contrast agents or superparamagnetic iron oxide nanoparticles. Unlike nuclear medicine, MRI cannot directly visualize the contrast agents bound to their targets. Binding of the targeted agents increases the relaxation rates of the water protons around the molecular targets to generate signal enhancement for molecular MRI.

Signal enhancement in molecular imaging is non-linearly correlated with the increase in the T_1 and T_2 relaxation rates of water protons around the targeted contrast agents. The increase in the relaxation rates is proportional to the relaxivity and concentration of the contrast agents. Effective molecular MRI requires the binding of a sufficient amount of targeted contrast agents with high relaxivities to generate detectable signal enhancement. Conventional MRI contrast agents have relatively low relaxivities. Targeted nanoparticles with high payload of paramagnetic materials, e.g. Gd(III) chelates and iron oxide, are often used to increase local concentration for detecting molecular targets expressed on the cell surface [9,10]. The effectiveness of the targeted paramagnetic nanoparticles for MR molecular imaging of cancer has been extensively demonstrated with animal models. However, clinical development of these nano-sized targeted contrast agents has been impeded by their slow excretion and consequent safety concerns.

The design and development of safe and effective targeted contrast agents specific to cancer biomarkers are critical for clinical application of molecular MRI. Any targeted contrast agent for clinical translation has to satisfy the safety requirements set forth by the regulatory agencies. Rapid and complete excretion from the body after diagnostic imaging is the ultimate priority in the design of targeted MRI contrast agents. Two approaches can be applied to address the challenges in designing clinically translatable targeted contrast agents for cancer molecular MRI, i.e., to target abundant cancer biomarkers and/or to apply paramagnetic materials with high relaxivities that meet the safety requirements, Fig. 1. Molecular targets of high concentration allow the binding of a sufficient amount of small molecular targeted contrast agents based on the existing clinical agents into tumors to generate detectable MR signal enhancement [11]. Identification of suitable molecular targets for molecular MRI requires clear understanding of cancer biology of the targets [12]. Ideally, the markers should have abundant expression only in tumor tissues, and not in the normal tissues. The use of paramagnetic materials with high relaxivities could significantly reduce the dose of the contrast agents to improve the sensitivity of MR molecular imaging [13,14]. Significant increase in the relaxivities of targeted MRI contrast agents can substantially reduce their doses, which could allow effective MR molecular imaging of the cancer markers of relatively low concentration.

Recently, significant progress has been made in the design of targeted MRI contrast agents using the aforementioned approaches. The feasibility of molecular MRI of cancer using the novel targeted contrast agents has been demonstrated in animal tumor models. The following sections summarize the recent progress in molecular MRI of cancer.

MR molecular imaging of abundant oncoproteins using small molecular targeted contrast agents

Effective MR molecular imaging with a small molecular targeted MRI contrast agent was first achieved by targeting the fibrin-fibronectin (FN) clots in tumor