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REVIEW

Echogenic nanoparticles for ultrasound technologies: Evolution from diagnostic imaging modality to multimodal theranostic agent

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Summary Ultrasound technology in combination with echogenic particles is currently having a considerable effect on the modern medical field, not only as a conventional diagnostic modality but also as a methodology that administers therapeutics to various lesions. The diagnostic and therapeutic effects of ultrasound technologies on diseased sites are governed by several primary factors such as the ultrasound technique itself and the physicochemical properties of echogenic particles. Therefore, rational design and a good combination of echogenic particles with the ultrasound technique are the most decisive factors in achieving optimal diagnostic and therapeutic goals. In this respect, great research advances in design and engineering of echogenic particles to meet these diagnostic and therapeutic demands have consistently been made.

Since echogenic particles exhibit quite different behaviors in response to ultrasound, the most important issue in achieving maximal therapeutic efficacy must be the establishment of technical rationales that depend on these particles' biomedical uses, from the selection of shell materials and gas types to the manufacturing techniques used to make particles of the proper diameter. Several attempts have been made to develop highly effective theranostic echogenic particles that have the proper particle size and yet can sustain intense echo signals for long enough to circulate repeatedly through the body, a primary requirement for targeting and

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accumulating at a diseased site. However, a very important challenge has been the technical barrier between the most favorable *in vivo* nano-size for desirable biodistribution and the obtaining of a strong echo intensity.

In this review paper, the present status and the critical issues for developing theranostic echogenic particles as an ultrasound contrast agent and drug delivery vehicle will be described. Firstly, conventional micro-sized echogenic particles are comprehensively introduced with their research history, diagnostic applications and intrinsic limitations. Then recent progress in developing more advanced echogenic particles for diagnostic and therapeutic purposes will be described. Most importantly, in this review paper, the design criteria for developing promising theranostic echogenic particles to satisfy recent research and clinicians' demands will be given, with special emphasis on overcoming the conflicting and insuperable size issue of echogenic particles.

Introduction

Among the several molecular imaging modalities such as computed tomography (CT), magnetic resonance imaging (MRI) and positron emission tomography (PET), ultrasound has consistently received attention in clinical fields. Ultrasound provides the comparative advantages over other imaging modalities of being noninvasive and providing indispensable real-time imaging with a high spatial resolution of a lesion [1,2]. Ultrasound technologies have also steadily changed to meet clinicians' demands, helped by the development of sophisticated ultrasound contrast agents (UCA). Initially, in the 1960s and 1970s, the concentration was on diagnostic ultrasound that did not harm tissue (2—15 MHz) [3]. More recently, the highlight is on medical ultrasound of high intensity focused ultrasound (HIFU) with frequencies of 0.8—3.5 MHz that has therapeutic applications and allows triggered drug delivery to destroy or cure diseased tissue directly.

Since ultrasound can be performed either by itself or in combination with drugs, broad medical applications are available such as those for diabetes, stroke, cancer, cardiovascular diseases, infections, osteoporosis, thrombosis, glaucoma, nerve damage, skin wounds and bone fractures (Fig. 1) [4]. In order to improve the therapeutic potential of ultrasound technologies and thus to enhance the quality of clinical care for patients, contrast-enhanced imaging and therapy techniques utilizing the adjuvant contrast enhancing agents, that is, UCA or echogenic particles, have gained great attention in the nanobiotechnology and clinical fields [5,6].

This review will broadly describe the research trends and recent progress of ultrasound technologies helped by echogenic particles, covering a range of applications from diagnostics to therapeutic ultrasound. Advanced ultrasound technologies aiming to overcome conventional conflicting and intrinsic issues stemming from echogenic particles will also be thoroughly discussed, with special emphasis on the size issue. Lastly, the development of highly qualified echogenic nano-sized particles will be introduced; these particles can function as both a ultrasound contrast enhancer and ultrasound responsive drug delivery cargo. They will also be examined in terms of rational design and medical applications.

Ultrasound imaging

Last for decades, molecular imaging modalities such as CT, MRI, PET, and Ultrasound have been developed for early diagnosis of disease in clinical field. The uses of their imaging methods were chosen as a complementary method for patient's disease but, it took high cost and inconvenient for patients. Recently, with the demand for more efficient patient friendly diagnostic method, several imaging techniques tend to blend each other to complement their weak points. In order to develop more powerful diagnostic imaging, their strength and weakness should be considered very carefully.

Computed tomography (CT) images, based on X-ray absorption provides high quality of anatomical information but, large amounts of iodine containing contrast agents are needed to enhance their sensitivity which can be result in side effects to patients. Magnetic resonance imaging (MRI) which is obtained by the difference of relaxation time after irradiation of strong magnetic fields gives us high resolution of anatomical information but, it cost so high and inconvenient for patients. For positron emission tomography (PET) imaging, radioactive isotope is used by labeling with drug or biological molecule. By using of γ-ray produced from emitting isotopes, PET imaging provide high sensitivity with depth whereas it cost high. Optical imaging method, which uses fluorescence/luminescent contrast agent have high sensitivity and easy accessibility but limited depth penetration and clinical uses. In brief, CT and MRI provide spatial resolution information of body but it is hard to detect disease more sensitively than PET and optical imaging. Otherwise, PET and optical imaging gives high sensitivity in diagnosis but spatial resolution is poor than CT and MRI.

Ultrasound imaging which provides spatial and temporal resolution is relative low cost than other imaging technique and easy to access for patients. Though ultrasound imaging has limitation in uses of gas containing organs, osseous structure for imaging, it can provide fast and real time imaging of internal organs, blood pool. With the assistance of contrast agent, more accurate diagnosis is enabled but it remains only blood pool images not the tissue penetrated images due to the size of contrast agent (>sub μm) which resulted in limited clinical application. Nevertheless, ultrasound