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Nano/Micro-particles and ultrasound contrast agents

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**Abstract**

Microbubbles have been used for many years now in the clinical practice, as contrast agents in ultrasound imaging. Recently, their therapeutic applications have also attracted more attention. However, short circulation time (minutes) and relatively large size (two to ten micrometers) of currently used commercial microbubbles do not allow effective extravasation into tumor tissue, preventing efficient tumor targeting. Fortunately, more multifunctional and theranositc nanoparticles with some special advantages over the traditional microbubbles have been widely investigated and explored for biomedical applications. The way to synthesize an ideal ultrasound contrast agent based on the nanoparticles, in order to achieve an expected effect on contrast imaging is a key technique. Currently a number of nanomaterials including liposomes, polymers, micelles, dendrimers, emulsions, quantum dots, solid nanoparticles, etc, have already been applied to the pre- or clinical trials. And multifunctional and theranositc nanoparticles with some special advantages, such as the tumor-targeted (passive or active), multi-mode contrast agents (magnetic resonance imaging, ultrasonography or fluorescence), carrier or enhancer of drug delivery, and the combined chemo- or thermal therapy, etc, are rapidly gaining popularity, and have shown a promising application in the field of cancer treatment. In this minireview, the trends and the advances of the multifunctional and theranositc nanoparticles are briefly discussed.

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**Key words:** Ultrasound contrast agent; Microbubble; Nanoparticle; Imaging; Nanomaterial

**Core tip:** The theranostic nanoparticles were defined as the nanoparticles with double functions (for both therapeutic and diagnostic purposes), and were commonly applied by simultaneous drug delivery and molecular imaging.

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**MICROBUBBLES**

Conventionally, the ultrasound contrast agents (UCAs) commercially used are microbubbles with sizes in the micrometer range, such as SonoVue®, Definity®, Luminity®,Sonazoid®,etc, which are mainly composed of insoluble gas (perfluorocarbons or sulfur hexafluoride) and an encapsulating shell (lipids, proteins or polymers)[1-5]. During the past decades, these UCAs had mainly been used for imaging in clinical practice[2-11]. Recently, microbubbles and their associated cavitation are playing an increasingly significant role in both diagnostic and therapeutic applications of ultrasound[12]. Besides that, microbubbles have also attracted more attention as drug carriers and enhancers of drug and gene delivery and have been widely investigated for these applications (especially in the area of anticancer research)[13]. However, short circulation time (minutes) and relatively large size (two to ten micrometers) of currently used commercial microbubbles do not allow effective extravasation into tumor tissue (pore size of tumor endothelium is typically in the range 380-780 nm), preventing efficient tumor targeting[14, 15].

**NANOMATERIALS**

Fortunately, with the development of nanotechnology, nanomaterials have been evolved also and now are widely recognized as a novel type of biomaterial, with very promising applications in the field of drug delivery[13, 16-21]. Currently a number of nanomaterials including liposomes, polymers, micelles, dendrimers, emulsions, quantum dots, solid nanoparticles, etc, have already been applied to the pre- or clinical trials[22-30]. In theory, nanomaterials can overcome the aforementioned shortcomings of microbubble due to their smaller sizes (in the nanometer range)[29, 31, 32]. The National Cancer Institute has defined the nanoparticle as any particle with at least one dimension under 100 nm, while in many articles some sub-micrometer particles have been regarded also as nanoparticles[1].

The way to synthesize an ideal ultrasound contrast agent based on the nanoparticles, in order to achieve an expected effect on contrast imaging is a key technique. According to some recently published articles, most of researchers were able to enhance the acoustic backscatter by using nanomaterial equipped with gas (perfluorocarbon), though the nanoparticle-based contrast agents for the imaging modalities discussed were in various stages of development[25-27, 33-35].

The use of nanomaterials as carriers for drug delivery, represents the mainstream in the field of biomedical research[29, 31, 36-39]. However, recently, multifunctional and theranositc nanoparticles with some special advantages, such as the tumor-targeted (passive or active), multi-mode contrast agents (MRI, US or fluorescence), carrier or enhancer of drug delivery, and the combined chemo- or thermal therapy, *etc.*, are rapidly gaining popularity, and have shown a promising application in the field of cancer treatment[13, 18-20, 29, 38-42].

For instance, Lammers *et al*[31] discussed the principles, pitfalls and (pre-) clinical progress of drugs (including those with nanoparticles) used for tumor-targeting. Most of nanoparticles can be easily functionalized with a wide variety of biomolecules or antibodies and could be used for the targeted recognition or imaging of specific tissue/organs[19, 43-47]. Besides, regarding to its multifunction and multi-mode imaging, Malvindi *et al*[48] reported a magnetic/silica nanocomposite as dual-mode contrast agent for combined MRI and US, which enables non-invasive detection of the molecular components of pathologic processes through multiple-mode imaging techniques[14, 48]. Wang *et al*[35] proposed that Au-nanoparticle coated mesoporous silica nanocapsule-based enhancement agents can be used as an inorganic theranostic platform for contrast-intensified US imaging, combined chemotherapy and efficient HIFU tumor ablation[42, 45, 49].

Nowadays, these kinds of nanoparticles with more novel functions are still the research focus of biomaterial and have being explored for further biomedical applications[1, 14, 18, 20, 35, 43, 48, 50].

We hope that the information presented in this minireview will stimulate the readers’ interest regarding the field of nano/microparticle and ultrasound contrast agents.

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