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Review

Insights into the unique functionality of inorganic micro/nanoparticles for versatile ultrasound theranostics

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ABSTRACT

The clinical ultrasound (US)-based theranostic biomedicine suffers from the critical issue that traditional microbubbles (MBs) have lots of drawbacks such as low stability, large particle size, difficult structural control, *etc*. The unique composition, structure and functionality of inorganic micro/nanoplatforms have shown their great prospect for solving these critical issues and drawbacks of traditional organic MBs. This review summarizes and discusses the state-of-art development on exploring inorganic micro/nanoparticles for versatile US-based biomedical applications, ranging from US imaging, photoacoustic imaging, sonodynamic therapy, high intensity-focused US ablation and US-triggered chemotherapy. These inorganic micro/nanoplatforms include silica-based particles, Au, carbon nanotubes, TiO_2, manganese oxide, iron oxide, Prussian blue, inorganic gas-generating nanoparticles and their versatile composite micro/nanosystems. Especially, their unique structure/composition-functionality relationships and biocompatibility/biosafety in US-based theranostics have been discussed and revealed in detail. Their facing challenges and future developments are finally discussed to promote their further clinical translations. It is highly expected that these inorganic micro/nanoplatforms will enter the clinical stage to benefit the personalized theranostics biomedicine based on their unique functionalities and high performance as necessarily required in US-based theranostics.

1. Introduction

Ultrasound (US) imaging (ultrasonography) is one of the frequently used diagnostic-imaging modalities for clinical practice [1–3]. Ultrasonography possesses non-invasive, non-ionizing, portable and real-time characteristics, as well as its low price per examination and high diagnostic safety [4,5]. As a typical mechanical wave, US can also be developed as a physical tool for therapeutic applications, such as high intensity-focused US (HIFU) [6–8], low intensity-focused US (LIFU) [9–12], sonodynamic therapy (SDT) [13–17] and US-triggered chemotherapy [18–22]. Compared to other irradiation source such as magnetic field, X-ray, microwave and radiofrequency, US is much safer for the therapeutic applications based on its non-invasive and non-ionizing features. In addition, US imaging can be easily integrated into US-therapeutic modality (theranostics) for guiding and monitoring the therapeutic process and efficiency. Therefore, US-based imaging and therapeutic modalities have found the broad applications in clinic for efficient diagnosis and treatment of various diseases.

The fast development of nanomedicine and biomaterial science has strongly demonstrated that the introduction of designed microparticles or nanoparticles (NPs) into theranostic biomedicine can substantially improve the imaging contrast/precision and enhance the therapeutic efficiency [23–29]. For instance, these micro/nano-scale materials can act as the contrast agents (CAs) for contrast-enhanced diagnostic imaging. In addition, they can also be used as the drug delivery system (DDS) for targeted drug delivery or as the synergistic agent for enhancing the therapeutic efficiency of various treatment modalities such as radiation therapy (RT), photodynamic therapy (PDT), photothermal therapy (PTT) or microwave therapy (MT) [30–35]. For US-based theranostics, microbubbles (MBs) have been extensively used for clinical US imaging based on their satisfactory hyperechogenic property [36–44]. These MBs are also featured with high biocompatibility, easy

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biodegradation and facile large-scale fabrication. In addition, the rational choice of organic-shell composition could endow MBs with photoacoustic (PA) imaging capability [45,46], and these MBs could enhance the delivery efficiency of anticancer drugs and gene transfection [47,48]. However, their large particle sizes (ca. 1–8 μm) determine their predominate location only in vascular systems after intravenous administration, which means that they cannot penetrate into the tumor microenvironment by tissue extravasation [49]. In addition, these gas-filled MBs suffer from the critical issues of low stability and short half-life during the transportation within the blood vessel because of the quick inner gas diffusion and organic-shell instability (Fig. 1). Typically, the stability of organic MBs could be improved by the rational choice of their shell composition. For instance, the traditional lipid shell could be replaced by poly(lactic-co-glycolic acid) (PLGA), or solid nanoparticle absorption to improve the MBs' stability [50–54].

Compared to traditional organic micro/nanosystems for US-based biomedical applications, inorganic micro/nanoparticles, as new hyperechnogenic biomaterials, are intrinsically featured with the following specific characteristics for US theranostics (Fig. 1). First, the inorganic framework is relatively stable as compared to organic counterparts, which means that they can be used for long-lasting US imaging or therapy [55]. Second, these inorganic micro/nanoparticles with abundant compositions/nanostructures usually exhibit the unique physiochemical properties responsible to US irradiation or some intrinsic functionalities for diagnostic-imaging guidance [55–60]. Especially, the particle size of some inorganic NPs is small enough to pass through the blood vessel and penetrate into tumor by tissue extravasation. Therefore, the US-based theranostic performance can be enhanced by this manner. However, these inorganic micro/nanoparticles usually show the low biodegradability and have unclear biological effect/biosafety, significantly restricting their further clinical translation. Typically, the acoustic responsibility of inorganic micro/nanoparticles is relatively lower as compared to traditional MBs for US imaging, but they can be designed with unique responsibility to intrinsic or external triggers, which can further improve the acoustic responsibility and imaging/therapeutic performance.

To solve the critical issues of traditional MBs and develop new theranostic applications of US-based biomedicine, various inorganic micro/nanosystems have been explored for US imaging and therapy (Fig. 2), including solid silica micro/nanoparticles, mesoporous/hollow silica NPs, Au NPs, TiO_2 NPs, carbon nanotubes, MnO_2 NPs, magnetic NPs, Prussian blue NPs and other inorganic composite nanosystems. These inorganic NPs act as the CAs for contrast-enhanced US imaging and PA imaging, or act as the synergistic agents (SAs) for US therapy, such as enhanced HIFU ablation, sonosensitizer-assisted SDT and US-triggered on-demand drug releasing. This review summarizes and discusses the recent important progress of this new research area, particularly focusing on the design principles and fabrication strategies to improve the theranostic performance of inorganic micro/nanoparticles in US-based theranostics. The biocompatibility and potential toxicity of these inorganic micro/nanosystems are also briefly mentioned/discussed. Finally, the facing challenges, unresolved critical issues and future developments of inorganic micro/nanoparticles for versatile US-based theranostics have been discussed and outlooked for promoting the clinical translations of these fascinating micro/nanoplatforms.

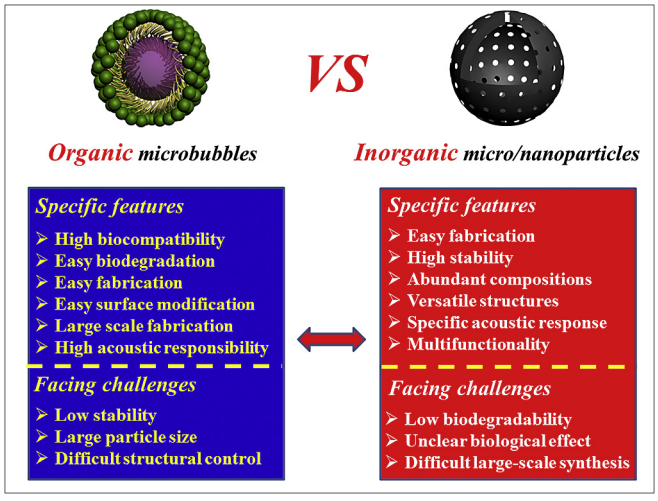

Fig. 1. The comparison between organic MBs and inorganic micro/nanoparticles for US-based diagnostic imaging and therapeutic applications.

2. Silica/silicon micro/nanosystems

As one of the mostly explored inorganic nanosystems, silica-based micro/nanoplatforms have found their broad application potentials in theranostic nanomedicine [32,61,62]. First, these silica micro/nanoplatforms can be endowed with unique structures, such as well-defined mesopores and unique hollow structure [63]. Second, they can easily integrate with other functional materials and moieties *via* either surface-coating strategy or framework-hybridization approach [64]. Third, the abundant silica chemistry makes their surface engineering possible, such as targeting conjugation or organic modification. Last but not least, these silica micro/nanoplatforms are biodegradable, and their biodegradation rate can be facilely controlled by either organic-inorganic hybridization or metal-ion doping [65–67]. These unique structure, composition and intrinsic physiochemical/biological property can guarantee their further potential clinical translation, which also show the promising application potentials in US-based theranostic biomedicine including US imaging and therapy.

2.1. Silica micro/nanosystems for US imaging

Based on the abundant compositions and structures of silica-based micro/nanoparticles, they can be developed as the contrast agents for US imaging provided that their unique structure/composition could be endowed with excellent hyperechogenic property. Solid silica NPs with the size of around 330 nm have been preliminarily demonstrated as the CAs for US imaging at conventional diagnostic frequencies [68]. After surface modification with monoclonal antibody Herceptin, mesoporous silica NPs were developed as the targeting CAs for increasing US image contrast and enhanced ultrasonography of breast cancer [69]. The structure of hollow silica-based micro/nanoparticles is similar to traditional MBs, which have been demonstrated to exhibit the particle size-dependent and shell elasticity-dependent US imaging capability [70].

Uniform surface-PEGylated hollow silica microspheres with unique hollow structure, thin shell and particle size of around 1250 nm exhibited excellent contrast-enhanced ultrasonography capability for both *in vitro* and *in vivo* US imaging [71]. By creating more US scattering/reflection interface, rattle-type hollow mesoporous silica NPs have been demonstrated to show much higher US-imaging capability as compared to traditional hollow mesoporous silica NPs with less US scattering/reflection interface [72]. In addition, the exosome-like silica NPs showed significant US-impedance mismatch, which were further used for labeling stem cells and regenerative imaging [73]. Mesoporous silica NPs with superhydrophobicity exhibited much longer US-imaging lifetime as