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News & Views

Mineral iron based self-assembling: bridging the small molecular drugs and transformative application

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The nanoparticle-based treatment and diagnosis of cancer remain challenging in clinical translation, mainly due to the hurdles that can be associated with the development of targeted delivery, biological side effects, poor drug loading efficiency (DLE), and instability and so on [1,2]. For example, one of the major challenges for targeted drug delivery to tumor tissues would be the biological barriers encountered during the process, including hemorheological flow limitations, endothelial association/extravasation and impaired delivery across tumor cell membranes and tissues [3]. In addition to overcome these biological barriers, the physiochemical properties, such as size, charge, morphology and surface chemistry, have also been emphasized in the biostability and biodistribution of drugs [4]. To address these issues, a number of multifunctional nanoparticle systems have been developed to enhance the delivery efficiency, such as cell surface cascaded landing location for active tumor targeting [5], and nanoscopic drug carriers (e.g., liposomes, nanoemulsions, nanoparticles or micelles) [6]. With the help of these delivery systems, functional cargos can be delivered to the tumor sites via physical entrapment or chemical conjugation [2,7]. However, most of these drug delivery systems or materials have little access for applying in clinical practice, especially the biosafety concerns of the carriers, which may result in the side-effects caused by immune rejection and serious inflammation to kidneys and other organs during degradation, metabolism, and excretion.

To avoid the safety issues of the traditional cargo delivery systems, a growing trend of using drug molecules themselves to generate the carrier-free and well-defined nanostructures with various sizes and shapes has been developed recently in nanomedicine [8]. This strategy creates self-delivering supramolecular nanomedicines with higher drug content, which challenges the traditional concept that the functional drug is solely a biologically active compound to be delivered [9]. Through rational design of the number and type of the drugs incorporated, the synthesized nanostructures could be tailored with desirable physiochemical/biological characters. More importantly, the designed carrier-free nanostructure is a self-constructible form of ligand-drug nanostructure that consists of almost entire therapeutic payloads, which could remarkably reduce the delivery system associated toxicities in therapeutic and diagnostic application [9]. For example, this strategy has been used in the nanodrug delivery systems generated by direct conjugation of hydrophobic drugs with a short oligomer ethylene glycol or a short peptide segment [10]. With these non-biotoxic materials, prodrug could self-assemble into a nanocapsule and the drug loading content could be effectively controlled. For another example, a novel self-delivery system of anticancer drugs without extra carriers has also been developed by amphiphilic drug-drug conjugation [8]. To be noticed, comparing with the traditional drugs or nanoparticle systems, these carrier-free delivery systems could not only obtain better biocompatible with fewer side-effects, but also improve cancer therapeutic efficacy by remarkably enhancing the drug loading capacity.

However, given the complexity of the microenvironment in vivo and dynamic physiological cellular environments of tumors, the performance of these hydrolyzable ester linkage or π-π stacking based drug containing nanostructures may be affected. To enhance the biostability of the nanostructures and maintain the physicochemical properties suitable for clinical treatments, it is therefore necessary to introduce modifications with high mechanical strength to the drugs. In recent years, the metal-organic nanostructures (MONs), consisting of metal ions or clusters and organic bridging ligands, have received tremendous attention in biomedical diagnosis and therapy [11]. Unlike the inorganic nanoparticles or organic conjugated polymers, MONs are self-assembled exclusively based on the strong bonds of inorganic clusters and tunable organic linkers (carboxylates, imidazolates or phosphonates) [12]. With this strategy, tunable physiochemical properties like pore size and connectivity can be achieved, which could be further adapted to deliver different drugs for medical diagnostics and treatments [13]. Therefore, by mediating the supramolecular self-assembly, the nanostructures with metal ions are of great advantages not only in biostability and biocompatibility, but also in drug loading efficiency and capacity, which are highly desired for drug delivery and clinical translations.

Recently, zinc ion (Zn^{2+}) was applied as the metal ion to design the theranostic nanoparticle [14]. In this work, Zn^{2+} was interacted with a photosensitizer indocyanine green (ICG) through complexation or ionic interaction with the two additional sulfonate anions to self-assemble the DPA-Zn-ICG MONs. Compared with the free

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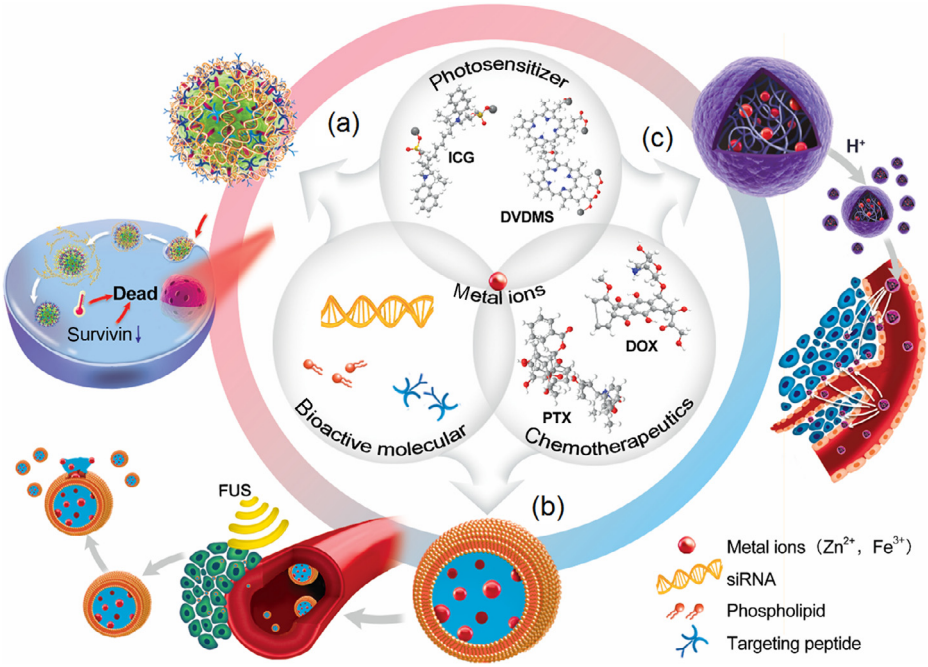

Fig. 1. (Color online) Schematic graph of mineral iron based self-assembling. (a) Metal ions could mediate the self-assembling of photosensitizer ICG and the bioactive molecules (such as targeting peptide and siRNA) for synergistic nanomedicine by combined photo/gene therapy. (b) Phospholipid, a kind of specific bioactive molecules introduced into the self-assembled metal-organic nanostructure systems. The synthesized microbubbles could respond to ultrasonic stimulation and improve the therapeutic effect and imaging sensitivity compared with the free molecule. (c) DVDMS and DOX could be mediated to assemble a functional nanomaterial (140 nm) that could release ultrasmall nanodrugs (5–10 nm) in response to the mild acidic tumor microenvironment, resulting in the combination of photodynamic therapy and chemotherapy with enhanced therapeutic efficiency for the deep tumors.

ICG, the engineered MONs obtained higher absorbance at 808 nm with stronger photoacoustic (PA) signals. Simultaneously, the therapeutic small interfering RNA (siRNA) was also loaded in the nanostructures, leading to the targeted delivery to specific proteins. Together, based on metal-organic coordination and self-assembly, the novel DPA-Zn/ICG/siRNA MONs developed in this study showed enhanced theranostic capability, which would be promising to develop a fluorescence and PA imaging guided photo/gene combinational therapy in personalized nanomedicine.

In addition to Zn^{2+}, the ferric ions (Fe^{3+}) has also been explored for the ICG-metal ion binding in the fabrication of a multi-level self-assembled nanoparticles (NPs) system, with the theranostic dye and metal ion encapsulated in a lipid microbubbles (MB) [15]. Compared with the pure phospholipid delivery system, this formulation of phospholipid-MONs system increased the generation of reactive oxygen species (ROS) by enhancing the transfer of sound energy in non-covalent contacts during sonodynamic therapy (SDT). Moreover, the Fe^{3+}/ICG@MB system enabled site-specific release of the Fe^{3+}/ICG, leading to improved drug accumulation at the tumor site and preventing spontaneous precipitation. Because of the higher efficiency, more specific targeting delivery and better biocompatibility, the Fe^{3+}/ICG@MB system could be optimized to achieve sufficient optical and acoustic signal intensities that allow imaging-guided SDT against orthotopic hepatocellular carcinoma (HCC), making the clinical SDT against deep-seated cancers feasible.

Furthermore, the Fe^{3+} has not only mediated the self-assembly of ICG, but also been studied with other photosensitizers. A novel strategy was designed to synthesize MONs through supramolecular co-assembly of photosensitizer sinoporphyrin sodium (DVDMS), chemotherapeutic drug doxorubicin (DOX) and Fe^{3+} [16]. Experimental results showed that compared with the free photosensitizer, the DVDMS/Fe^{3+}/DOX produced 3-fold more ROS through the energy transfer-mediated fluorescence quenching. Moreover, the synthesized MONs exhibited extremely high DLE for two types of drug molecules co-assembled. Remarkably, the self-delivering supramolecular (140 nm in diameter) could release ultrasmall-nanodrug (5–10 nm in diameter) in response to the mild acidic tumor microenvironment, which in turn would overcome the above-mentioned issues like drug penetration barriers across complex biological systems, poor circulation stability and limited drug loading efficiency.

In summary, these strategies of the metal-organic nanostructure synthesis may provide a basis to design the carrier-free delivery system via the combination of multiple therapeutic agents and mineral irons (such as ferric ions and zinc ions) with imaging functions, which perhaps could contribute to more effective nanotheranostics due to the increased drug loading, overcome the leakage issue associated with encapsulated drugs, and avoid the concerns for drug carriers associated toxicities (Fig. 1). Moreover, the mineral iron based self-assembling system could protect functional cargos from the endogenous bioactivator and the natural defense systems, therefore displaying better biostability and biocompatibility. We believe that the rapid growth of non-biotoxic mineral ions based molecular assembly provides a potential opportunity for improving the clinical prospects of precision medicine solutions and holds great promise for future research in cancer theranostics.

Conflict of interest

The authors declare that they have no conflict of interest.

Acknowledgments

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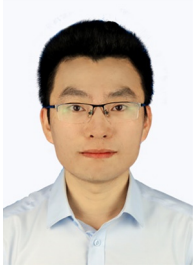

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