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Mesoporous silica as micro/nano-carrier: From passive to active cargo delivery, a mini review

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ABSTRACT

Mesoporous silica has been widely explored for biomedical applications due to its unique structure and good biocompatibility. In particular it exhibits superior properties as micro/nano-carriers in the biomedical field. We explore their potentials in controlled drug/gene co-delivery and photodynamic therapy for cancer treatment both *in vitro* and *in vivo*. By incorporating mesoporous silica nanoparticles (MSNP) with two-dimensional nanomaterial, graphene oxide nano-sheet, we utilize MSNP in cellular bio-imaging with squaraine dye. Meanwhile, through delicate combination between mesoporous silica micro/nano carriers with catalytic/bio-catalytic reactions, we manage to achieve self-propelled micro/nano-motors based on mesoporous silica that are capable of transporting cargos in an active manner. Especially, enzyme powered mesoporous silica motors can be powered by physiologically available fuels such as glucose and urea, which are advantageous for future biomedical use. Motion control on both velocity and movement direction provides a powerful tool for targeted drug delivery. Therefore, such mesoporous silica based active carriers pave way to the solution of targeted drug delivery for cancer treatment in future nano-medicine field.

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1. Introduction

Mesoporous silica was first invented by two research groups independently in early 1990s [1,2]. Then, researchers started to develop other types of mesoporous silica which mainly can be categorized by pore size. Due to its uniform pore size, high surface area, large pore volume, high drug loading capability, good biocompatibility and easy surface functionalization, mesoporous silica has been widely explored in many fields. With the development of nanomedicine during the past decade, many research efforts have been made for the biomedical use of mesoporous silica nanoparticles (MSNP). Generally, MSNP is used as nano-carrier that can load and transport biomedical reagents for specific applications in biomedical field [3–6]. Depending on the types of loaded cargos, the MSNP based nano-carriers can be used for various purposes in biomedical field. For instance, fluorescent dyes or photosensitizers were either physically trapped inside the nano-channels or chemically bonded onto the surface of MSNPs based nano-carriers for bio-imaging [7] and photodynamic therapy in cancer treatment [8–10]. MSNP nano-carriers were used to deliver anticancer drugs into cancer cells by endocytosis mechanism, where the drug molecules were loaded inside the nano-pores [11]. In these applications, the MSNP nano-carriers were transported in the biological environment *via* free diffusion, or moving with blood stream. Such passive delivery manner is still the most widely utilized method in nano-medicine field.

One major challenge of nano-carriers based drug delivery is to develop specific target drug delivery systems that can transport chemo-therapy reagents to the target locations specifically without affecting any normal cells. Therefore, target drug delivery is at extremely high demanding. In passive delivery manner, many nano-carriers are believed to accumulate in tumor tissue by enhanced permeability and retention (EPR) effect, leading to tumor targeted drug delivery [12,13]. Another commonly used strategy is to functionalize tumor targeting ligands onto nano-carriers to induce specific interaction and endocytosis of the nano-carriers into cancer cells [14,15]. For instance, tumor targeting ligands such

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as folic acid, anti-body, specific designed peptides or aptamers, were grafted onto the surface of nano-carriers in order to enhance the cellular uptake of nano-carriers into tumor cells selectively, and avoid normal cells' uptaking. In recent years, active drug delivery by micro/nano-motors has emerged as new strategy to achieve target drug delivery. Taking advantage of the self-propulsion and cargo loading capabilities, the active micro/nano-carriers can carry drugs to the target locations as designed [16]. There were only a few reports about using self-propelled micro/nano-motors to deliver drugs to target cancer cells *in vitro* [17–19]. Such strategy can directly transport drugs to the target location in a positive manner, and therefore brings promising future for target drug delivery in nano-medicine field.

This review article first introduces the use of MSNP as passive nano-carriers for drug/gene co-delivery, intracellular bio-imaging and photodynamic therapy (PDT). By further combination with catalytic/bio-catalytic reactions powered self-propulsion systems, mesoporous silica based micro/nano-carriers can move by themselves as active drug delivery vehicles, which is a newly developed research field and provides possible solution for target drug delivery for future cancer treatment. We also focus on the use of non-toxic fuel and enzymes to provide the driving force for the mesoporous silica micro/nano-carriers, which helps to solve the problem of the toxicity of the fuel used to power these active carriers.

2. Biomedical applications of MSNP as nano-carriers

2.1. Drug/gene co-delivery by MSNP

During cancer treatment, traditional chemo-therapy is lack of efficiency due to drug resistance of cancer cells developed during long-term administration of anti-cancer drugs [20]. Integration of gene-therapy with traditional chemo-therapy can avoid drug resistance by suppressing specific protein expression that is responsible for drug resistance. Therefore, it is of great significance to develop nano-carriers that are capable of delivering both anti-cancer drug and gene simultaneously [21–23].

We developed a series of drug/gene co-delivery strategies based on MSNP to realize controlled intracellular drug/gene co-delivery, such as methods shown in Fig. 1(A, B) based on MSNP [24] and hollow mesoporous silica nanoparticles (HMSNP) [25], respectively. The morphology of typical MSNP such as spherical shape and mesoporous structure were shown by the transmission electron microscopy (TEM) images in Fig. 1(C, D), exhibiting average diameter of 150 nm which can be tuned by the reaction conditions. Fig. 1(E) shows the hollow structure of HMSNP. In order to achieve controlled drug release, we developed several methods to seal the loaded drug molecules in mesoporous silica, avoiding the drug pre-release until the MSNP is uptaken by cancer cells. Different capping methods will response to corresponding triggering and releasing mechanisms.

For instance, redox-responsive disulfide bond has been employed to design and fabricate a series of stimuli-responsive drug delivery systems [26,27]. We functionalized disulfide bond linked amine groups on the MSNP, and then use the electrostatic interaction between negatively charged ssDNA (model gene) and positively charged ammonium-functionalized MSNPs to obtain ssDNA-coated nanoparticles (MSNP-SS-NH_3^+ + ssDNA), which could block the drug inside the mesopores. When we add the reducing agent DTT or GSH, the disulfide bond will cleave and then the ssDNA and drug were triggered to release from the MSNPs. After the cell uptaking, the drug and ssDNA would be released inside the cells on account of that the cells contain rich intracellular GSH, realizing drug/ssDNA co-delivery [28]. By controlling drug release inside the cancer cells, the drug delivery efficiency was improved and the cancer killing effect was enhanced by about 100% compared to the control group in which cancer cells were treated with the same amount of free Dox. We further developed this method into a dual-responsive drug/gene delivery system. As Fig. 1(A) shown, we functionalized the 15-mer single-stranded DNA (ssDNA) onto the surface of the MSNPs *via* disulfide bond linkage, after loading the drug into the MSNP, another longer 33-mer complementary ssDNA could hybridize with the short 15-mer single-stranded DNA to form double-stranded DNA (dsDNA), which block the pores and avoid the drug leakage before the endocytosis. This system had two methods to release the drug/gene including redox-responsive release or thermal-responsive release. The first way is based on cleavable disulfide bond. In the second way, when the temperature increased to a value higher than the melting temperature (T_m = 40.3 °C) of dsDNA, leading to the denaturization of the hybridized dsDNA, and thus drug release [24].

Also, we utilized disulfide bond to link supramolecular host-guest system, adamantine (AD) and ethylenediamine-modified β-cyclodextrin (CD-2NH_2) complex onto the surface of the MSNP for drug blocking [29]. We could introduce the siRNA onto the MSNPs through electrostatic interaction between positively charged amino groups of CD-2NH_2 and negatively charged siRNA, making it possible to deliver drug and siRNA at the same time. In this report, we carried experiments on the transgenic zebrafish larvae to observe the delivery of the drug/gene *in vivo*. Injecting siRNA/CD-2NH_2-capped MSNPs into larvae brain, the expression of green fluorescence protein (GFP) decreased. And when we injected Dox-loaded CD-2NH_2- capped MSNPs into the transgenic larvae, the development of the liver tumor was markedly inhibited with a decrease of the tumor area by 35.5% on average, proving that the drug/gene co-delivery system were feasible both *in vitro* and *in vivo*.

In further research, we used HMSNP as the carrier, which could enhance the drug (Dox) loading capability from 7.6 wt% for conventional MSNP to 15.6 wt% for HMSNP with the same amount of silica [25]. After loading the anticancer drug (Dox) into the HMSNP, we capped the mesopores with folic acid conjugated polyethyleneimine (PEI-FA) through the electrostatic interactions between the phosphate groups and partially positively charged amino groups of PEI-FA. Furthermore, the negatively charged siRNA were combined onto the surface of HMSNPs through electrostatic interactions with the positively charged amino groups of PEI-FA, realizing co-delivery of drug and siRNA. The drug/gene release was pH-responsive. Since most of the cancer cells possess an acidic environment, the drug/gene would be released after the HMSNPs internalized into the cancer cells. We carried out drug/gene co-delivery study with two different cancer cells lines (HeLa and MCF-7) and achieved combined cancer killing effect with the delivery of Bcl-2 siRNA and anti-cancer drug Dox. The Bcl-2 protein expression was significantly inhibited for the HeLa cells which are folic acid receptor positive (Fig. 2(D)), leading to effective cancer killing effect due to synergetic gene and chemo-therapy process (Fig. 2(E)).

2.2. Bio-imaging and photodynamic therapy by MSNP

Squaraine dyes are zwitterionic dyes that have good photophysical properties in the near infrared (NIR) region, which is suitable to be applied in biological area, including bio-imaging and photodynamic therapy (PDT) [30,31]. However they are sensitive to nucleophilic attack, which renders its applications in physiological environment. We utilized MSNP as the nano-carriers combined with graphene oxide (GO) to overcome this drawback. In our strategy, we put squaraine dyes into the nanopores of MSNP and use GO nano-sheets to wrap the nanoparticle surfaces, as illustrated in Fig. 3(A). With the physical isolation and protection by the wrapped

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