Mesoporous silica nanoparticles: facile surface functionalization and versatile biomedical applications in oncology

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Abstract

Mesoporous silica nanoparticles (MSNs) have received increasing interest due to their tunable particle size, large surface area, stable framework, and easy surface modification. They are increasingly being used in varying applications as delivery vehicles including bio-imaging, drug delivery, biosensors and tissue engineering etc. Precise structure control and the ability to modify surface properties of MSNs are important for their applications. This review summarises the different synthetic methods for the preparation of well-ordered MSNs with tunable pore volume as well as the approaches of drugs loading, especially highlighting the facile surface

functionalization for various purposes and versatile biomedical applications in oncology. Finally, the challenges of clinical transformation of MSNs-based nanomedicines are further discussed.

Keywords: Mesoporous silica nanoparticles; synthesis method; surface functionalization; drug delivery; biomedical application.

1. Introduction

With the rapid development of nanotechnology, a broad range of nanomedicines have been developed for drug delivery, diagnosis, and imaging [1]. Compared with traditional drugs, nanomedicines exhibit many advantages such as improved pharmacokinetic profiles, increased bioavailability, elevated drug targeting distribution capability, and reduced toxicity [2]. A series of organic nano-carriers such as liposome, albumins, and polymer micelles have achieved successful clinical translation. On the contrary, most inorganic nanomedicines are still at the stage of preclinical research. Among these, mesoporous silicas nanoparticles (MSNs) have been considered to be an attractive and promising candidate due to their unique properties including facile synthesis and functionalization, tailorable mesoporous structure, high surface areas, large pore volumes, good physicochemical stability, and favorable biocompatibility [3].

Silica has been classified as “Generally Recognized As Safe” (GRAS) by the FDA for over 50 years and used in tablet pharmaceutical preparations as an excipient [4]. In the past few decades, silica-based nanoparticles have attracted extensive research as the drug delivery carriers. And in 1983, amorphous silica was first proposed as a drug carrier [5]. In 1992, the first ordered mesoporous molecular sieves called MCM-41 was synthesized by Kresge [6]. This achievement has been regarded as a breakthrough in MSNs fabrication, and proposed the potential application of silica based nanocarrier. In 2001, the MCM-41 mesoporous silica nanoparticle was first developed as a drug delivery platform for encapsulation of anti-inflammatory drug ibuprofen, this work opened up the possibility to design silica-based nanoparticle for medical applications

[7]. In 2003, Lai et al. reported that cadmium sulfide-functionalized MCM-41 mesoporous silica nanoparticles exhibited the controlled release profile of vancomycin and adenosine triphosphate, and profiled this drug delivery system (DDS) which possesses good biocompatibility and high delivery efficiency [8]. This achievement further motivated researchers to develop silica-based nanoparticles for biomedical applications. Since then, MSNs have become one of the significant research frontiers, and a series of MSNs based nanocarriers with different compositions, structure, and morphologies have been successfully designed and synthesized [9-11].

Nowadays, MSNs are widely used as nanocarriers for the treatment of complex diseases, however, the FDA approval and further clinical translation of MSNs remain great challenges. The unique properties of MSNs, including uniform particle size, controllable pore volume, and fine biocompatibility, promote its further biomedical application. The number of studies on MSNs has increased dramatically and their applications in drug, gene, and protein delivery are emphasized in numerous reviews [1, 12-14]. The recent advancements in MSNs towards diagnostic and theranostic applications for cancer are also summarized [15-17]. These reviews mainly provide a comprehensive background of MSNs in biomedical application.

In this review, the methods of synthesis, modulation of pore sizes, surface functionalization, drug loading of MSNs are highlighted and their applications in drug delivery are summarized.

2. Synthesis of MSNs

2.1 Synthesis approach of MSNs

2.1.1 Sol-gel process

The majority of MSNs are fabricated through the Stöber method, also known as sol-gel process [18]. The synthesis can be accomplished in the basic, acidic, or neutral aqueous solution, with two critical steps: hydrolysis and condensation. In general,

pore templates (amphiphilic surfactants and biomacromolecules) could self-assemble into micelles at a concentration higher than the critical micelle concentration (CMC). Following this, the silica precursors condensate over the templates and form a silica wall around the surface of the micelles. In the final step, the template surfactant is completely removed either by the traditional extraction or calcination to generate pores as shown in Fig.1 [19].

Hydrolysis: ≡Si-OR + H_2O ⇌≡Si-OH + ROH

Condensation: ≡Si-OH + OH-Si≡ ⇌≡Si-O-Si≡ + H_2O

≡Si-OH + RO-Si≡ ⇌≡Si-O-Si≡ + ROH

2.1.2 Evaporation-induced self-assembly

Firstly, soluble silica species and surfactant are dissolved in water/ethanol solvent at specific mole ratio to acquire a homogeneous solution, where the initial surfactant concentration is below than the CMC. Subsequently, progressive preferential evaporation of ethanol is performed which concentrates the non-volatile surfactant and silica species, resulting in the self-assembly of silica-surfactant micelles and their further organization into lyotropic liquid crystalline mesophases. After removing the surfactant, the highly ordered mesoporous films are obtained. It is worth noting that through variation of the initial alcohol/water/surfactant mole ratio, it is feasible to get different final meso-structures by following different trajectories in composition space. Another advantage of evaporation-induced self-assembly method is that it can be used to fabricate organic-inorganic hybrid composites [20].

2.1.3 Microwave assisted technique

Microwave assisted technique is a low-cost approach for the synthesis of MSNs. By microwave heating the precursor gel to around 150 °C for one hour or less, a high-quality hexagonal mesoporous material with good thermal stability can be obtained. The advantage of microwave synthesis is that the reaction vessel can be heated homogeneously to realize more uniform nucleation, and the crystallization time is shorter when compared with the sol-gel process [21].

2.1.4 Ultrasonic synthesis

In 2004, Run et al. reported an ultrasonic synthesis method, which is performed under acidic conditions by using a cationic surfactant and an organic silica source [22]. The acquired MSNs exhibit a well-ordered hexagonal meso-structures with surface area over 1100 m^2/g, primary pore size in the range of 22-30 Å, and the pore volume around 1 cm^3/g. In addition, one of the main advantages is the total synthesis time is reduced from days to minutes, which is much shorter than the conventional sol-gel process [22].

The merits and shortcomings of these four synthetic methods of MSNs are summarized in Table 1.

Table 1 The merits and shortcomings of these four synthetic methods of MSNs

Synthetic strategy	Merits	Shortcomings	Ref.
Sol-gel	Reliable; Controllable particle size and structures	Laborious, time consuming	[18, 19]
Evaporation-induced self-assembly	Save time and energy; Allow foreign objects to be encapsulated conformally during synthesis.	Less adjustable of pore size and pore structure	[20, 23]
Microwave assisted technique	Save time; Higher reaction yields	Less adjustable of pore size and pore structure; Complicated preparation	[21, 24, 25]
Ultrasonic synthesis	Save time and energy	Lower structural uniformity; Lower yield	[22, 26]

2.2 Particle size and pore volume

2.2.1 Control of particle size

The particle size is one of the key factors which impacts the pharmacokinetics of MSNs. Mou and co-workers proved the influence of particle size on the cellular uptake of MSNs by Hela cells, indicating that 50 nm particles showed maximum cellular uptake (50 nm > 30 nm > 110 nm > 280 nm > 170 nm) [27]. Another study carried out by He et al. investigated the biodistribution of MSNs with different particle sizes *in*

vivo. Although MSNs of various particles size were mainly restrained in liver and spleen, they still exhibited different distribution tendencies because of the delicate balance between uptake and excrete [28]. After intravenous injection, the distribution of relatively smaller particle sizes (80 and 120 nm) in liver and spleen exhibited a decreased tendency, which then conversely increased before finally decreasing. However, the larger size particles (200 and 360 nm) decreased continuously after injection [28]. The particle size also greatly influences drug loading and release profiles of MSNs. Monzano et al. proved that the smaller MSNs were better candidates with high loading capacity and controlled drug release profiles than the large ones for model drug Ibuprofen in the similar circumstance [29]. Also, particles of smaller size exhibit better colloidal stability and suspendability, which are highly expedient for biomedical applications [11].

In general, the particle size of MSNs can be modulated by tuning of the synthesis conditions, such as pH, surfactant concentration, silica source, and the addition of organics and organosilane [30]. Wu et al. systematically investigated the effects of the essential reaction conditions (e.g., amount of TEOS, pH, and reaction time) on the particle size of MSNs by experimentally controlling the variables, indicating that the pH was the most significant factor affecting the particle size [30]. In a separate study, pH has also been proved to be highly associated with the hydrolysis and condensation of the silica sources [31]. Lu et al. further reported that the hydrolysis rate of silica source linearly increased along with OH^- concentration, but the condensation rate was not altered. The highest condensation rate could reach a maximum of around pH=8.4, and above this pH the condensation rate of silicates would conversely decrease due to the silicates being negatively charged as the OH^- increases. In a basic solution, the primary silicate species can assemble with surfactants to form micelle-silicate assemblies and when condensation continues, the nuclei of new 2D hexagonal phase is formed. As the hydrolysis progress, more and more primary silicate species are condensed to the 2D nuclei, making it larger. Finally, as the primary silicate species are depleted, the synthesized MSNs can reach a defined size. At higher pH values, there

are fewer numbers of nuclei, and the hydrolysis rate of primary silicate species is faster, which leads to the larger size, and the particle size can increase from 30 to 280 nm when the pH reaches 12 [27].

Qiao et al. [32] also demonstrated that the particle size can be effectively controlled by using the additives agents to adjust the hydrolysis and condensation process of silica source, including alcohols, amine, inorganic bases, and inorganic salts. In fact, most additives agents are supplements for OH^- directly or indirectly in the reaction mixture, and the OH^- acts as the basic catalyst for the sol-gel process of silica. Other reactants and synthesis parameters equally influence the mean particle size of MSNs.

Chiang et al. [31] investigated the influence of reaction time and TEOS amount on the particle size by the Taguchi method, which follows the basic principle of orthogonal arrays (OA) to evaluate the effects of certain synthetic factors, including pH value, the amount of TEOS, and reaction time with minimum of experiments. It was demonstrated that the particle size increased with the reaction time extension only when the total reaction time was less than 4 h. Otherwise, inordinately long reaction times in basic condition often accompanied with the corrosion of the MSNs silica framework, leading to a reduction in particle size. These results also showed that the greater amount of TEOS could increase the particle size of MSNs, however, the increase in particle size was not proportional to the increased amount of TEOS. Nevertheless, neither the longer reaction time nor the increased TEOS affects the morphology of the MSNs. The reaction temperature was also found to have a profound impact on the size, and as the reaction temperature increases from 30 to 70°C, the particle size enlarges gradually [18]. This is probably due to the increased rate of the silica monomer polycondensation, resulting in a larger size and dense silica structure [18].

It is well known that the nature of the templates also plays an important role for adjusting particle size [33]. Adding a block copolymer agent as co-template, the particle size could be controlled. Suzuki et al. [33] developed a co-surfactant method

to synthesize small sized well-ordered MSNs by using cetyl trimethyl ammonium chloride (CTAC) and a triblock copolymer (Pluronic F127) as cationic and nonionic surfactants. The results showed that the addition of Pluronic F127 could suppress the grain growth and stabilize the mesostructured silica. This method is used to prepare the ordered MSNs with a particle size of less than 50 nm (Fig. 2).

2.2.2 Control of pore volume

In order to broaden the application of MSNs, research has focused on the synthesis of mesoporous silica materials with specific properties such as large pore volume. Several studies have reported that an enhanced loading efficiency of drugs with large molecular weight can be achieved with an increase in pore volume [34, 35]. Currently, both the morphology and size of MSNs can be easily controlled through the regulation of synthesis condition [36]. However, the effective modulation of pore volume remains a great challenge, which limits the application for encapsulation of macromolecules including proteins, enzymes, antibodies, RNA, and DNA [37]. Since the first successful synthesis of mesoporous silica materials, the scientists have made great efforts to obtain MSNs with large pores. In 1998, Zhao et al. [38] prepared a well ordered hexagonal mesoporous silica structures with varying pore size from 46 to 300 angstroms by using amphiphilic block copolymers as organic structure-directing agents. Recently, great success for fabricating large pore MSNs has been achieved by using suitable organic molecules as the auxiliary templating agents [29, 30]. A different synthetic strategy using amphiphilic copolymers with longer hydrophobic chains as pore templates has been developed to synthesize large pore MSNs [39]. With surfactant-micelle-templated synthetic strategy, the addition of swelling agent always leads to the structural disorder or heterogeneity of MSNs. Michal et al. [40] assumed that the swelling agent dissolved moderately in the micelle of a specific surfactant could produce a clear micelle template structure with the significantly enlarged pores. Based on this assumption, 1, 3, 5-triisopropylbenzene (TMB), cyclohexane, xylene, ethylbenzene, and toluene have been identified as swelling agents for the synthesis of ultra-large pore spherical mesopores. Although the pore expanding method can

significantly increase the pore size of MSNs, it makes the excessively thin pore walls unstable [41]. Fan et al. found that addition of TMB during the synthesis of MSNs could significantly increase the pore size to about 30 nm, however, it could cause the pore walls unstable because of the excessively thin pore walls [42]. Further studies also exhibited the correlations between the wall thickness and pore size of MSNs, and the excessive pore expanding could lead to a thinner pore wall, causing the pore walls to be mechanically unstable [40, 43].

In recent years, dendritic mesoporous silica nanoparticles (DMSNs) with open 3D dendritic super structures and center-radial pore channels have attracted special attention because of their unique properties [44]. The DMSNs have been prepared in an aqueous solution using tetraethoxysilane (TEOS) and bis(triethoxysilyl)ethane (BTEE) as precursor and hexadecyl trimethyl ammonium bromide (CTAB)/ sodium salicylate (NaSal) as structure-directing agents. Systemic studies have revealed that the increased molar ratio of CTAB/NaSal from 0.75/1 to 1/1 could expand the pore size from 8.1 to 17.5 nm, which is mainly attributed to the enhanced micelle penetration capability of Sal^-. Another critical factor, affecting the structural parameters of DMSNs, is the molar ratio of BTEE / TEOS, which decreases the pore size along with the increase of BTEE [45, 46]. Shi and co-workers recently reported the hollow silica nanoparticles (HMSNs), the pores of which can be modulated from 3.2 nm to 10 nm through a surfactant-directing alkaline etching (SDAE) process. From a chemical point view, the sol-gel process is a reversible process, and the elaborative control over the reversible Si-O bond breakage and reformation process provides an opportunity for the preparation of desired nanostructured materials [47] and there are some extra pore expanding methods which are summarized in Table 2.

2.3 Synthesis of biodegradable mesoporous silica nanoparticles

For biomedical applications, the biodegradability and clearance of MSNs must be taken into serious consideration. It is believed that MSNs can degrade into silicic acid including monomeric silicic acid and polysilicic acids under physiological conditions

through successive hydration, hydrolysis, and ion-exchange steps. The biodegradable by-products can be excreted through the urine with good biocompatibility [10]. However, it has been widely recognized that the degradation process of MSN is relatively slow owing to its stable Si-O-Si frameworks, and this reluctant biodegradation of MSNs could lead to unwanted accumulation within the body, which could possibly cause severe tissue inflammation or other long-term safety risk [48]. Therefore, the improvements of MSNs with better biodegradability to promote their further clinical translation have aroused extensive interests [49].

Recently, several strategies have been proposed to improve the biodegradability of MSNs. For example, framework reconstruction of silica nanoparticles by metal ions-doping can tune the degradation rate of MSNs. Yu et al. reported that the doping of Mg^{2+} into the framework of silica could change the degradability of the obtained HMSNs due to the much weaker Si-O-Mg network compared to the Si-O-Si network [48]. In brief, the addition of Mg salt into the reaction systems caused the introduction of Mg^{2+} into the silica network and substituted some Si within the Si-O-Si bonds to form Si-O-Mg bonds which were sensitive to mild acidic environment, including tumor tissue. The breaking up of Mg-O bonds can generate abundant defects within the framework and accelerate the framework biodegradation. At the same time, Mg^{2+} can easily be extracted from the framework of HMSNs because of the breaking up of Mg-O bonds, and finally be excreted from the cells [48]. Other than the Mg element, the Ca, Mn, Zn, and Na elements have also been introduced into the framework of MSNs to obtain biodegradable MSNs, and the rapid degradation of hybrid MSNs is triggered by typical tumor microenvironment such as pH (for Ca and Mn), specific proteins (for Fe) or glutathione (for Mn). The biodegradation property of MSNs enables the controllable release of guest molecules, which benefits the *in vivo* applications [50].

Another strategy to optimize the biodegradability of MSNs is to employ the disulfide cleavable or oxamide/ester cleavable silsesquioxanes to insert into the silica nanoparticle for controlled biodegradability by addition of glutamine or esterase [51]. However, the disulfide or oxamide/ester doped MSNs have been found nonporous or

low porosity [4]. In order to improve the mesoporosity of the obtained MSNs, a mixture of bridged silsesquioxanes can be integrated into the framework of MSNs [52]. For instance, Chen et al. successful fabricated a redox-triggered degradable hollow MSN by using phenylene and bis (propyl) tetrasulfide-bridged organoalkoxysilanes, where the phenylene directed the formation of porosity, and the bis (propyl) tetrasulfide acted as a self-destruction trigger in reductive environment [53]. Croissant et al. reported an enzymatically degradable MSNs by using phenylene and oxamide-bridged organoalkoxysilanes [43]. The phenylene directed the formation of mesoporosity and the oxamide in the framework endowed the MSNs with enzymic-responsive biodegradability, which could be triggered in the presence of trypsin. This research provided an opportunity to deliver drug to organs containing specific proteins for targeted therapy [54]. The disulfide containing silsesquioxanes is the most frequently applied material for the preparation of degradable MSNs, however, developing other available silsesquioxanes with cleavable bounds is encouraged to focus on specific trigged degradable strategies [55].

Table 2 Synthesis conditions and applications of different large pore MSNs

Type of MSNs	Pore expanding method	Pore diameter	Particle size	Application	Ref

MSNs	Pore-swelling N, N-dimethylhexadecylamine (DMHA)	4.6 nm	150 nm	Adsorption of cytochrome c	[56]
MSNs	CTAB-templated, base-catalyzed condensation reaction	5.4 nm	265 nm	Loaded cytochrome c	[57]
LPMSN	Pore-templating with Pluronic P104	6.5 nm	300×500 nm	Loaded Porcine liver esterase	[58]
MSNs	Pore-swelling Decane	8.0 nm	100 nm	Immobilized lysozyme	[59]
MSNs	Pore-swelling trioctylphosphine oxide (TOPO)	8 nm	180 nm	Positron emission tomography	[60]
LPMSN	Postsynthetic etching of with aqueous NaBH4	9.28 nm	232 nm	Delivery of paclitaxel	[61]
MSNs	pore-swelling Trioctylmethylammonium bromide (TOMAB)	15.9 nm	288.5 nm	Adsorption of nerve growth factor	[62]
MSNs	CTAB/ PS-b-PAA co-templated	18.5 nm	150 nm	Loaded ibuprofen,	[63]
DMSN	Hexadecyltrimethylammonium/ p-toluenesulfonate co-templated	21 nm	120 nm	Delivery of siRNA	[64]
DMSN	CTAB/ NaSal co-templated	22.7 nm	200 nm	Delivery of Ovalbumin and a toll-like receptor 9	[65]
MSNs	Pore-swelling 1,3,5-trimethylbenzene (TMB)	23 nm	200 nm	Delivery of siRNA	[66]
MSNs	Pore-swelling ethyl acetate	30 nm	180 nm	Delivery of IL4	[67]
Ultra-LPMSN	Post synthetic etching of MSNs with methanolic solution of calcium nitrate or magnesium nitrate	47.5 nm	200 nm	Adsorption of large proteins and antibodies	[68]

3. Surface functionalization

The surface functionalization of nanomaterials plays critical roles in their physical and chemical properties, as well as their applications [69]. Therefore, modification or functionalization of the particle surface is important in the fabrication of MSNs as drug delivery vehicles. The surface of MSNs with high amounts of silanol groups guarantee the easy multi-functionalization [70, 71] through several strategies to improve their biocompatibility, targeted activity, and control release of cargoes inside [72].

3.1 Functionalization for improving biocompatibility

The biocompatibility of nanoparticles is strongly influenced by surface properties, and surface modification plays a pivotal role in improving the biocompatibility of MSNs. The silanol groups exposed on the surface of MSNs can interact with biological molecules, resulting in their damage [73]. On the other hand, the non-functionalized MSNs will rapidly associate with serum proteins, and then be cleaned from circulation by phagocytic cells [19]. In order to improve the biocompatibility of MSNs and prolong their circulation time *in vivo*, the surface of MSNs can be coated with biocompatible organic substances. One of the most well-established surface modification approaches is PEGylation [74]. PEGylation of MSNs can significantly alleviate the hemolytic activity and cytotoxicity, and prevent MSNs from being captured by phagocytic cells [28]. Liposome is a biocompatible material that has been used in clinical studies, several research groups have demonstrated that coating lipid on the surface of MSNs can improve the biocompatibility and performance of MSNs *in vivo* [75, 76]. Brinker et al. reported the successful synthesis of lipid bilayer coated MSNs which can be used for drug delivery, combining the advantage of liposome and MSNs [77].

The colloidal stability of MSNs is one of the most important factors regarding their *in vivo* applications. Formulations with poor colloidal stability can result in administration issues and inappropriate dosage frequencies. In addition, nanoparticles with poor colloidal stability could cause undesirable aggregation once in the blood circulation and lead to severe thrombosis [11]. Unmodified MSNs are

easily aggregated in aqueous solutions because of hydrogen-bonding interaction between the surface silanol groups [78]. Coating MSNs with PEG or liposomes not only increases the biocompatibility of MSNs, but also enhances their colloidal stability.

It has been known that the surface potential is another crucial parameter that influences the biocompatibility of nanoparticles [19, 79] and positively charged nanoparticles will induced more cytotoxicity than the neutral and negatively counterparts [19]. Due to the flexible processing of silica chemistry, the surface potential of MSNs can be precisely controlled by different functionalization via amino ($-NH_2$), carboxyl (-COOH), phenyl (-Ph), and methyl phosphonate ($-PO^{3-}$) groups [1, 80, 81].

3.2 Functionalization for increasing targeted activity

Tumor targeting is one of the biggest challenges of nano-based cancer targeted therapy. In general, active targeting can be achieved by integrating the specific targeting ligands on the surface of nanoparticles, including mannose, transferrin, folic acid, and RGD peptides [82]. These specific targeting moieties are capable of binding to the cancer cell surface receptors or ligands, and thus enhances the specific retention and uptake of nanoparticles by cancer cells [83-85] (Fig. 3A). Furthermore, this strategy of active targeting may play an important role in MSNs-based nanocarriers owning to the facile modified surface property of MSNs.

Recently, antibody-conjugated MSNs have shown tremendous advantages in targeted therapy for tumor [86]. Gao and co-workers developed a safe and effective active targeting nano-system, in which they grafted the monoclonal antibody EpCAM onto the surface of MSNs. As expected, this antibody conjugated MSNs could efficiently target EpCAM, which is highly expressed colorectal cancer cells compared to nonconjugated MSNs [87]. The major challenges of using full-length monoclonal antibodies as targeting ligands are the recognition by immune system and rapid clearance from the blood circulation [88]. The single chain variable fragments (scFvs) are the smallest fragments of antibody that can also be attached to the surface of MSNs as the targeting motif [89]. Compared with the full-length monoclonal antibody,

scFvs exhibit similar advantages of high affinity, specificity, stability, deep tumor penetration, elevated antigen binding capability, and reduced immunogenicity [90].

3.3 Functionalization for controlling drug delivery

Modification of MSNs by different functional groups directly affects the drug release behavior by increasing drug diffusion resistance [91]. Therefore, surface modification of MSNs plays a pivotal role in the process of drug delivery and controlled release. Sustaining drug release using unmodified MSNs can also be achieved through the regulation of the pore structure, particle-size, and pore diameter. However, the inevitable premature drug release still remains a challenge [1]. A widely pursued strategy is to design a target-specific DDS in the process of eradicating cancer. To achieve this goal, a variety of gatekeepers have been introduced on the surface of MSNs for the preparation of controlled DDS. The gatekeepers are opened only upon exposure to specific internal or external stimuli to reduce the side effects caused by toxic substances such as chemotherapeutic drugs [92]. Generally, gatekeepers are comprised of organic molecules, supramolecular assemblies, or nanoparticles. Different stimuli-responsive strategies, including redox, enzymatic, temperature, pH, and photo irradiation, are applied as trigger signals to achieve controlled cargoes release (Fig. 3B) [93]. The controlled delivery of the drug via tumor microenvironment (pH-/Redox-/Protease) stimulus is one of the promising ways for cancer treatment.

3.4 Cell membrane coated MSNs

With the rapid development of nanoparticle synthesis and engineering technology, cell membrane-camouflaged nanoparticles have been highlighted in the past decades because of their improved physicochemical properties and biocompatibility [94]. Cell membrane-camouflaged MSNs are promising strategies to integrate the advantages of both synthetic and biological systems, which hold great potential to improve the therapeutic efficacy. To date, the cell membranes derived from red blood cells [95-97], platelet [98], stem cells [99], T cells [100], and macrophages [101] which are intrinsically biocompatible have been successfully applied in the preparation of cell membrane camouflaged MSNs (Fig. 3C). For example, platelets and immune cells membrane-wrapped nanoparticles exhibited reduced macrophage uptake and potent

active tumor-targeting ability inherited from the donor cells [98, 102]. This biomimetic strategy depicted great possibility to eradicate the residual tumor cells in the circulation for prevention of metastases [103].

Compare with normal cells, cancer cells have unique homotypic targeting ability, which allows tumor cell to bind to each other. The homologous targeting of cancer cell is attributed to the homophilic adhesion domains on the cancer cell membrane such as N-cadherin, epithelial cell adhesion molecule (EpCAM) or galectin-3 [104]. To exploit the natural homotypic adhesion properties of cancer cells, their membranes have been used to wrap nanoparticles which can naturally traffic to the primary tumor and realize the purpose of highly specific and effective cancer therapy with the 'homotypic targeting' effect [104]. For example, a doxorubicin and mefuparib hydrochloride loaded MSNs were first coated with a PEGylated liposome to generate the lipid bilayer-coated MSNs, which were further wrapped with a layer of human breast adenocarcinoma cell membrane. The obtained nanoparticles showed an obvious yolk-shell structure and could be transformed into an ellipsoidal shape to enhance the tumor penetration. In addition, the nanoparticles could effectively escape the host immune system and display homotypic targeting capacity to the primary tumor. The *in vivo* experiments exhibited enhanced anticancer efficiency compared with Doxil [105].

In order to evade the immune surveillance and enhance tumor targeting, Xie et al. designed the CMSN-GOx method, in which MSNs were loaded with glucose oxidase (GOx) and then encapsulated with cancer cell membranes. The obtained nanoparticles could readily avoid immune clearance and target tumor tissue. *In vivo*, CMSN-GOx complex can ablate tumors and induce dendritic cell maturity to stimulate an antitumor immune response to enhance the antitumor efficacy of anti-PD-1 immunotherapy (Fig. 4) [106].

4. Cargo loading into MSNs

4.1 Cargo loading methods

The unique features of MSNs, including high drug loading capacity and sustained drug release profile, make them widely employed as multifunctional drug delivery carriers because of the large pore volume and high surface area. A variety of cargoes

such as small molecule drugs, proteins, contrast agents, and bio-sensing agents can be loaded into MSNs through three main methods: 1) cargoes loading during fabrication; 2) cargoes loading by electrostatic interaction; 3) cargoes loading by chemical reactions.

4.1.1 Cargo loading during fabrication

MSNs can be fabricated by the reaction of organosilane reagents with TEOS in the presence of the drugs, which allows easy encapsulation of drugs into the silica matrix. For instance, methylene blue (MB), a photosensitizer, was mixed with silica matrix during the synthesis procedure of MB loaded MSNs [107]. Because of the negatively charged property of silica matrix, the positively charged drugs such as MB exhibited increased loading efficiency.

4.1.2 Cargo loading by electrostatic interaction

The most common approach for loading drugs into MSNs is adsorption method via mixing MSNs with drug solution [107]. However, this method may lead to too early release of the payload *in vivo* before reaching the target tissue thus limiting the therapeutic efficacy. To overcome this drawback, the surface of MSNs can be functionalized with various groups, including phosphate, carboxyl, amine, or sulfhydryl groups, to improve the electrostatic attraction between cargoes and MSNs. Xie et al. [108] prepared a carboxylic-group functionalized MSNs, achieving higher doxorubicin loading by regulating electrostatic interaction between MSNs and protonated drugs with the Improved DOX encapsulation efficiency of 21.6% and controllable drug release rates.

4.1.3 Cargo loading by chemical reactions

In addition, chemical reactions between therapeutic drugs and carriers can be applied in the loading of cargo into MSNs [82]. Yan et al. [109] successfully designed camptothecin (CPT) loaded MSNs via Thiol-Ene click chemistry. In this study, the antitumor prodrug dimethyl bifunctional silyl ether of CPT was successfully tethered onto the surface of thiol functionalized MSNs through a silyl ethers bonds, and the silyl ethers bonds showed an acid-responsive function (Fig. 5). The acid-cleavable silyl ether

bonds remained stable in normal plasma conditions (pH=7.4) and could be degraded at the acidic pH in tumor issues(pH=6.8). More interestingly, the release rate of CPT was controlled by changing the space volume of substituents on silicon atom. Trimethyl silyl ether and triethyl silyl ether were chosen as linkages and the synthesized carriers, named as MSN-Me-CPT and MSN-Et-CPT, were investigated for their drug release profiles. The results showed that both MSN-Me-CPT and MSN-Et-CPT displayed controllable drug release rate, and the cumulative release of CPT from MSN-Me-CPT and MSN-Et-CPT was calculated as 20% after 8 hours. The authors also reported that the release of CPT from MSN-Me-CPT was faster than that from MSN-Et-CPT due to the different steric bulk of the substituent on the silicon atom. In a separate study, aldehyde-functionalized MSNs could conjugated with DOX through covalent attachment, and the constructed DDS was sensitive to pH to realize DOX burst release, which provided a versatile and easily assemble approach for MSNs platforms [110].

4.2 Cargo loading efficiency

The drug loading capacity is one of the key standards of nanoparticulate carriers for rapid or controlled delivery. MSNs are expected to be promising carriers with advantage of superb drug loading capacity and high chemical stability. The relatively simple synthesis process makes them widely used in the delivery of small molecules as well as macromolecules. Therefore, tremendous efforts have been devoted to improving the drug encapsulation efficiency of MSNs and broadening their application. Hollow mesoporous silica nanoparticles (HMSNs) were synthesized and developed for the biomedical application as drug-delivery nanoplatforms which possessed large hollow cavity exhibiting distinctive and promising drug carrying. Chen et al. [111] demonstrated that HMSNs generated by a modified hard-templating method could achieve a high drug loading capacity of 1129.2 mg/g, which was 3-15 times higher than regular MSNs. HMSNs functionalized with amino groups also showed enhanced cellular uptake and active tumor targeting capacity. In addition, the distinctive structure of HMSNs makes them possible for loading multiple drugs. Palanikumar et al. [112] have reported a HMSNs-based delivery platform for both hydrophobic and

hydrophilic drugs with a high loading efficiency using noncovalently bound PEG-PDS-DPA copolymer as gatekeeper. At a neutral pH, the PEG-PDS-DPA polymer gatekeepers might form a dense layer on the surface of MSNs and blocked the pores to prevent drug leakage. Low pH=5.0-5.5 lead to the protonation of the polymer gatekeeper, followed by copolymer loose and cargo release from the surface of HMSNs. In the presence of intracellular GSH, the PEG-PDS-DPA gatekeeper that cross-linked by disulfide bonds will be degraded, causing the second cargo released from the inside pores.

The structural properties of MSNs, especially the pore volume, also play a significant role in drug loading efficiency. The strong interactions between molecules may prevent the drugs incorporating into mesopores channels, but MSNs with high pore volume can avoid this influence. The loading efficiency of cargoes increase as the pores size increases. Hence, pore expansion is an effective strategy to incorporate large amounts of therapeutic agents into MSNs. A series of pore expanding agents such as DMHA (N,N-dimethylhexa-decylamine), trioctylamine (TOA), aqueous ammonia, alkanes/ethanol, and decane were employed in the fabrication procedure to obtain MSNs with larger pores [18]. For example, Kim et al. [34] have successfully synthesized monodispersed mesoporous silica nanoparticles (MMSN) with the pore size of 17.4 nm, which presented superior loading capacity for plasmids compared with conventional MSNs with small pores (~2 nm). The influence of pores arrangement in cargoes loading has been evaluated by some researchers as well. Heikkilä et al. [113] demonstrated that three materials with different pore systems (TUD-1, MCM-41, and SBA-15) displayed similar drug loading capacity for oral drug delivery using Ibuprofen as the model drug. The drug feeding ratio is also a critical factor that has a profound impact on drug encapsulation efficiency of MSNs. The improvement of drug feeding ratio would result in higher loading capacity. As reported by Palanikumar et al. [112], the Dox loading efficiency improved two folds when the DOX concentration increased from 2.5 mg/mL to 7.5 mg/mL.

5. Biomedical application of MSNs

As a typical nanocarrier, MSNs possess tailorable mesoporous structure, easily functionalized surface as well as superior drug delivery manner. These properties endow them with unique advantages to encapsulate a variety of therapeutic agents and deliver these agents to the desired location to be widely used in various fields for different applications. This section will focus on the potential application of MSNs as nanocarrier for drug delivery.

5.1 Deliver fragile molecules

Some molecules, such as gene, peptide and protein, which achieve remarkable anticancer effects *in vitro*, however, the desired efficiency is not displayed *in vivo* due to their instability and easy degradation [114-117]. MSNs possess a strong inorganic oxide framework and the interior core, providing room to accommodate therapeutic molecular and protect them from harmful denaturing chemicals and conditions, which are extremely beneficial for delivery of fragile molecules.

Gene therapy has gained wide attention in cancer therapy [118, 119]. The naked gene will be digested by the nucleases in the blood serum when injected into the body, which limits the effectiveness *in vivo*. As a versatile carrier, MSNs have been introduced in this field. Pan et al. [116] reported a DDS coloaded with Bcl-2 siRNA and DOX. The surface of the MSNs was modified with a zeolitic imidazole framework-8 (ZIF-8) film to convert the charge of MSNs from negative to positive. This modification obviously improved siRNA loading capacity ascribing to the enhanced electrostatic interactions between nanocarriers and RNAs. This nanoparticle presented significantly increased anticancer efficacy for MCF-7/ADR and SKOV-3/ADR *in vivo*, providing a promising approach to overcome multiple drug resistance. In another study, Xue et al [120]. used HMSNs as vehicles for the delivery of miR-375 and DOX. This strategy promoted the internalization of DOX and inhibited the cell viability of both HepG2/ADR cells and HCC cells. The enhanced antitumor activity was further confirmed on HCC tumor bearing mice. So, it has been fully proved that MSNs-based nanocarriers could be feasible for gene delivery.

A large amount of pharmaceutical proteins has entered the preclinical or clinical

stage over the past decades. The complex structure of proteins confers them not only specific therapeutic effects but also pose a great challenge hampering their wide application. An alternative drug carrier needs to be developed to address the limitations of therapeutic proteins, such as short half-life, frangibility to physical and chemical stimulation, and poor bioavailability. MSNs are particularly useful in the delivery of proteins due to their unique structure. Cytochrome c is an apoptosis-inducing, membrane impermeable protein. Slowing et al. [121] prepared an MCM-41 type of MSNs with an average pore diameter (5.4 nm) to delivery cytochrome c, and demonstrated that it could be internalized by living HeLa cells. Moreover, cytochrome c remained active after its release from MSNs and induced apoptosis in Hela cells.

5.2 Stimuli-responsive smart nanocarrier

MSNs can be used in tissue targeted drug delivery due to the drug release at a specific time or location though integration of specific targeting ligands and stimuli-responsive components into the MSNs-based nanocarrier. The stimuli can be of two types, that is, internal and external stimuli. The internal stimuli includes pH, redox potential, and enzymes, while the photo irradiation, temperature, and magnetic field are the external stimuli [93, 122, 123].

5.2.1 pH-response

The pH of cancer tissue (<6.8) is lower than that in normal tissue (7.4) [117]. Thus, the difference in pH values could be useful in designing DDS using various materials. Meng and co-workers prepared a β-cyclodextrin capped MSNs DDS [122]. In which, the aromatic amines stalks were attached covalently to the nanopore opening, and β-cyclodextrin were introduced to encircle the stalks for blocking the nanopore openings and trap the included cargo molecules. The noncovalent bonding interaction between β-cyclodextrin and stalks would be weakened under endosomal acidic conditions due to the protonation of the aromatic amines, leading to β-cyclodextrin cap release and drug diffusion from the nanopore [122]. Wang et al. [123] built a controlled drug delivery nanoplatform to co-deliver microRNA-31 (miR-31) and DOX, which was loaded into the pore via disulfide bond, subsequently miR-31 and branched polyethyleneimine (PEI) were sequentially coated on MSNs surface through layer-by-

layer method. Finally, hyaluronic acid (HA) was grafted on PEI through covalent bond. In acidic and redox environment of tumors, the constructed nanocarrier can realize release of miR-31 and DOX sequentially. This combination can exert synergistic effects and increase anticancer efficacy (Fig. 6).

5.2.2 Redox-response

Like the pH responsive DDS, the redox actuation takes advantage of intracellular conditions due to the different glutathione (GSH) expression levels between cancer cells and normal cells. Previous studies have shown that the concentration of GSH in extracellular space (2 μM) is much lower than that in cytosol (10 mM). Furthermore, the expression level of GSH in tumor cells was several times higher than that in the normal cells [124]. Kim et al. reported the GSH stimulus-responsive MSNs, in which β-cyclodextrin was covalently attached to the particle surface via disulfide bonds. *In vitro* study revealed that the addition of GSH could remove the gatekeeper through the cleavage of the disulfide stalk moiety and then release the guest anticancer drug in the pore [125].

5.2.3 Enzymes-response

It is commonly accepted that matrix metalloproteinases (MMPs) are overexpressed in tumor microenvironment, and are involved in the process of tumor invasion and metastasis [126]. Based on this phenomenon, Zhang et al. designed a targeted and MMP-actuatable DDS [127]. MSNs was firstly coated with β-cyclodextrin through a tumor environment-triggered cleavable disulfide bond followed by decoration with a peptide sequence containing RGD motif and MMPs' substrate peptide PLGVR through hosting guest interaction [127]. Then, a biocompatible and degradable poly (aspartic acid) (PASP) was covalently coupled with azide moiety in PLGVR via click chemistry to form a protection layer, which could prevent the nanoparticles from being up taken by normal cells [127]. This would guarantee the MMPs caused hydrolysis of PLGVR when the nanoparticles arrived at the MMP-rich tumor cells, accelerating the internalization due to the exposed targeting RGD motif (Fig. 7). Subsequently, the high level of GSH in cytosol removes the gatekeeper of β-cyclodextrin leading to the cleavage of the disulfide linkers and drug release intracellularly [127].

5.2.4 Other stimuli-response

Apart from the pH/redox/enzymes -responsive drug release strategies based on the inherent characteristic of tumor, the external stimulus responsive release has also become a promising strategy, which takes full advantages of 'specific or specified' location, intensity and exposure of external stimulus. Poly-N-isoproplyacrylamide (PNiPAM) is one of the most investigated temperature-sensitive polymers, which can undergo a hydrophilic-hydrophobic transition at the lower critical solution temperature (LCST) at approximately 32°C [117]. Shi and co-workers developed a thermo-switchable polymer-masked mesoporous silica drug-nanocarrier by modifying PNiPAM on the surface of MSNs. When temperature was below LCST, the polymer chain tightly wrapped around the surface of the particle and blocked the pore to prevent drug leakages. Once the temperature rises above LCST, the polymer chains become hydrophobic and shrunk within the mesopores, which leads to the opening of the pore outlets [128]. Kim and co-workers prepared o-nitrobenzyl ester functionalized MSNs with light responsive behavior. The photocleavable linker and the β-cyclodextrin were introduced onto the surface of MSNs by click chemistry. Upon UV irradiation, the photolysis of o-nitrobenzyl ester lead to the removal of β-cyclodextrin nanocaps resulting in the release of guest molecules [129].

5.3 Sequential delivery

MSNs possess a large specific surface area and pore volume; MSNs can be assigned to sequentially delivery different kind of cargos with huge discrepancy. Several large therapeutic biomolecules, including proteins and RNA, can be anchored to the surface of MSNs via electrostatic interactions, while small molecules drugs loading inside the pores [130, 131]. In this type of smart nanocarrier, the biological molecules and small molecules are spatially separated from each other on the surface and in the inner mesopores of MSNs, respectively, allowing sequential and time-interleaving drug release, which is critical in maximizing their synergistic effects [118, 132, 133].

Sun et al. developed a core-shell hierarchical mesostructured silica nanoparticle (H-MSNs), in which there are large and small mesopores present separately in the shell

and core, respectively. The fabricated H-MSNs can effectively protect the siRNA from nuclease degradation and promote cellular uptake in tumor. During the therapeutic process, H-MSNs could sequentially release the siRNA and DOX payloads in the reductive tumor microenvironment. The siRNA in the shell of MSNs was initially released to suppress the P-gp expression for pre-inhibition of multiply drug resistance, and then the DOX in the core was subsequently released to kill cancer cells [134]. Therefore, by virtue of the unique core-shell hierarchical structure, HMSNs realized a sequential release of therapeutic agents loaded in different space for further synergetic efficacy. In another work, mitochondria-targeted and intramitochondrial microenvironment-responsive prodrug, FeCO-TPP, was wrapped in hyaluronic acid coated MSNs. This smart MSNs can control the release of CO in a step-by-step disassembly way in tumor sites (Fig. 8) [132].

5.4 Diagnostic and theranostic

Early diagnosis to gain physiological information about healthy and pathological tissues is important for the treatment of various disease. During the past decades, a variety of imaging techniques have been successfully exploited for early detection, diagnosis, and personalized treatment of disease. Magnetic Resonance Imaging (MRI) is one of the most representative *in vivo* imaging technologies due to its intrinsic merits of high spatial and temporal resolution. A series of MRI contrast agents have been successfully used in clinic. Recently, nanoparticle-based MRI contrast agents have been developed to further enhance the detection sensitivity with the accumulation of a large number of paramagnetic complexes in a single nanocarrier [135, 136]. MSNs based nanocarriers offer a promising option for delivery of MRI contrast agents owing to the high surface area/pore volume [136]. Several paramagnetic complexes have been incorporated into MSNs to produce stable MRI contrast agents with enhanced signal [135-138]. For example, Taylor and co-workers applied Gd-Si-DTTA complex for grafting traditional MSNs via a covalent complexation inside the mesopores to obtain a MSN-based MRI contrast agent (MSN-Gd) [138]. The DBA/1J mouse *in vivo* imaging also demonstrated the enhanced signal of MSN-Gd in aorta and liver, functioning as a promising intravascular and liver MRI contrast agent.

Photoacoustic (PA) imaging is a burgeoning imaging modality combining the

properties of light and sound, which provides deep tissue penetration and refined spatial resolution for diagnosis [139]. Indocyanine green (ICG) is one of the common PA imaging agents approved by FDA for human application. However, the *in vivo* application is restricted by limited photostability and fast clearance under physiological conditions [140]. MSNs possess a rigid nanostructure, which can protect ICG from photolytic and/or thermal degradation [140]. Additionally, a high payload of ICG incorporated within a single MSNs can enhance the optical absorption to improve the quality of imaging [139]. Ferrauto et al. [141] developed an ICG encapsulated and PEGlylated MSNs based PA imaging probe to increase both the stability and photoacoustic effect of ICG. The resulted ICG-MSN probe showed better biocompatibility and enhanced photostability *in vivo* imaging. Remarkably, the photoacoustic imaging efficiency of ICG-MSN was four times higher than that of free ICG.

The smart integration of different functional moieties into one system has become the requirement of times. Over the past decades, tremendous efforts have been devoted to designing a multifunctional nanoparticles (NPs) that combine drug molecules and diagnostic agents in the same platform. MSNs possess unique three well-defined domains (the silica framework, the internal pore walls, and the outer surface) that could be independently exploited or functionalized [135]. Luminescent materials and magnetic materials such as $NaYF_4$:Yb^{3+}/Er^{3+}, Au, Fe_3O_4, organic dye fluorescein isothiocyanates can be included in the MSNs framework or covalently conjugated to the MSNs surface while the therapy agents can be loaded inside MSNs pores [135, 142]. This type of multifunctional nanocarrier allows the collection of diagnostic information and provides therapeutic results simultaneously (Fig. 9) [143]. Ferrauto et al. [144] prepared a MSN-based theranostic nanosystem, in which the anticancer drug mitoxantrone was loaded into MSNs pores, while ICG attaching to the surface of the amino functionalized MSNs. This innovative theranostic nanosystem showed 1.75 times enhanced photoacoustic efficiency with respect to free ICG. In particular, the drug delivery and release behavior of this theranostic nanoprobes could be directly monitored by using photoacoustic imaging.

MSNs are the promising platform for diagnostic and theranostic use due to their

unique structure. However, it should be noted that there is still much work to improve the bio-imaging and theranostic capabilities of MSNs. Nanoparticle with small particle size (<50 nm) as well as high colloidal stability are known to show higher imaging efficiency due to their sufficiently long circulation time in the blood. However, the size of multifunctional MSNs is usually large than 100 nm. In addition, when compared to other inorganic nanoparticles (e.g., iron oxide, gold, and cerium oxide NPs), the blood circulation time of MSNs is very limited [136]. Therefore, more work needs to be undertaken to develop smaller MSNs with enhanced colloidal stability and blood retention for diagnostic and theranostic application.

6. Envisioning clinical translation

Silica-based nanoparticles hold great promise to be develop as drug carrier arming toward clinical application due to that silica has been used as a food additive in various commercial products [19]. Recently, several silica-based nanoparticles have received the FDA approved for clinical trials [11, 145]. For instance, the dye-doped fluorescent silica C-dot have been approved for clinical stage I for molecular imaging of cancer [11]. In another case, silica-based nanomaterials (NANOM-FIM) is entering clinical trials, and being used in cardiac TE with good biocompatibility and high efficiency as therapeutic biomolecules [145]. The trials' outcomes have displayed lower risk of cardiovascular death in humans with the NPs-treated group and no apparent toxicity has been observed [146]. In addition, the plasmonic photothermal therapy of atherosclerosis with NANOM-FIM has shown high safety , decreased rate of mortality and major adverse cardiovascular events when compared with the clinically used stent XIENCE V [147]. Currently, there is still no reported clinical or in clinical trial application of MSNs, however, the promising results of regular silica-based nanoparticles give us the confidence about future of MSNs, especially in cancer therapy.

7. Conclusions and Outlook

Nanotechnology has made considerable strides over the past decades and provided an opportunity for the development of innovative and multifunctional nanocarriers. MSNs have gained wide attention owing to their unparalleled advantages for the diagnosis and treatment of diseases. As a promising nanocarrier, MSNs possess large

and tunable pore size for cargoes loading, easily functional surface for target delivery, and stable property for its safe use. In addition, MSNs with versatile modification can overcome the limitations of regular therapeutics such as low internalization and undesired side effects.

Although substantial amount of work has been carried out to design and develop advanced nano-DDS based on MSN, some obstacles remain ahead of the translation into clinic. The bio-safety evaluation is the very first issue to be considered for the therapeutic and diagnostic applications of MSNs [10]. The validity of treatment effect within the scope of bio-safety still lacks adequate evidence due to the difference between small-animal models and human. In order to deal with the complicated environment and biological process in the body, the physical and chemical properties of MSNs as well as their *in vivo* biodistribution and metabolic behaviors must be clearly defined. In most cases, the biodegradation of MSNs is a gradual process, and the continuous administration for required drug concentration may lead to the accumulation of NPs in the body and result in undesired long-term side. Therefore, the focus on bio-safety of MSNs should be shifted from acute toxicity to chronic influence because of the uncertainty of degradation.

From the perspective of production, it is hard to fabricate MSNs with uniform characteristics and reliable quality in the large scale due to technical restrictions [18]. Several groups have successfully synthesized monodisperse nonaggregate MSNs at the kilogram scale (0.1-0.5 kg) [148, 149]. However, the transformation of MSNs towards industrial production is still a long way off.

Taken together, MSNs hold great promise for the future of drug delivery nanocarriers. However, there is still a long way to go for the development of simple, stable, cost-effective, and scalable methods to synthesize MSNs with satisfactory therapeutic efficiency as well as improved biocompatibility.

Conflicts of interest

There are no conflicts to declare.

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