Mesoporous organosilica nanoparticles: Degradation strategies and application in tumor therapy

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Abstract
Biodegradation is a crucial issue for silica-based mesoporous nanoparticles that is related to the biosafety in tumor therapy. Nowadays, mesoporous silica nanoparticles (MSNs) have been intensively developed to construct multifunctional nanosystems for tumor therapy due to their biocompatibility, high drug loading capacity and easy functionalization; however, their biodegradation is relatively slow and still under debate. To improve the biodegradability of silica-based mesoporous nanoparticles, a simple organic-inorganic hybridization strategy to synthesize mesoporous organosilica nanoparticles (MONs) has been successfully developed. By hybridizing the silica framework (\(-\text{Si-O-Si}\)–) with stimuli-sensitive organic moieties to form organic-inorganic network (\(-\text{Si-R-Si}\)–, R: organic moiety), when exposed to the stimuli environment, the breakdown of the organic-inorganic network could accelerate the degradation of MONs, which is great promising for MONs as a multifunctional therapeutic nanoplatform in tumor therapy. This review aims to summarize the degradation strategies for MONs to improve biodegradability in recent years, and highlight the potential applications of MONs in tumor therapy. Finally, we also discuss the challenges of MONs for tumor therapy in future clinical translation.

KEYWORDS
biodegradation, hybridization, mesoporous organosilica nanoparticles, tumor therapy
1 INTRODUCTION

Malignant tumor is a serious threat to human health. Nowadays, chemotherapy with toxic antitumor drugs is still a common therapeutic modality in tumor therapy. However, direct administration of free antitumor drugs shows a low therapeutic efficacy and causes serious side effects on normal cells/tissues.1–2 To overcome these drawbacks, one of the most attractive strategies is to develop nanocarriers for antitumor drug delivery, which could achieve targeted delivery and controlled drug release, and thereby enhance the therapeutic efficacy and minimize the side effects.3–6 Furthermore, the diagnostic agents/probes and antitumor drugs/therapeutic agents are coloaded in nanocarriers, which could make it possible to integrate with diagnosis and therapy or achieve an imaging-guided tumor therapy.7–10

To date, a variety of materials (liposomes, polymers, gold, Fe₃O₄, mesoporous silica, upconversion nanoparticles, and metal-organic frameworks)11–15 have been developed to construct nanocarriers for delivering various therapeutic agents like antitumor drugs, inhibitors, proteins, nucleic acids, and even probes in tumor therapy.16–18 Among them, mesoporous silica nanoparticles (MSNs) have achieved increasing attention in biomedicine for tumor therapy due to their biocompatibility, mesoporous structure with large specific surface area and pore volume, and easy surface functionalization, which facilitate to deliver guest cargos.19,20 For example, Rao et al proposed to construct a MSNs-based nanoplatorm as a reactive oxygen species (ROS)-responsive magnetic resonance (MR) imaging-guided photodynamic chemotherapeutic agent (DOX-R-MSN). Gadolinium (Gd)-DOTA complex, chlorin e6 (Ce6), and DOX were utilized as a ROS-responsive gatekeeper, a ROS generator and a chemotherapeutic drug, respectively.21 When irradiated by 660 nm laser, the 1O₂ was produced for photodynamic therapy, and the DOX releaseratewasacceleratedtoenhancechemotherapeutic efficacy. Simultaneously, the Gd ions from Gd-DOTA gatekeepers could be a contrast agent for MR imaging. However, the biodegradability of MSNs is still under debate, because the slow biodegradation might cause the potential accumulation risk when intravenous injection of MSNs as nanocarriers, and thereby give rise to the trouble of biosafety issue.22

Generally, MSNs are composed of the stable pore wall frameworks containing –Si–O–Si– network and –Si–OH surfaces. The –Si–O–Si– bond can be slowly hydrolyzed into –Si–OH in aqueous media, but the degradation rate is very low. In fact, the degradation behavior of MSNs is often dependent on many factors, such as the framework condensation degree (the content of –Si–O–Si– bonds), particle size, specific surface area, and surface functional groups. For example, He et al reported that MSNs had a three-stage degradation behavior in simulated body fluid (SBF).23 Both low specific surface area and high concentration of MSNs decreased the degradation rate. On the other hand, the calcined MSNs exhibited significantly low degradation rate compared to the MSNs that removed the surfactants by extraction, which was attributed to the higher condensation degree of -Si-O-Si- network in the MSNs framework after calcination.24 Stephanie et al found that surface functionalization could alter the degradation kinetics of MSNs. For example, the aminated MSNs exhibited a better degradation behavior than the carboxylated MSNs and pure MSNs.24 Similarly, Bein et al investigated the degradation behavior of PEGylated MSNs with different PEG-chain length, and found that the PEGylation significantly decreased the degradation rate of MSNs in SBF, and the longer PEG chain could slow down the degradation rate.25 Hao et al investigated the effect of MSNs morphology on the degradation behavior, and found that MSNs with different aspect ratios showed different degradation rate under the same condition; that is, the spherical MSNs exhibited much rapider degradation rate than rod-like MSNs.26 However, the degradation rate of MSNs mainly depends on the framework condensation degree. Hence, a great deal of effort has been made to construct the pore wall framework of MSNs with biodegradable network for improving the biodegradability.

Inspired by the stimuli-triggered degradation of organic moieties, the organic-inorganic hybridization within the silica framework of MSNs to form mesoporous organosilica nanoparticles (MONs) could regulate the structure stability of the silica frameworks, and thereby promote the biodegradation. Fortunately, the synthesis of MONs with organic moieties directly hybridized in the silica framework by using the organo-bridged alkoxy silanes (R'O)₃Si–R–Si(OR')₃ (R: organic moiety) has been well developed since the reports on the organic-inorganic hybrid mesoporous materials in 1999.27–29 To date, various organo-bridged alkoxy silanes have been used to synthesize MONs, such as bis[(triethoxysilyl)propyl]tetrasulfide (BTETS, R: –(CH₂)₃–S–S–S–(CH₂)₃–), bis[(triethoxysilyl)propyl] disulfide (BTEDS, R: –(CH₂)₃–S–S–(CH₂)₃–), bis[triethoxysilyl]phenylene (BTEP, R: –C₆H₄–), bis[triethoxysilyl] ethylene (BTETEE, R: –CH₂–CH₂–), bis[triethoxysilyl] ethane (BTEE, R: –CH₂–CH₂–), N,N'-bis[(triethoxysilyl) propyl]oxamide (BTEO, R: –(CH₂)₂–CONH₂–CONH₂–(CH₂)₃–), bis[(triethoxysilyl)propyl]diselenide (BTESDSe, R: –(CH₂)₃–Se–Se–(CH₂)₃–), and bis[triethoxysilyl] biphenyl (BTEBP, R: –C₆H₄–C₆H₄–).30–33 Among them, many organic moieties of organo-bridged alkoxy silanes could be triggered to degrade due to the specific stimuli like redox, pH and enzymes in physiological environment. For example, disulfide bond and tetrasulfide bond can

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specifically respond to the reducing microenvironment in tumor cells or tumor tissues. Thus, the direct hybridization of thioether moiety into the silica framework makes MONs realize the redox-triggered biodegradation in tumor microenvironment (TME), which would be highly promising for MONs as nanocarriers in biomedicine.

Hence, the development of MONs could overcome the biodegradation issue, and thereby enhance the biosafety of silica-based mesoporous nanoparticles, which further advance silica-based mesoporous nanoparticles to be nanocarriers for application in biomedicine. This article reviews several important hybridization synthesis strategies for biodegradable MONs, mainly including the redox-, pH-, and enzyme-triggered degradation behaviors, and further summarizes the recent achievements and progress in biodegradable MONs-based nanoplatforms for tumor therapy. Finally, the conclusion and prospects on the future development of biodegradable MONs for tumor therapy are discussed.

2 SYNTHESIS STRATEGIES FOR BIODEGRADABLE MONS

It is well known that the stable silica framework determines the slow degradation rate of MSNs in aqueous media due to the slow hydrolysis of the –Si–O–Si– bonds. To accelerate the degradation rate of MSNs, one of the most efficient strategies was proposed to regulate the framework stability of MSNs by introducing various organic-inorganic moieties into the silica frameworks. Among them, the introduction of metal ions (e.g., M = Ca, Fe, Mn, Mg, Cu, etc) into the MSNs framework could accelerate the degradation to some extent, because the hydrolysis of the –M–O–M– bonds is relatively easy compared with the –Si–O–Si– bonds. However, the amount of metal ions introduced in the MSNs framework is limited, and the introduction of more metal ions into the MSNs framework could cause the collapse of mesoporous structure.

Generally, organic-inorganic hybridized silica frameworks can be achieved by cocondensation of tetraethoxysilane (TEOS)/tetramethoxysilane (TMOS) and organo-bridged alkoxysilanes via a sol–gel process. The hydrolysis of organo-bridged alkoxysilanes can form the Si–OH groups at both ends of the bridged molecules, and subsequent condensation process can induce the formation of –Si–O–Si– bonds that connect the hydrolyzed organo-bridged molecules together. Nowadays, a variety of organo-bridged alkoxysilanes have been developed, which offer the candidates to be hybridized into the MSNs framework associated with TEOS/TMOS to form the –Si–R–Si– bonds. Furthermore, mesoporous structure still can be achieved even at a high ratio of organo-bridged alkoxysilanes to TEOS/TMOS during the synthesis process. Hence, when organic moieties with stimuli-triggered degradation behavior in organo-bridged alkoxysilanes are hybridized into the MSNs framework to form MONs, the degradation rate could be regulated in a wide range. Depending on the composition of the organic-inorganic hybridized framework, the MONs is able to respond effectively to different microenvironments, which facilitate to achieve a controllable degradation behavior.

To date, various organo-bridged alkoxysilanes that contains organic moieties with stimuli-triggered degradation behavior have been utilized to synthesize biodegradable MONs, such as BTEDS, BTETS, BTEO, and BTEDSe. Typically, the organic moieties in these organo-bridged alkoxysilanes are sensitive to the stimuli like redox, pH, and enzyme. Biodegradable MONs is often classified into MONs with redox-triggered degradation, MONs with pH-triggered degradation, MONs with enzyme-triggered degradation and MONs with multiple-triggered degradation according to the degradation mechanisms of organic moieties in MONs. Some typical synthesis strategies for biodegradable MONs based on different degradation mechanisms are summarized in Table 1.

2.1 MONs with redox-triggered degradation

It is well known that a high glutathione (GSH) level in TME induces a reducing environment. Interestingly, some organic moieties are sensitive to the reducing environment that could cause the cleavage of chemical bonds, such as disulfide bonds, thereby result in the structure collapse and further macroscopically degradation. Hence, inspired by such mechanism, the hybridization of the redox-sensitive organic moieties into the silica frameworks has been proposed to develop MONs with redox-triggered degradation.

Chen et al first reported on a simple and controllable chemical homology principle to synthesize hollow MONs with multiple functional organic moieties in the silica frameworks. As an example, BTETS with thioether group and BTEP with phenylene group were cohydrolyzed and cocondensed with TEOS to synthesize a unique dual-hybridized hollow MONs. Hollow MONs exhibited the time-dependent biodegradation behavior in SBF at a GSH concentration of 10 mM due to the GSH-sensitive thioether groups hybridized in the silica frameworks. The GSH-triggered degradation was also confirmed by the drug release behavior from hollow MONs; that is, 69% of DOX was released from hollow MONs in PBS with a GSH concentration of 10 mM for one day, but only 21.8% of DOX was released in PBS without GSH. It was speculated that the
| Biodegradation strategy | Synthesis method | Structure-directing agent | Catalyst | Silica sources | Characteristics | Ref. |
|-------------------------|-----------------|---------------------------|----------|---------------|----------------|------|
| 1 Redox-triggered       | CHEMICAL HOMOLOGY PRINCIPLE | CTAC | TEA | BTEDS; TEOS | Less than 50 nm in particle size; physiologically active disulfide bond was directly incorporated into silica framework | 22 |
|                        | CHEMICAL HOMOLOGY PRINCIPLE | CTAB | NH₃·H₂O | BTETS; BTEP; TEOS | Multiple organic groups incorporated within the organosilica framework | 33 |
|                        | MICELLE/PRECURSOR COTEMPLATING ASSEMBLY STRATEGY | CTAC | TEA | BTETS; TEOS | Propose micelle/precursor cotemplating assembly strategy | 32 |
| 2 pH-triggered          | SOLUTION SYNTHESIS | Ethanol | NH₃·H₂O | 3-isocyanatopropyltriethoxysilane (ICPTES–sorbitol); TEOS | Unique hydrolysable silica nanoparticles by the incorporation of carbamate linkages into silica matrix | 46 |
|                        | SOFT-TEMPLATING | CTAC/CTAB | TEA/NH₃·H₂O | BTEDS/BTETS/BTEE; TEOS | The large-scale fabrication of monodispersed MONs with controllable nanostructure, composition, and morphology | 40 |
|                        | ONE-POT SYNTHESIS | Sodium salicylate; CTAB | TEA | BTETS; TEOS | The different degradation effect with different pore structure | 38 |
| 3 Enzyme-triggered      | SOL-GEL REACTION | CTAB | TEA | Oxalyl chloride; APTES | Enzyme-triggered MONs based on nature-inspired oxamide bridges in organosilica framework | 52 |
|                        | SOL-GEL REACTION | CTAB | NaOH | 1,4-bis(triethoxysilyl) benzene; BTEO | Biodegradable oxamide-phenylene bridged-MONs in response to trypsin proteins | 31 |
| 4 Multiple-triggered    | SOL-GEL REACTION | CTAC | TEA | Cystine; BTEs; TEOS | A self-fluorescent and pH/glutathione dual responsive nanocarrier | 54 |
|                        | MODIFIED SOL–GEL METHOD | Ethyltrimethylammonium tosylate | TEA | BTESDSe; TEOS | Dual responsive MONs with diselenide-bond in silica framework | 30 |
GSH-triggered degradation of hollow MONs contributed to the relatively rapid drug release.\(^\text{33}\)

To simplify the synthesis process and optimize the mesopore size of MONs with thioether moieties, Wu et al proposed a facile micelle/precursor coassembly strategy to synthesize MONs with ultrasmall particle size.\(^\text{32}\) As shown in Figure 1A, cetyltrimethylammonium chloride (CTAC) and triethanolamine (TEA) were used as the structure-directing agent and basic catalyst, respectively. BTETS was selected to cohydrolyze and cocondense with TEOS to synthesize organic-inorganic hybrid MONs. Because the hydrolysis and condensation rates of BTETS are much lower than that of TEOS,\(^\text{39}\) the as-hydrolyzed BTETS molecules with hydrophobic \(-(\text{CH}_2)_3\text{S-S-S-S-CH}_2\text{)}_3\) chains can penetrate the hydrophobic domains of the CTAC micelles, which induce the enlarged micelles, thereby form much enlarged pore sizes of MONs correspondingly. Interestingly, the mesopore sizes of small MONs (≈30 nm) can be simply regulated from 6 nm to 13 nm by varying the amount of organo-bridged alkoxy silane or TEA catalyst (Figure 1B).\(^\text{32}\)

To control the morphology of MONs with thioether moieties, Yu et al reported the synthesis of spherical MONs by using CTAC and TEA as the structure-directing agent and basic catalyst, and rod-like MONs by using CTAB and triethanolamine (TEA) as the structure-directing agent and basic catalyst.\(^\text{40}\) These hybrid MONs with less than 50 nm in particle size exhibited GSH-sensitive biodegradation behavior, and the biodegradation rate can be regulated by changing the ratio of thioether moiety in the silica framework. More importantly, the GSH-sensitive biodegradation of MONs induced the concurrent GSH-triggered anticancer drug release from MONs.\(^\text{40}\)

Furthermore, Yang et al investigated the effect of pore structure on the GSH-sensitive degradation behavior of MONs with thioether moieties.\(^\text{38}\) They proposed to use sodium salicylate and CTAB as the structure directing agents, and BTETS and TEOS as silica sources to synthesize dendritic MONs (DMONs), and the large-pore DMONs and small-pore MONs could be achieved by changing the amount of sodium salicylate. Interestingly, a unique pore structure-dependent GSH-sensitive degradation behavior was observed. For normal cells with relatively low intracellular GSH level, the degradation rates of both types of nanoparticles were similar. However, for tumor cells with relatively high intracellular GSH concentration, large-pore DMONs exhibited a much faster degradation rate than small-pore MONs.

Moreover, the hybridization of disulfide (–S–S–) bonds in the –Si–O–Si– network also can improve the degradation of MONs. Huang et al synthesized hollow MONs with hybridizing –S–S– bonds into the silica frameworks based on a “chemical homology” mechanism.\(^\text{22}\) The hybridized silica frameworks with disulfide-bridged moieties were coated on MSNs by the hydrolysis and cocondensation of TEOS and BTEDS, and hollow MONs were achieved after etching the MSNs cores with ammonia solution (Figure 2A). The biodegradation behavior of hollow MONs in SBF containing GSH demonstrated that the GSH-contained SBF could initiate the biodegradation of hollow

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**Figure 1** (A) Schematic illustration of the organic–inorganic hybrid MONs with thioether moiety. (B) TEM images of MSNs and MONs synthesized with different TEA and BTETS amounts: (a–c) MSNs synthesized with TEOS and different TEA amounts (a: 0.1 g, b: 0.2 g, and c: 0.8 g); (d–f) MONs synthesized with 0.65 g of BTETS and different TEA amounts (d: 0.4 g, e: 0.6 g, and f: 0.8 g); (g–i) MONs synthesized with 1.3 g of BTETS and different TEA amounts (g: 0.4 g, h: 0.6 g, and i: 0.8 g). Reprinted with permission.\(^\text{32}\) Copyright 2014, Wiley-VCH.
MONs, and high GSH concentration could induce more significant biodegradation (Figure 2B). It was attributed to the sensitiveness of disulfide bonds within the silica frameworks of hollow MONs to the reducing GSH, resulting in the breakage of the frameworks, thereby accelerating the biodegradation. After endocytosis of hollow MONs by cancer cells, bio-TEM observations showed that a large number of hollow MONs were located in the cytoplasm of cells in 1-day culture, but the nanoparticle collapse and dissolution behavior were occurred with the prolonged culture duration, and only very few hollow MONs with collapsed nanostructures were observable after 7 days culture (Figure 2C). It confirmed the easy biodegradation behavior of hollow MONs intracellularly due to the reducing microenvironment in cancer cells.22

In addition, Du et al synthesized disulfide-hybridized mesoporous organosilica nanobowls by one-pot dissolution and growth method,41 and several other groups also demonstrated the synthesis of multi-hybrid MONs with tetrasulfide bonds. Due to the redox sensitivity of the disulfide and tetrasulfide bonds, these above MONs possessed GSH-sensitive degradation behavior for potential application in tumor therapy.42–44

2.2 MONs with pH-triggered degradation

It is considered that the pH value in TME (< 6.8) is usually lower than that of normal cells/tissues (~7.4). For example, the pH value in the tumor cell nucleus is 5–6.5, and the lysosome is only 4.5-5.37 In fact, a variety of organic bonds like amide bonds could be cleaved in acidic or weakly acidic environment. It can be imagined that the structures containing acid-sensitive bonds could be destroyed when they are exposed to acidic environment, and thereby accelerate the degradation. Hence, inspired by such mechanism, the hybridization of the pH-sensitive organic moieties into the silica frameworks could endow the MONs with pH-triggered degradation.

Gao et al first reported hollow MONs with pH-triggered degradation based on the hybridization of sorbitol moiety into the silica framework.45 A sorbitol-bridged alkoxysilane was synthesized by grafting of deliquescent sorbitol to 3-isocyanatopropyltriethoxysilane (ICPTES), and the pH-sensitive hollow MONs were obtained by the hydrolysis and condensation of the mixture containing ICPTES-sorbitol bridged alkoxysilane and TEOS. The results showed that hollow MONs containing sorbitol moiety could occur the hydrolysis at neutral pH and degrade after 3 months, but they were observed to be broken into irregularly spherical pieces only after 3 weeks at pH 4. It indicates that the degradation of sorbitol-hybridized hollow MONs could be accelerated in an acidic environment.

Yang et al reported a novel pH-sensitive biodegradable hollow MONs (PBHMONs) based on the pH-sensitive cleavable bonds containing acetal moieties.46 Here, a pH-sensitive acetal-bridged alkoxysilane was prepared, and then mixed with TEOS to form a silica source.
Biodegradable PBHMONs was synthesized by using CTAC as a structure directing agent and silica nanoparticle as a hard template. The results confirmed the pH-triggered degradation behavior for PBHMONs due to the cleavage of acetal moieties in an acidic environment. Furthermore, PBHMONs could biodegrade rapidly in acidic tumor tissues, leading to a rapid excretion and contributing to the potential clinical translation of such system. Similar with the pH-sensitive cleavage mechanism of organic bonds, Zhang et al prepared a histidine-bridged alkoxysilane and mixed with TEOS as a silica source, which was applied to synthesize a pH-sensitive biodegradable MONs by using P123 as a structure directing agent. The results showed that the histidine-hybridized MONs possessed pH-triggered degradation behavior due to the cleavage of histidine moieties in acidic environment, which contributed to the relatively rapid drug release from MONs.

Studies demonstrated that the imine groups are highly reactive towards hydrolysis in aqueous solution, and the imine groups could be introduced into the silica network via a simple hydrolysis and condensation process of the imine-bridged alkoxysilane and TEOS. Inspired by these ideas, Travaglini et al proposed to synthesize the diimine-bridged MONs for enhanced degradation in acidic aqueous solution with acidic pH values. Here, the diimine linker was prepared by the reaction of terephthaldehyde with (3-aminopropyl)-triethoxysilane in dry ethanol under N₂ atmosphere, and the diimine-bridged MONs were synthesized by cocondensation of the diimine linker with TEOS by using CTAB as a structure directing agent. Interestingly, the diimine-bridged MONs could be highly degradable, and the enhanced degradation occurred with decreasing the pH value of solution.

### 2.3 MONs with enzyme-triggered degradation

Besides the above mentioned redox and acidic characteristics in TME, some enzymes in TME could also be the endogenous stimuli to trigger the cleavage of some chemical molecules or bonds, which also offer the possibility to construct biodegradable MONs.

The carbamate, ester and amide linkers are enzymatically cleavable, which are often applied for constructing nanoparticles with enzyme-triggered degradation. Fatieiev et al reported biodegradable bridged silsesquioxane nanoparticles synthesized via a sol-gel reaction of an oxamide-bridged alkoxysilane inspired from the nature with the common enzymatically-catalyzed metabolism processes, and such bridged silsesquioxane nanoparticles could be degraded in the presence of trypsin enzymes in PBS, but did not degrade in PBS without enzymes. Inspired from the degradation mechanism of oxamide bonds by trypsin enzymes, Croissant et al proposed to synthesize biodegradable MONs based on oxamide-phenylene bridged alkoxysilanes. Here, the MONs with a particle size of 100 nm and a high surface area of 850 m²/g were synthesized from the cocondensation of 1,4-bis(triethoxysilyl)benzene and N,N'-bis((triethoxysilyl)propyl)oxamide with the help of CTAB as a structure directing agent, which allowed the homogeneous distribution of oxamide moieties in the nanoparticles (Figure 3A). After the incubation of MONs in PBS with the presence of trypsin proteins, the degradation of the MONs was confirmed, which was performed by the MONs changes that decreased from ca. 100 nm nanoparticles to 20 nm nanofragments after incubating for 24 hours and 48 hours, respectively (Figure 3B).

In addition, the peptides are often sensitive to the peptidase that can induce the degradation of the peptides. Thus, the hybridization of the peptides into the silica framework could also realize the enzyme-triggered degradation. Laura et al proposed to utilize a short peptide sequence as an organic moiety to hybridize into the silica framework by a self-assembling of tri-L-lysine (Lys3), 3-(triethoxysilylpropyl)isocyanate (TESPIC), TEOS and CTAB, resulting in the formation of the ring-shaped Lys3-hybridized nanoparticles (named NDs) that can be cleaved with peptidases in cancer cells. The results showed that the NDs changed the morphology after exposed to the solution containing enzymes, and the released Si content increased with increasing the enzyme amount, suggesting the occurrence of the enzyme-triggered degradation. In vitro cytotoxicity evaluation on the DOX-loaded nanoparticles (DOX-NDs) further confirmed the NDs degradation in Hela cells. Free DOX showed a limited killing effect that only decreased the cell viability to be 90% after 3 days. However, the DOX-NDs were able to decrease the cell viability in a dose-dependent manner, and decreased 70% of cell viability after 3 days, which indicated the high cell uptake of DOX-NDs, and the enzyme-triggered degradation of NDs induced intracellular drug release from DOX-NDs.

### 2.4 MONs with multiple-triggered degradation

As mentioned above, many types of stimuli in TME including GSH, pH and enzymes can be used to trigger the cleavages of chemical bonds in MONs for accelerating the degradation. It can be imagined that the construction of MONs with multiple cleavable organic moieties could offer the possibility of multiple-triggered degradation, and thereby facilitate to control the degradation of MONs.
Hu et al developed a dual-sensitive MONs by incorporating the acetaldehyde-modified-cystine (AMC) moieties into the mesoporous silica frameworks. Here, a Schiff base AMC contains a –S–S– bond and two –C = N– bonds, which could be cleaved in the presence of GSH and in an acidic medium, providing MONs with the capability for triggering pH and GSH dual-sensitive degradation. The results verified this hypothesis; that is, in an acidic environment containing a high concentration of GSH, the –S–S– and –C = N– bonds in the MONs were cleaved, resulting in the pH and GSH dual-triggered degradation. In this study, the drug release behavior in the presence of different pH values and different GSH concentrations were also investigated, and the results showed that the drug release rate increased with a higher GSH concentration at the same pH value, as well as with a lower pH value at the same GSH concentration. It could be attributed to the pH/GSH dual-sensitive degradability of the nanoparticles.

Selenium (Se) is an essential element in the human body with a wide range of biological functions because of its antioxidant properties. Compared with sulfur, selenium possesses a larger atomic radius and weaker electronegativity, leading to a lower bond energy for a diselenide bond compared with a disulfide bond. Thus, diselenide bond can be more easily cleaved either by oxidation to form seleninic acid or reduction to form selenol in different redox conditions. Therefore, the hybridization of diselenide bonds into MONs would be possible to achieve oxidative and redox dual-triggered biodegradation behavior. Shao et al for the first time reported the synthesis of diselenide-bridged MONs and their dual-sensitive degradability behavior. Here, MONs with diselenide bonds were synthesized by a modified sol–gel method by mixing ethyltrimethylammonium tosylate as a structure-directing agent, and TEOS and bis[(triethoxysilyl)propyl]diselenide (BTEDSe) as a silica source in the presence of TEA. The contents of diselenide bonds in MONs could be controlled by changing the ratio of TEOS to BTEDSe. Either in oxidation condition or in reduction condition, diselenide bonds could be easily cleaved. Both in the intracellular ROS conditions (H₂O₂, 100×10⁻⁶ M) and in the redox condition (GSH, 5×10⁻³ M), the diselenide-bridged MONs was rapidly degraded in 3 days, which might facilitate the renal clearance of diselenide-bridged MONs in vivo.

3 | APPLICATIONS IN TUMOR THERAPY

Traditional tumor therapies (eg, chemotherapy, radiation therapy, and surgical resection) often suffer from serious side effects and bring much pain for patients. A variety of modalities have been explored for more effective and non-invasive tumor therapy, such as targeted drug therapy, immunotherapy, photothermal therapy (PTT), photodynamic therapy (PDT), sonodynamic therapy (SDT), chemodynamic therapy (CDT), and starvation therapy. However, to achieve the impactful therapeutic goal, the corresponding therapeutic agents should be effectively delivered to tumor sites. Similar to MSNs, biodegradable MONs has high surface area, large pore volume, easy functionalization as well as biodegradability, which offer them to be as an ideal drug nanocarrier. Meanwhile, a variety of functional components could be integrated into biodegradable MONs to form multifunctional nanoplatforms, which endows biodegradable MONs with more potential applications in tumor therapy. To date, various delivery systems based on biodegradable MONs have
been developed for chemotherapy, PTT, SDT, starvation therapy, synergistic therapy, etc, which show great potential for applications in tumor therapy.72–75

3.1 Biodegradable MONs-based single-mode tumor therapy

As a highly lethal disease, malignant tumor has been a serious threat to human health. With the advancement of therapeutic strategies, more and more therapeutic modalities have been developed to treat tumors. For example, chemotherapy, using special drugs, can effectively kill tumor cells by means of delivering toxic chemotherapeutic drugs to tumor sites.43 PTT can achieve favorable therapeutic outcomes based on the principle of local hyperthermia, which is generated by near infrared (NIR) irradiation of photothermal agents located in tumor sites.61 PDT and CDT can produce toxic ROS by NIR irradiation of photosensitizers or catalytic reactions, which can efficiently induce tumor cell death.62–63,67 Other therapeutic modalities, like SDT, immunotherapy and starvation therapy, also have great ability to combat tumors. However, for each therapeutic modality, the key issue to achieve highly efficient therapeutic outcome is dependent on the delivery of therapeutic agents including chemotherapeutic drugs, photothermal agents, photosensitizers, immune agents, nanocatalysts, etc. Otherwise, serious side effects and the decreased therapeutic efficiency are often occurred owing to the toxicity, low bioavailability, poor targeting ability, and stability of therapeutic agents. Hence, the delivery of therapeutic agents using nanocarriers is an efficient strategy to enhance tumor therapeutic outcomes. With the help of nanocarriers, more therapeutic agents could arrive at tumor sites or tumor cells, which not only enhance the therapeutic efficacy, but also minimize the side effect.76–77 Considering the unique characteristics including biodegradability, biocompatibility, high surface area, adjustable mesopores, and the hybridized frameworks with diverse organic moieties, MONs, as a nanocarrier, has been intensively utilized to construct various therapeutic nanopreparations for tumor therapy.78–79

Chemotherapy as a common tumor therapy modality has serious side effects because the toxic chemotherapeutic drugs often attack to normal cells/tissues before arriving at tumor sites, which make the patients miserable. Nowadays, the development of appropriate nanocarriers for sustained/controlled drug delivery is considered as a common and effective strategy for enhancing the chemotherapeutic efficacy and minimizing the side effects of chemotherapy. Among them, biodegradable MONs is ideal for drug delivery owing to their inherent features. The high surface area and mesoporous channels provide numerous sites and space for drug loading; the organic-inorganic hybridized frameworks facilitate the hydrophobic and hydrophilic drugs to load. Furthermore, MONs is easy to be modified with functional components to realize controlled drug release, preventing the loaded drugs from premature release before arriving at tumor sites. Most importantly, MONs could be accelerated to degrade by the stimuli like reducing, acidic pH, and/or enzyme environments, while these characteristics including high level of reducing GSH, weak acidity, and enzymes are occurred in TME. Thus, biodegradable MONs as nanocarriers could enhance the chemotherapeutic efficacy and biosafety of the drug delivery system. Hence, a variety of studies has demonstrated the possibility of biodegradable MONs as drug nanocarriers for chemotherapy.80–81

Hu et al reported the GSH and polyacrylic acid (PAA) modified biodegradable MONs (MONs-PAA-GSH) for pH-sensitive drug delivery.82 Here, MONs were grafted with amino groups for conjugating PAA to form MONs-PAA, and the MONs-PAA-GSH was achieved by the conjugation of the reduced GSH on the activated MONs-PAA via an amide reaction. It was well known that reduced GSH could form small tripeptides (glycine and cysteine) connecting to mucin glycoproteins by disulfide bonds. Hence the MONs-PAA-GSH showed a high DOX loading capacity (ca. 43.75%) and exhibited a better cellular uptake by Hela cells (0.19 pg per cell) compared with the MONs-PAA (0.05 pg per cell). Interestingly, the DOX release rate increased with decreasing the pH value, which was attributed to the accelerated degradation of MONs in acidic environment. On the other hand, by incubating with Hela cells, the MONs-PAA and MONs-PAA-GSH are biocompatible, but the DOX-MONs-PAA-GSH group showed the lowest cell viability (<40% cell viability at a concentration of 10 ppm), indicating that the MONs-PAA-GSH as drug nanocarriers would be promising for tumor chemotherapy.82

Zhang et al proposed to integrate the thioether-bridged MONs with Cy5.5 and pH (low) insertion peptide (pHLIP) to construct a TME-responsive drug delivery system (MONs-Cy5.5-pHLIP) (Figure 4A).83 The results showed that the antitumor drug DOX could be efficiently loaded by MONs with 334 mg/g, and the DOX release from the DOX@MONs-Cy5.5-pHLIP in the 5 μM and 10 μM GSH solutions were estimated to be 52.34% and 63.67%, respectively. Compared with the GSH-free group (29.12% of DOX release), the DOX@MONs-Cy5.5-pHLIP system exhibited a GSH-responsive drug release behavior, which favors an enhanced cytotoxicity to tumor cells and lower toxic side effect to normal cells due to the high GSH level in TME. On the other hand, it was observed that the DOX release from the DOX@MONs-Cy5.5-pHLIP system was responsive to the pH environment; that is, the DOX release rate in acidic medium was much faster than
that in neutral medium, facilitating to enhance chemotherapeutic efficacy due to the weakly acidic characteristic in TME (Figure 4B). In vitro evaluations with MCF-7 tumor cells demonstrated that the DOX@MONs-Cy5.5-pHILIP system possessed much higher efficiency for killing tumor cells compared to the free DOX group (Figure 4C). Furthermore, an orthotopic tumor model was used to evaluate in vivo tumor-targeting ability and therapeutic effects of the DOX@MONs-Cy5.5-pHILIP system, and the results also confirmed the higher tumor growth inhibition compared to other groups based on tumor volumes (Figure 4D). It indicated that the MONs-Cy5.5-pHILIP would be a potential drug nanocarrier for tumor chemotherapy.83

Hypoxia is another important factor in TME that can be applied for those hypoxia-activated prodrugs, which can be converted from a nontoxic to cytotoxic formulation via hypoxia-induced reduction and further kill tumor cells.84 It is important to develop effective nanocarriers for delivering hypoxia activated prodrugs to tumor tissues or in tumor cells. Yang et al reported a cascade delivery system for a hypoxia-activated prodrug AQ4N and glucose oxidase (GOx) based on biodegradable tetrasulfide-bridged MONs (YS-DMONs-AQ4N-GOx). The high level of GSH in TME stimulated the cleavage of tetrasulfide bonds in the framework, accelerating the degradation of MONs that induced a rapid release of GOx and AQ4N. The released GOx could
react with glucose in TME to deplete O₂, and further cause hypoxia, which significantly promote to activate prodrug AQ4N.84

Generally, the chemotherapeutic efficacy of some hydrophobic antitumor drugs is often limited for clinical application owing to their poor aqueous solubility, low gastrointestinal absorption, and short residence time. To overcome this issue, biodegradable MONs has been proposed as a drug nanocarrier to deliver hydrophobic antitumor drugs for improving chemotherapeutic efficacy. For example, Zhang et al reported a biodegradable MONs with histidine moieties for tumor chemotherapy.47 Here, pH-sensitive histidine was hybridized in MONs to achieve pH-triggered degradation. The hybridization of histidine in the silica framework enhanced the loading capacity of hydrophobic antitumor drug paclitaxel (PTX) to 28 mg/g, owing to the imidazole groups of histidine as binding sites for hydrophobic PTX. More importantly, the PTX release rate at low pH value (pH 5.2) was much faster than that at neutral pH value (pH 7.4), suggesting that more hydrophobic PTX drugs could be released in acidic tumor sites for enhancing the chemotherapeutic efficacy.47

Yue et al designed HepG2 cell membrane (CM) coated disulfide-bridged MONs (ss-MONs) for hydrophobic Berberine (Ber) delivery. After loading Ber in carboxylated ss-MONs (ss-MONs-Ber), HepG2 cell membrane was coated on ss-MONs-Ber to obtain MONs-based Ber delivery system (CM-ss-MONs-Ber), which increased the homologous targeting property and immune escape capacity (Figure 5A). The CM-ss-MONs-Ber had uniform spherical morphology with a diameter of 53 nm, and exhibited much higher cell uptake in HepG2 cells than in human liver normal HL-7702 cells due to the HepG2 cell membrane coating (Figure 5B). The Ber release from the CM-ss-MONs-Ber was 55% at pH 5.5 without GSH, much higher than 5% at pH 7.4 without GSH, and further accumulated to 80% at pH 5.5 with GSH, which indicated a pH and GSH dual-triggered release behavior (Figure 5C). In vitro evaluations showed that the inhibition of HepG2 cells by the CM-ss-MONs-Ber group was enhanced compared to the ss-MONs-Ber and free Ber groups, owing to the super homotypic targeting ability of the CM-ss-MONs-Ber (Figure 5D). In vivo results also confirmed the significant enhanced tumor inhibition ability of the CM-ss-MONs-Ber compared to other groups, because the mice treated with CM-ss-MONs-Ber had the smallest tumor volume (Figure 5E). Hence, the CM-ss-MONs would be a promising candidate nanocarrier for hydrophobic drug delivery in tumor treatment.85

Except for toxic chemotherapeutics, protein drugs are another category of antitumor drug that are one of the most effective interventions at the molecular level with- out adverse effects due to their high targeting specificity. However, due to the easy degradation of protein drugs in physiological environment, it is challenging to deliver protein drugs to specific tumor sites. Hence, biodegradable MONs has also be proposed as nanocarrier to deliver protein drugs for tumor therapy. Shao et al fabricated diselenide-hybridized MONs to load RNase A into the mesopores via electrostatic interaction, and the RNase A release from MONs could be controlled via a matrix-degradation mechanism upon exposure to oxidative or reduct condition.30 Due to the sensitivity of diselenide bonds to the reduct environment, the RNase A-loaded MONs exhibited a rapid drug release in GSH-containing medium as well as H₂O₂-containing medium. From in vivo evaluation with Hela tumor-bearing female nude mice, the RNase A-loaded MONs group showed significant reduced tumor volumes and weights compared with the free RNase A group, demonstrating that the diselenide-hybridized MONs would be promising nanocarriers for protein drug delivery.30

Apart from the delivery of therapeutic drugs, biodegradable MONs can also integrate with other therapeutic agents like photothermal agents, photosensitizers, and nanocatalysts for tumor therapy. PTT is an important light-induced therapy modality for tumor treatment, which applies the photothermal agents (PAs) to generate heat under an NIR irradiation, thereby causes the local temperature increase at tumor sites to kill tumor cells. Currently, the most widely used PAs, such as Au nanoparticles, carbon dots, graphene oxide, copper chalcogenides (CuS, CuSe), indocyanine green (ICG), and prussian blue, are often need to be functionalized with specific components for improving the biocompatibility, stability, and/or targeting ability.59,86–90 Biodegradable MONs is one of promising candidates to functionalize the PAs for PTT. For example, Yang et al reported hollow MONs by hybridization of perylene diimide (PDI) within the silica framework via an “in situ framework growth” method, which were used as the PAs (HMPDINs) for PTT owing to the excellent thermal stability and high photothermal conversion of PDI.91 Interestingly, HMPDINs showed great photothermal effect that could increase the temperature of almost 60 °C with 671 nm laser irradiation at 1 W/cm² in 300 seconds. The photothermal conversion efficiency of HMPDINs was calculated to be 45%. In vitro and in vivo results indicated that HMPDINs could significantly suppress tumor cells and inhibit tumor growth under an NIR irradiation. Hence, the PDI-hybridized hollow MONs would be great potential for photothermal therapy.91

PDT is another type of NIR light–mediated photother- apy with minimal side effect and higher efficacy for tumor therapy. PDT can cause massive tumor cells death due to the ROS produced by photosensitizers (PSs) under NIR
irradiation.\textsuperscript{92,93} Similar to PAs, most of PSs suffer from the limitations, such as solubility, instability, aggregation tendency, and self-quenching in living body. Using biocompatible components to integrate PSs to form nanoplatforms can greatly overcome these drawbacks. Therefore, biodegradable MONs has been applied to functionalize PSs for constructing PDT nanoplatforms due to their biocompatibility, stability and easy modification for targeting. For example, Lin et al reported the encapsulation of a photosensitizer, protoporphyrin IX (PpIX), in biodegradable MONs for PDT.\textsuperscript{94} The results showed that the photobleaching rate of MONs-PpIX was attenuated to >90% compared to that of free PpIX. Under 660 nm laser irradiation, MONs-PpIX significantly decreased the cell proliferation rate compared to free PpIX.

The generation of $\text{IO}_2$ for killing tumor cells during PDT consumes oxygen, while the hypoxia microenvironment in tumor sites greatly hinders the therapeutic efficacy of PDT. Thus, reducing tumor hypoxia is a promising strategy for improving PDT efficacy.\textsuperscript{95–96} Hence, Yang
et al constructed a MONs-based nanoplatfrom that encapsulated Prussian blue (PB) in MONs and loaded photosensitizer (Ce6) in mesoporous channels of MONs (PB@PMO-Ce6) (Figure 6A). Here, PB could catalyze \( \text{H}_2\text{O}_2 \) to produce \( \text{O}_2 \), which reduced hypoxia and thereby improved the PDT efficacy (Figures 6B-C). It could be found that cell viability of U87MG cells significantly reduced to be \(< 10\%\) after 660 nm laser irradiation for 5 minutes even at a Ce6 concentration of 4 \( \mu \text{M} \) for PB@PMO-Ce6, which was much lower than those of MONs-Ce6 and free Ce6 (Figure 6D). Correspondingly, in vivo results showed that much higher \( \text{O}_2 \) regenerated after 660 nm laser irradiation for the PB@MONs-Ce6-treated U87MG tumor-bearing mice, and the tumor growth was significantly inhibited after PDT, which was confirmed by different tumor volumes of mice; that is, the tumor volumes were much smaller for the PB@MONs-Ce6-treated group than other groups (Figure 6E).

Owing to a vital role of oxygen in PDT, real-time monitoring of the oxygen content facilitates to predict the treatment response and optimize the therapeutic protocols. Hence, it is important to design a nanoplatfrom that could deliver the photosensitizers associated with oxygen probes. Fortunately, biodegradable MONs has been applied to construct a nanoplatfrom for PDT with oxygen monitoring. Yang et al reported a Ce6-incorporated hollow MONs (HMONs-Ce6) that synthesized via the reduction of thioether-bridged hollow MONs to react with Ce6 photosensitizer, and then loaded \([\text{Ru(dpp)}_3]\text{Cl}_2\), an oxygen-sensitive molecule, into HMONs-Ce6 (HMONs-Ce6-\([\text{Ru(dpp)}_3]\text{Cl}_2\)) for PDT with detecting oxygen changes. The results showed that the loading of \([\text{Ru(dpp)}_3]\text{Cl}_2\) into MONs improved its biocompatibility. The oxygen changes between 1% and 20% could be detected by the HMONs-Ce6-\([\text{Ru(dpp)}_3]\text{Cl}_2\) in solution and cells during PDT treatment, which was determined by the changes of fluorescence intensity at 620 nm. In vivo experiments also showed a significant therapeutic effect. Therefore, MONs could be used to construct a nanoplatfrom for achieving enhanced PDT efficacy with oxygen monitoring.

Similar to PDT, SDT can also induce tumor cell death, because the ultrasound (US) could activate the sonosensitizers to generate ROS. SDT possesses much higher tissue-penetrating depth, but the sonosensitizers suffer from similar limitations like low chemical and biological stability, biosafety of the sonosensitizers. Hence, how to deliver the sonosensitizers to tumor sites is a key issue to enhance the SDT efficacy. Huang et al proposed for the first time to construct a MONs-based sonosensitizer delivery system for SDT. Biodegradable disulfide-bridged
HMONs were modified with amino groups to anchor the sonosensitizer PpIX, and Mn$^{2+}$ was chelated into the rings of PpIX to form HMONs-MnPpIX nanoplatform. PEGylation of HMONs-MnPpIX (HMONs-MnPpIX-PEG) was aimed to enhance the biocompatibility and stability in aqueous solution. Interestingly, the developed HMONs-MnPpIX-PEG had controllable biodegradation behavior and high biocompatibility, and further exhibited significantly high SDT efficacy for inducing tumor cell death in vitro and inhibited tumor growth in vivo. The tumor inhibition rate of the HMONs-MnPpIX-PEG + US group was estimated to be 75%, which was much higher than those of the HMONs-MnPpIX-PEG group (17.4%) and the US only group (43.1%).

3.2  |  Biodegradable MONs-based synergistic tumor therapy

It has been demonstrated that multimodal tumor therapy, combining two or more therapeutic modalities, can often effectively enhance the therapeutic efficacy and minimize the side effects. For example, the combination of chemotherapy with hyperthermia therapy can enhance the sensitivity of chemotherapeutics, which makes chemotherapy with much lower drug dosage, and thereby greatly minimize the side effects. Fortunately, the MONs can be functionalized with specific components and as nanocarriers for loading therapeutic agents, which endow MONs with a function to construct a synergistic therapeutic nanoplatform. To date, a variety of MONs-based synergistic therapeutic nanoplatforms have been reported for tumor therapy.

Instead of only applying PTT to kill tumor cells, the development of therapeutic strategies associated with PTT could achieve a remarkable improvement for therapeutic efficacy. Among them, the most commonly used strategy is to combine chemotherapy with PTT for enhanced tumor therapy with minimal side effect. For example, Wu et al proposed to utilize MONs to load DOX and bovine serum albumin-folic acid-modified MoS$_2$ nanosheets (MONs-DOX@MoS$_2$-PEI-BSA-FA) for synergistic chemo-photothermal therapy. The results showed that the MONs-DOX@MoS$_2$-PEI-BSA-FA system exhibited pH- and NIR-triggered DOX release behavior, due to the pH-sensitivity of MONs and the photothermal effect of MoS$_2$. The MCF-7 cell viabilities treated by different groups revealed that the MONs-DOX@MoS$_2$-PEI-BSA-FA+NIR group had the lowest cell viability after 48 hours. Correspondingly, in vivo evaluation confirmed the smallest tumor volume for the MONs-DOX@MoS$_2$-PEI-BSA-FA+NIR-treated mice, indicating the enhanced therapeutic efficacy of MONs-DOX@MoS$_2$-PEI-BSA-FA under NIR irradiation.

Chen et al reported a stimuli-responsive chemo-photothermal therapy nanoplatform by using CuS nanocrystal as a photothermal agent and phase-change material (PCM) as a gate keeper to modify biodegradable HMONs (HMONs@CuS@PCM). HMONs could degrade in TME due to the GSH-sensitive disulfide bonds in the framework of HMONs, the decorated CuS nanocrystals could induce the melting of PCM to open the mesopores of HMONs under an NIR irradiation due to the photothermal effect. Thus, the DOX release from HMONs@CuS@PCM was accelerated from about 10% at 37°C to almost 55% at 50°C, and further increased over 85% in 5 mM GSH solution at 50°C, owing to the temperature-sensitivity of PCM and the GSH-responsibility of HMONs. From in vivo evaluation, tumor temperature of the HMONs@CuS/DOX@PCM-treated MDA-MB-231 tumor-bearing mice increased to almost 45°C with 808 nm laser irradiation for 5 minutes. The tumor inhibition rate of the HMONs@CuS/DOX@PCM+NIR-treated group (92.9%) was much higher than those of the free DOX+NIR-treated group (42.5%) and the HMONs@CuS@PCM+NIR-treated group (54.4%).

Similarly, the combination of gas therapy with PTT also can achieve enhanced therapeutic efficacy. Tang et al utilized HMONs to load Mn$_2$(CO)$_{10}$, a typical paradigm of CO-releasing molecule, and further attached ultrasmall molybdenum-based polyoxometalate (Mo-POM) onto the surface of HMONs for tumor-specific self-assembly and synergistic therapy. The Mo-POM-modified HMONs (HMOPMs) can be aggregated in acidic TME. Meanwhile, the reductive TME will induce the Mo(VI)-to-Mo(V) reduction that can reproduce strong NIR absorption for photoacoustic (PA) imaging as well as PTT. Furthermore, the hyperthermia of PTT can decompose the Mn$_2$(CO)$_{10}$ payload to release CO for gas therapy.

As a promising strategy for treating tumors, the generation of toxic ROS by dynamic process has been demonstrated to be an efficient approach for tumor therapy, such as CDT, PDT, and SDT. Nowadays, several groups have proposed to construct the MONs-based nanoplatforms to combine CDT/PDT/SDT with another therapy modality for synergistic tumor therapy. For example, Li et al reported a HMONs-based nanoplatform for sonotoxicity-enhanced chemotherapy of Hepatocellular carcinoma (HCC), which was constructed by the covalent anchoring of PpIX and arginine-glycine-aspartic acid (RGD) on HMONs, and then loading DOX in HMONs-PpIX-RGD to form the DOX@HMONs-PpIX-GRD (Figure 7A). The results showed that the DOX@HMONs-PpIX-GRD degraded in TME due to the GSH-sensitive disulfide bonds in HMONs, and induced the rapid DOX release (Figure 7B), and the US irradiation also could accelerate the DOX release.
Figure 7. (A) Schematic illustration of the HMONs-PpIX-RGD and synergistic chemo-SDT against HCC tumor xenograft on nude mice. (B) DOX release from DOX-loaded HMONs-PpIX-RGD at different GSH concentrations. (C) DOX release from DOX@HMONs-PpIX-RGD triggered by US irradiation at elevated power density. (D) The time-dependent tumor volume after different treatments. Reprinted with permission. Copyright 2018, Wiley-VCH.

In vitro evaluation revealed that the HMONs-PpIX-RGD was biocompatible, but the cell viability exhibited a significant decrease after US irradiation, indicating the SDT effect of HMONs-PpIX-RGD. More importantly, DOX@HMONs-PpIX-RGD had much lower cell viability after US irradiation compared to HMONs-PpIX-RGD, confirming synergistic chemotherapy and SDT. In vivo results showed that the tumor inhibition rate of the tumor-bearing mice treated by DOX@HMONs-PpIX-RGD with US irradiation was estimated to be 49.7%, much higher than that of free DOX (21.4%) (Figure 7D), revealing an enhanced chemotherapeutic process via sonotoxicity. Hence, HMONs are promising for constructing functional nanoplatforms with synergistic SDT and chemotherapy.

Wang et al designed MONs-based immunogenic nanoparticles that combine PDT and magnetic hyperthermia. The photosensitizer Ce6 was loaded into disulfide-bridged magnetic MONs (M-MONs) to form M-MONs@Ce6. Compared with PDT alone and magnetic hyperthermia alone, synergistic therapy induced tumor cell death with the lowest cell viability. Furthermore, M-MON@Ce6 could induce more immunogenic phenotypes like calreticulin (CRT) and chromatin-binding protein high mobility group B1 (HMGB1), stimulating the irradiations with laser and alternating magnetic field (AMF). In vivo experiments had evaluated the therapeutic efficacy and tumor-specific immune responses. The mice treated with M-MSN@Ce6 + Laser + AMF exhibited significantly delayed growth and decreased weights of primary tumors. Combining anti-CTK4 with M-MON@Ce6 + Laser + AMF, primary 4T1 tumors were completely eradicated with prevented development of the pulmonary metastatic nodules, indicating the significant effect of synergistic therapy.

In addition, Shan et al reported a MONs-based nanoplatform (HMBRN-GOx/TPZ) with synergistic starvation therapy and chemotherapy that codeliver glucose oxidase (GOx) and tirapazamine (TPZ). Here, bilirubin...
(BR)-hybridized MONs (HMBRN) was synthesized by using TEOS and BR-silane as a silica source. Glucose oxidase (GOx) and TPZ were coloaded into HMBRN, which could rapidly deplete intratumoral glucose/oxygen to promote a synergistic starvation therapy. In vitro results showed that HMBRN-GOx/TPZ induced a decrease in glucose level and an increase of H₂O₂ level for U87MG and MDA-MB-231 tumor cells due to the oxygen-involved glucose decomposition reaction by HMBRN-GOx/TPZ, which aggravated tumor hypoxia. Simultaneously, deoxygenation-activated tumor hypoxia could stimulate TPZ to generate toxic BTZ radical species for enhanced bioreductive chemotherapy. In vivo evaluation showed that HMBRN-GOx/TPZ had the highest inhibition rate of 75.45% for tumor growth, which was much higher than that of HMBRN-GOx (55.08%) and HMBRN-TPZ (27.8%). Hence, HMBRN-GOx/TPZ showed great promising for synergistic starvation therapy and chemotherapy.  

3.3 Biodegradable MONs-based imaging-guided tumor therapy

Imaging-guided tumor therapy is becoming more popular owing to its integration of diagnosis and therapy, which can achieve more accurate and visual treatments. Imaging is widely used in tumor diagnosis, because it is traceable during the treatment process. Generally, magnetic resonance (MR) imaging, computed tomography (CT), positron emission tomography (PET), near-infrared fluorescence (NIRF) imaging, photoacoustic (PA) imaging, and ultrasound (US) imaging are the major approaches for tumor diagnosis. In practice of multifunctional tumor therapeutic strategies, the achievement of imaging capability is generally accompanied by sacrificing therapeutic efficacy to certain extent. To achieve reasonable penetration depth and spatial resolution, unnecessary radiation dose has to be used for patients and may bring potential damages. On the other hand, nonionizing radiation ways, such as fluorescence, NIR, optical coherence tomography (OCT), are nondestructive and high chemical specificity, but have low penetration depth into tissue. Nanocarriers can be used to load imaging agents to reduce necessary dosage and to improve penetration depth into tissue owing to the passive targeting accumulation at tumor sites. Among these nanocarriers, silica-based nanoparticles have well-defined morphology with large reservoir to load cargos for biomedical applications. Biodegradable MONs, as one of interesting silica-based nanoparticles, with facile functionalization, large surface area and pore volume and low cytotoxicity, provide a valuable nanoplatform to design therapeutic strategy with a tracing capability. To date, a variety of studies have been reported to use biodegradable MONs for imaging-guided tumor therapy.

US imaging is widely used in clinic due to its low cost and safety, which is also an important approach for diagnosis during tumor therapy. However, the production of microbubbles is the key factor to achieve high-quality US imaging that influence the therapeutic strategy. Hence, it would be promising to design a nanoplatform that possesses a therapeutic function associated with producing high-quality microbubbles for US imaging. Xu et al developed a biodegradable hollow MONs nanoplatform with hyperthermia-induced bubble ability for highly efficient US imaging-guided chemo-photothermal therapy. Here, DOX and perfluoropentane (PFP) were encapsulated into a polydopamine (PDA)-modified hollow MONs (PHDP). PDA modification endowed PHDP with excellent photothermal effect for PTT. Simultaneously, the heat generation of PHDP under 808 nm laser irradiation induced the liquid-gas phase transition of PFP, resulting in the production of nanobubbles and microbubbles, which could intensify the US imaging signals for diagnosis. MDA-MB-231 tumor-bearing mice were used as in vivo model for evaluation, and the results showed that the US signals in both B-mode and contrast mode were significantly enhanced in the PHDP group under laser irradiation for 5 minutes, compared to that without laser irradiation. Furthermore, the tumor growth inhibition for the PHDP-treated group was more significant than other treated groups, indicating an excellent synergistic chemophotothermal therapy.

Based on HMONs, PA imaging-guided tumor therapy nanoplatform has also been developed recently. Li et al designed an HMONs-based nanoplatform with TME-responsive biodegradability and synergistic chemophotothermal therapy. Here, CuS@BSA with an excellent photothermal conversion efficiency of 51.5% was incorporated in HMONs to achieve the functions of PTT and PA imaging, and the DOX loading offered HMONs with chemotherapy. In vitro results showed that CuS@BSA-HMONs-DOX exhibited PA imaging contrast enhancement with Cu concentrations. Only less than 20% Saos-2 cells survived after treated with the CuS@BSA-HMONs-DOX + laser at a relatively low concentration of DOX, which was much lower than the CuS@BSA-HMONs-DOX group and the CuS@BSA-HMONs + laser group, indicating the potential enhanced PA imaging and synergistic chemophotothermal therapy of CuS@BSA-HMONs. Correspondingly, in vivo evaluation confirmed that the PA signal intensities of tumor sites enhanced remarkably in the CuS@BSA-HMONs-DOX + laser group, and the tumors were significantly suppressed without recurrence after treated with the CuS@BSA-HMONs-DOX plus laser irradiation.
Due to hollow cavity and mesoporous channels in HMONs, Wu et al developed a HMONs-based nanoplatform (ICG/PFP-HMOP-PEG) that loaded indocyanine green (ICG) and PFP and decorated a paclitaxel prodrug to be a redox-sensitive gatekeeper for US/PA imaging-guided chemo-photothermal therapy. Here, ICG as a photothermal agent generated mild hyperthermia with 808 nm laser irradiation, and thereby induced the liquid-gas phase transition of PFP and produced bubbles that could be used for US imaging. Paclitaxel prodrug could also be released in this process for chemotherapy. Only a faint US signal in tumors was detected after injection of ICG/PFP@HMOP-PEG for 24 hours without NIR laser irradiation, but the US signal in B-mode was significantly enhanced after mild NIR laser irradiation (1.0 W/cm², 5 minutes). Simultaneously, such treatment could raise the tumor temperature to be around 50°C, leading to the generation of PFP nanobubbles and their coalescence into microbubbles. On the other hand, PA signals from tumor sites increased with time, and reach a maximum at 12 hours postinjection, and a strong PA signal was still visible at 24 hours. The mice treated with the ICG/PFP-HMOP-PEG nanoplatforms were irradiated by 808 nm laser (1.0 W/cm²) for 10 minutes after injection of NIR laser irradiation, but the US signal in B-mode was significantly enhanced after mild NIR laser irradiation (1.0 W/cm², 5 minutes). Simultaneously, such treatment could raise the tumor temperature to be around 50°C, leading to the generation of PFP nanobubbles and their coalescence into microbubbles. On the other hand, PA signals from tumor sites increased with time, and reach a maximum at 12 hours postinjection, and a strong PA signal was still visible at 24 hours. The mice treated with the ICG/PFP-HMOP-PEG nanoplatforms were irradiated by 808 nm laser (1.0 W/cm²) for 10 minutes after injection of NIR laser irradiation, but the US signal in B-mode was significantly enhanced after mild NIR laser irradiation (1.0 W/cm², 5 minutes).

In addition, Wu et al proposed to use HMONs for loading 17AAG and serum albumin-iridium oxide (BSA-IrO₂) to prepare a 17AAG@HMONs-BSA-IrO₂-PPEG (AHBIP) nanoplatform for CT/PA imaging-guided anti-inflammation and tumor therapy. 17AAG is a typical heat shock protein 90 (Hsp90) inhibitor for reducing the expression of Hsp90, and thereby inhibiting the glucose metabolism, thus overcoming the heat resistance of tumor cells for improved photothermal therapy. Iridium-based nanomaterials are ideal theranostic agents for CT imaging due to the high atomic number of Ir. The light absorption by IrO₂ can spread to NIR region to achieve photothermal imaging and PTT. BSA-IrO₂ nanoparticles can convert H₂O₂ into O₂ for enhancing PDT efficacy. Therefore, AHBIP can utilize a single laser irradiation to provide synchronous implementation of PDT and PTT without changing lasers, facilitating to operate during therapy. AHBIP exhibited excellent photodynamic effect for PDT, extraordinary photothermal conversion efficiency (61.2%) for low-temperature PTT and high 17AAG loading (35.4%). On the other hand, the pH/GSH-sensitive BSA-IrO₂ not only served as a gatekeeper via the conjunction of disulfide bonds to control the 17AAG release, but also enhanced the PA and CT signals for PA and CT imaging. When AHBIP were injected intravenously into the MDA-MB-231 tumor-bearing mice, CT imaging was greatly enhanced with an enhanced UH value of 54.2, much higher than that before injection (22.9 HU). Similarly, the PA intensity also increased within 12 hours. Furthermore, the AHBIP + laser group exhibited the greatest inhibition of tumor growth, indicating the high tumor therapeutic efficacy by synergistic PDT and PTT treatments with a single NIR laser irradiation in vitro and in vivo.

Hu et al designed a multifunctional MONs-based theragnostic nanoplatform that combines drug delivery and real-time imaging tracing. Acetaldehyde-modified-cysteine (AMC) and MONs were used to prepare dual-responsive degradable skeleton nanostructure (MONs-AMC). DOX can further directly conjugate on MONs-AMC through electrostatic interaction between DOX and AMC (MONs-AMC-DOX). Here, AMC, a self-fluorescent Schiff base, was used as an acid-sensitive linker in polymer chains due to the easy hydrolysis of the Schiff base bond at low pH, and provided the tracing capability due to its fluorescent nature. The in vitro and in vivo results demonstrated the therapeutic effect and trajectory tracking effect. Such tracing capability could guide the therapeutic process, and thereby enhance the therapeutic efficacy. Due to the important role of oxygen to increase the sensitivity of hypoxic tumor cells to X-ray radiation and thereby enhance the ability for the radiotherapy-induced DNA damage, delivering oxygen into tumor sites is an effective strategy for enhanced radiotherapy. Lu et al. designed a HMONs-based nanoplatform (HMC) that was modified with sub-50 nm CuS as a PA agent and 63Cu as a PET agent, and such nanoplatform could loaded hydrophobic PFP for efficient oxygen storage (O₂-PFP@HMC). Thus, the O₂—PFP@HMC could produce microbubbles owing to the mild hyperthermia caused by CuS nanoparticles under NIR irradiation, and increase rapidly the dissolved oxygen concentration simultaneously, which endowed the O₂—PFP@HMC with PET/PA/US multimodality imaging-guided radiotherapy (Figure 8A). Hypoxic U87MG cells were used to examine the O₂—PFP@HMC for overcoming hypoxic resistance and improving the radiotherapeutic efficacy. The results showed that the O₂—PFP@HMC-treated cells exhibited a rapid decrease of cell viability after X-ray irradiation, which was more significant compared to the HMC and PFP@HMC groups, indicating that the rapid O₂ release induced by PFP microbubbles greatly increased the sensitivity of hypoxic U87MG cells to X-ray radiation (Figure 8B). From in vivo experiments, the quantitative PET imaging demonstrated that the HMC quickly accumulated at U87G tumor sites within 1 hour after injection (Figure 8C), while PA imaging confirmed the optimal tumor accumulation of nanoplatforms at 24 hours postinjection based on the strongest PA signal at tumor sites. The enhanced US imaging could address the diminished hypoxia and enhanced oxygenation of tumors (Figure 8D). More importantly, tumor volumes could...
FIGURE 8  (A) Schematic illustration of the construction of O$_2$–PFP@HMCP for PET/PA/US imaging and therapy. (B) Representative coronal PET images of a U87MG tumor-bearing mouse at 1, 6, 24, and 48 hours postinjection of 100 μCi 64Cu-labeled HMCP. (C) The relative cell viabilities of hypoxic U87MG cells incubated with HMCP, PFP@HMCP, and O$_2$–PFP@HMCP after exposure to 6 Gy of X-ray irradiation for 24, 48, and 72 hours. (D) In vivo PA imaging, B-mode US imaging and the overlay of PA oxygen saturation mapping and US imaging of the U87MG tumors. (E) Tumor growth curves of mice bearing U87MG tumors with different treatments. Reprinted with permission. 117 Copyright 2018, American Chemical Society

significantly decrease in the O$_2$–PFP@HMCP+NIR+RT group and finally eradicate in 20 days, indicating the superior therapeutic efficacy (Figure 8E). 117

4  CONCLUSION AND OUTLOOK

Mesoporous organosilica nanoparticles (MONs) have been a promising nanopplatform for tumor therapy due to their mesoporous structure, easy functionalization, and unique stimuli-responsive biodegradation behavior in TME. In this review, we summarized recent advances in the synthesis strategies of biodegradable MONs and their application in tumor therapy.

To achieve enhanced degradation ability of MSNs, stimuli-sensitive organic moieties are proposed to hybridize into the silica frameworks of MSNs to form MONs, which determine their biodegradation behaviors.
Particularly, TME features the acidic pH, overexpressed GSH and H$_2$O$_2$ levels and enriched enzymes, the pH-, redox-, and enzyme-sensitive organic moieties, such as tetrasulfide, disulfide, oxamide, and diselenide, have been introduced into MONs to achieve the pH-, redox-, and enzyme-triggered degradation behaviors. On the other hand, the biodegradation rate could be regulated by controlling the amount of stimuli-sensitive organic moieties or hybridizing multiple organic moieties into the silica frameworks. Thus, as a nanoplatform, the controllable degradation behavior of MONs could contribute to the biosafety of tumor therapy.

To date, much effort has been made to design and construct biodegradable MONs-based functional nanoplatforms for tumor therapy. The chemotherapeutic drugs, proteins, genes, photothermal agents, photosensitizers, and other therapeutic agents are loaded into MONs, which endow MONs with specific therapeutic modality, such as chemotherapy, immunotherapy, photothermal therapy, photodynamic therapy, sonodynamic therapy, and chemodynamic therapy, and thereby achieve excellent tumor therapeutic outcomes. To optimize the therapeutic nanoplatforms, biodegradable MONs could integrate with multiple therapeutic agents to achieve multimodal tumor therapeutic modalities, such as synergistic chemophotothermal therapy, synergistic immune-photothermal therapy, synergistic chemodynamic-photodynamic therapy, synergistic starvation, and chemotherapy, etc, which not only enhance the therapeutic efficacy, but also minimize the side effects. To achieve the purpose of precise therapy, the diagnostic agents/probes and therapeutic drugs/agents are coloaded in biodegradable MONs to obtain imaging-guided tumor therapeutic nanoplateforms, and realize more accurate and visual tumor treatments.

MONs, which greatly inherit the advantages of MSNs in structure and functionalization, could solve the limitation in degradation issue, and it would be a promising nanocarrier candidate for tumor therapy. However, there are still several obstacles for MONs to achieve clinical applications further. Tumor microenvironment is complex, such as acidic pH, overexpressed GSH and H$_2$O$_2$ levels, enriched enzymes, and hypoxia. The interplay between biodegradable MONs and TME should be elucidated clearly to guide the design and construction of MONs-based nanoplateforms for tumor therapy. Nowadays, few studies concern the long-term effect of the degradation behavior of MONs for tumor therapy. Those introduced organic moieties could significantly improve the biodegradation ability of MONs, which is vital for their future clinical translation. Thus, it is necessary to further study the optimal content of organic moieties for the enhancements of particle stability, therapeutic efficacy, and biosafety. It would also be necessary to understand the degradation mechanisms and preservation condition to confirm how to control degradation rate of MONs and whether the degradation products will further decompose to produce harmful substances or not. Besides that, in vivo biodistribution and biological metabolism of MONs should also be studied. More attention should be paid to the metabolic cycle of organic moieties that are released during the degradation process in vivo. In order to be safe vectors for tumor therapy, MONs should ensure that the organic moieties produced during its degradation do not accumulate and pose a potential risk to normal organs prior to metabolism. Further, the synthesis process of MONs should be able to provide criteria to ensure the scale preparation, which is also important for practical clinical applications. On the other hand, more stimuli-sensitive organic moieties should be developed to hybridize into the frameworks of MONs for regulating the degradation behavior.

Studies demonstrated that MONs-based nanoplatforms could be significantly accumulated at tumor sites due to the enhanced permeability and retention effect or targeting-mediated endocytosis after the functionalization of various ligands on MONs. However, such strategies should be further considered for the specific tumor types, because different types of tumors possess their intrinsic properties. At the same time, the therapeutic efficacy of these designed MONs-nanoplatforms should be optimized further for highly effective and safe tumor treatment. This means we should pay much more attention on the researches about the relationship between MONs-based nanoplatform and the loaded components. More focus should be given for the study of more favorable combinations between different classes of drugs or agents and degradable MONs containing different organic components. Establishment of composite standards is of great significance for practical clinical transformation. Last but not least, further studies also need to lucubrate the biosafety of the MONs-based nanoplatform including its payload. As therapeutic vectors, MONs need to ensure that its payload of drug or agents can be maximally concentrated at tumor site. In conclusion, with the deepening of the integration of nanotechnology and nanomedicine, there is no doubt that biodegradable MONs are great promising as multifunctional nanoplatforms for tumor therapy in future.

**CONFLICT OF INTEREST**

The authors declare no conflict of interest.

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