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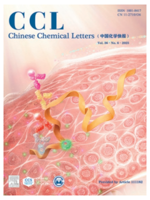

Recent trends of biodegradable mesoporous silica based nanoplatforms for enhanced tumor theranostics

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ABSTRACT

Mesoporous silica nanoparticles (MSNs) are thought to be an attractive drug delivery material because of their advantages including high specific surface area, tunable pore size and morphology, easy surface modification and good biocompatibility. However, as a result of the poor biodegradability of MSNs, their biomedical applications are limited. To break the bottleneck of limited biomedical applications of MSNs, more and more researchers tend to design biodegradable MSNs (b-MSNs) nanosystems to obtain biodegradable as well as safe and reliable drug delivery carriers. In this review, we focused on summarizing strategies to improve the degradability of MSNs and innovatively proposed a series of advantages of b-MSNs, including controlled cargo release behavior, multifunctional frameworks, nano-catalysis, bio-imaging capabilities and enhanced therapeutic effects. Based on these advantages, we have innovatively summarized the applications of b-MSNs for enhanced tumor theranostics, including enhanced chemotherapy, delivery of nanosensitizers, gas molecules and biomacromolecules, initiation of immune response, synergistic therapies and image-guided tumor diagnostics. Finally, the challenges and further clinical translation potential of nanosystems based on b-MSNs are fully discussed and prospected. We believe that such b-MSNs delivery carriers will provide a timely reference for further applications in tumor theranostics.

1. Introduction

With the continuous progress of nanotechnology, mesoporous nanoparticles (NPs) are attracting attention in the field of anticancer drug delivery due to their unique mesoporous structure. These NPs include mesoporous carbon NPs, mesoporous polydopamine (PDA) NPs, metal oxides NPs and mesoporous silica NPs (MSNs). Among them, mesoporous carbon NPs have excellent photothermal conversion efficiency and enzyme-like activity, but their low biocompatibility and the complex preparation process limit further application [1,2]. Although mesoporous PDA NPs are biocompatible and degradable, they also have to face the aggregation caused by van der Waals forces and electrostatic attraction between NPs [3]. For metal oxide NPs, excellent catalytic ability attracts extensive research, but potential toxicity problems to normal tissues *in vivo* prevent their direct application [4,5]. Since the early 1990s [6], MSNs have received widespread attention and research interest because of their attractive characteristics, including large surface [7], efficient cargo loading [8], adjustable pore size [9], good biocompatibility [10] and easy to modify for controlled and targeted drug release [11]. Therefore, MSNs have potential research significance as drug delivery carriers. In 2001, Vallet-Regi and colleagues [12] demonstrated the sustained release of ibuprofen in an aqueous solution using MCM41-type MSNs as a drug delivery vehicle. In order to avoid premature leakage of the drug and to achieve controlled drug release, cadmium sulfide nanocrystals were used as gatekeepers on the surface of MCM41-type MSNs by Lai *et al.* [13] in 2003. These gatekeepers stimulated the reactive release of vancomycin and adenosine triphosphate through intracellular reduction reaction under the activation of molecules containing dithiothreitol and mercaptoethanol. Since then, MSNs-related research has entered an era of rapid development, becoming a research hotspot. However, the inert biodegradation of inorganic MSNs poses a serious obstacle to their practical clinical translation [14]. Generally, for conventional MSNs, a biodegradation process of several days is required [15] and several weeks are needed for their excretion [16], which may be troublesome for the *in vivo* elimination and long-term biosafety [17]. Furthermore,

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many studies have reported that the low biodegradability of MSNs may result in severe bioaccumulation of the particles, resulting in a range of unpredictable toxicity risks [18,19], limiting further clinical application. Fortunately, the advent of biodegradable MSNs (b-MSNs) offers promising hope for conventional MSNs.

The b-MSNs offer several advantages over conventional MSNs, including improved cargo release, enhanced efficacy, and reduced systemic toxicity due to their superior biodegradability and biocompatibility. For example, the b-MSNs nanocarrier was able to achieve a release rate of 45.54% of doxorubicin hydrochloride (DOX) in pH 5.0 phosphate buffered saline (PBS) and 10 mmol/L glutathione (GSH) by the dual reaction of GSH and pH [20]. In addition, biodegradable mesoporous organosilica NPs (MONs) can play a key role in cancer immunotherapy through controlled drug delivery, enhancing drug efficacy and tumor immunogenicity. For example, Shao *et al.* [21] developed degradable MONs with X-ray and reactive oxygen species (ROS)-sensitive diselenide bond bridging and demonstrated controlled release of DOX at the tumor site, leading to DOX-mediated immune cell death at low doses of X-ray radiation. Furthermore, the dual responsiveness of b-MSNs to GSH and ROS using diselenide-bonded bridging offered promising opportunities to achieve controlled delivery of bioactive proteins [22]. Additionally, Qian *et al.* [23] homogeneously incorporated polymer-coated carbon dots (CDs) into an ordered framework of MSNs to obtain CD@MSNs that could biodegrade and selectively accumulate in tumors and enhance photothermal therapy (PTT) *in vitro*/*vivo*.

With the rapid growth of nanotechnology, many efforts have been made to regulate the biodegradability of MSNs. In recent years, the research trend of MSNs nanomaterials has gradually evolved from concentrating on synthetic methods to modulate microscopic properties to exploring *in vivo* applications that favor medical advances, enabling precise cancer therapeutics [24,25]. Compared to other reviews focusing on pore structure and particle size modulation of MSNs and discussions on factors affecting the biodegradability of MSNs [26], this review is unique in its innovative summary of the advantages of b-MSNs and their application in precisely controlling drug release to enhance tumor theranostics. Specifically, this review first briefly describes the classification and synthesis methods of b-MSNs-based nanoplatforms and focuses on their superiority such as improved biodegradability, controlled cargo delivery, multifunctional frameworks, nanocatalysis, bio-imaging capabilities and enhanced therapeutic effects. Then, the latest enhanced tumor theranostics of b-MSNs are detailed, including enhanced tumor chemotherapy, providing nanosensitizers for nanodynamic therapies, delivering gas molecules, biomacromolecules, initiating immune responses and various imaging technology-mediated tumor therapy. Finally, the challenges and opportunities presented by b-MSNs in cancer treatment and clinical aspects are discussed. Moreover, the advantages and applications of b-MSNs-based nanoplatforms in schematic form (Fig. 1) are summarized for the first time.

2. Classification and synthesis of b-MSNs

In recent years, MSNs have been attracting extensive attention as nano-delivery materials with broad application prospects thanks to a series of advantages including large specific surface area [27], tunable morphology and structure [28], easy surface modification [29] and excellent biocompatibility [30]. However, despite the high efficacy and low toxicity of MSNs, it is imperative to solve the following two major problems. Firstly, MSNs are poorly biodegradable and tend to bioaccumulate after long-term administration. Secondly, when cargoes-loaded MSNs are internalized into cancer cells, only part of the cargo could be released from the NPs, and most of the cargo might remain in the pores, which cannot fully exert the anti-cancer effects and may limit MSNs clinical application. Fortunately, the numerous silanol groups on the surface of MSNs could be highly functionalized [31]. At the same time, the variability of the MSNs framework also provides more possibilities for improving the biodegradability of MSNs, which can confer degradable biological functions to MSNs, facilitating targeted drug delivery and controlled release while avoiding *in vivo* accumulation [32].

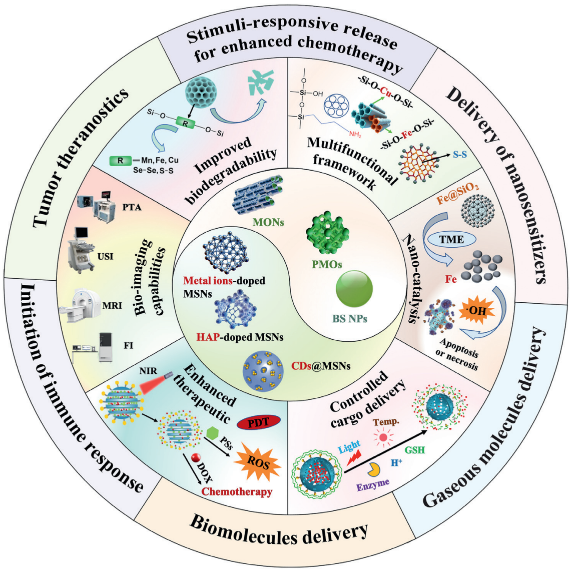

Fig. 1. The advantages and applications of b-MSNs nanoplatforms for enhanced tumor therapy.

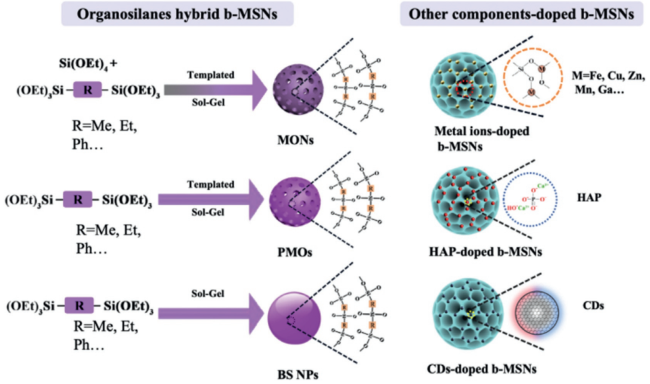

Fig. 2. Schematic classification of b-MSNs.

With the further development of b-MSNs nanoplatforms, they can be roughly divided into organosilanes hybrid b-MSNs and other components-doped b-MSNs (Fig. 2). Among them, organosilicon hybrid b-MSNs can be classified into the following three categories: MONs, periodic mesoporous organosilica NPs (PMOs), and bridge silsesquioxane NPs (BS NPs) [33,34]. At present, the most widely used synthetic method of MSNs is mainly based on the improvement of the well-known Stöber method, that is the sol-gel method. To further produce mesoporous structural particles, cationic surfactants (*e.g.*, cetyltrimethylammonium bromide) are often used as structure guiding agents to direct the above reaction process. The mesoporous structural particles can be obtained in two steps: first, the micelles formed by surfactants self-assemble around organic templates, and the silica structure grows around these micelles, then the mesoporous materials are obtained after the removal of the organic template *via* either calcination or extraction [35,36]. Notably, using only a silica precursor such as tetraethoxysilane (TEOS) ($Si(OEt)_4$) in the templated sol-gel reactions, the final product is MSNs. However, if TEOS is mixed with organosilane during the manufacturing process, the final product will be MONs. Comparatively, PMOs substantially differ from the abovementioned two nanoplatforms since they are synthesized only by using bridged organosilanes precursors in the templated sol–gel reactions without an additional silane source. Similarly, non-porous bridged BS NPs could be generated by constructing bridged multi-organoalkoxysilanes [37-39]. Therefore, proper modulation of the sol-gel reaction *via* altering the reactants or experimental conditions is of great importance for regulating the structure/composition properties of MSNs-based nanomaterials with excellent degradability to achieve the purpose of different applications.

In addition to organosilanes hybrid b-MSNs, other components-doped b-MSNs have also been extensively developed. Among these, metal ions-doped b-MSNs have a readily fractured backbone structure that can undergo degradation and release the carried therapeutic agents for tumor treatment. Furthermore, b-MSNs doped with hydroxyapatite (HAP) can be degraded under acidic conditions in the tumor microenvironment (TME), while doping with CDs can trigger the collapse of the backbone structure of b-MSNs. The introduction of these dopants opens up new possibilities for the functional expansion of b-MSNs and may provide potential benefits for applications in drug delivery, bio-imaging and tumor therapy.

2.1. Organosilanes hybrid b-MSNs

In order to precisely tune key parameters such as biodegradation, biosafety and excretion of MSNs, researchers have worked on introducing organosilanes into the Si–O–Si framework of inorganic MSNs [40,41]. This allows the integration of the respective advantages of inorganic and organic components while overcoming the disadvantages of each, making organosilanes hybrid b-MSNs possible to solve the aforementioned dilemmas and showing excellent synergistic effects to benefit various downstream applications. More importantly, the selection of different types of organosilane precursors may offer a broad range of possibilities to design and optimize the biological and physicochemical properties of b-MSNs [42]. This has driven the generation of a large number of organosilane hybrid b-MSNs structures, which can be generally classified into three main categories, namely MONs (combining conventional MSNs and organosilane precursors) [43], PMOs (produced using organosilane precursors only) [44], and BS NPs (consists of repeated organosilane precursors) [45]. Notably, these three types of organosilane hybrid b-MSNs could maintain the high specific surface area and controllable mesoporous structure of the inorganic MSNs, and the incorporation of organosilanes may reduce the stability of the silica framework by reducing -Si-O-Si- network condensation and enhance the biodegradability of the MSNs, which could give b-MSNs a strong advantage in terms of cargo delivery and release.

2.1.1. MONs

MONs are a mixture of organic and inorganic materials synthesized by the co-condensation of organosilane units and silica precursors (*e.g.*, TEOS) during the sol-gel process [35]. MONs not only have the advantage of an inorganic matrix to load functional cargoes, but also own the adjustable biodegradability of organic units. Therefore, MONs-based nanoplatforms have potential clinical applications in delivering and releasing cargo and are expected to be more attractive alternatives to conventional organic or inorganic nanomaterials in the field of biomedicine. To further enhance the *in vivo* safety of MONs nanocarriers, the hottest approach currently investigated is to introduce biologically active chemical bonds, such as disulfide [46], tetrasulfide bonds [47] and Se–Se bonds [48] into the MONs framework in response to GSH to obtain enhanced biodegradability and rapid *in vivo* clearance. For example, Qian *et al.* [49] prepared tetrasulfide bond-bridged MONs, the tetrasulfide bond in the framework of MONs could react with GSH in the TME, causing MONs to degraded into fragments.

2.1.2. PMOs

PMOs are nanomaterials with well-defined ordered mesoporous structure. They are synthesized under acidic or alkaline conditions through hydrolysis and co-condensation of bridged silsesquioxane precursors (typically represented as $(R'O)_3Si\text{-}R\text{-}Si(R'O)_3$, where OR' representing methoxy or ethoxy groups), in the presence of structure-directing agents [50-53]. Indeed, one intriguing and distinctive characteristic of PMOs materials is the even distribution of the organic groups (R) throughout the pore walls [54,55], thus allowing the modification and functionalization of PMOs by using various organic reactions. Therefore, the –R– of POMs will significantly affect their physicochemical properties such as controllable morphology, high drug loading capacity, and good biocompatibility. To improve the *in vivo* safety of PMOs, typically, –R– in precursors could be used to engineer biodegradability into PMOs, like making biodegradable chemical bonds uniformly distributed in the silylated framework [56], which may be the main factor to accelerate skeleton collapse and rapid biodegradation of PMOs. Therefore, it is necessary to select an ideal degradable linker between the two silicon atoms to facilitate PMOs degradation and safe and timely excretion of the cargo *in vivo* after delivery to the target site. Besides, PMOs have a large number of pores, which could contribute a large surface area for various chemical modifications that can alter the surface properties [57].

2.1.3. BS NPs

BS NPs nanomaterials are prepared by distributing multi-organoalkoxysilane precursors in the robust and easily functionalized silica matrix. Therefore, in addition to having the known chemical properties and stability of silica, the BS NPs have 20–80 wt% organic functional groups [58]. It is noteworthy that the features of BS NPs can be extensively tailored depending on the organic groups existing in the organoalkoxysilane precursors, which means that the degradation of BS NPs may be easier. To effectively degrade BS NPs that have completed their therapeutic effects, the structural stability of the BS NPs backbone can be adjusted by the introduction of organic functional groups or other types of degradable ligands, allowing these ligands to be cleaved under specific physiological conditions. Among them, the incorporation of amide bonds into the framework of BS NPs is of particular concern, since intracellular trypsin could trigger the cleavage of amide bonds in the BS NPs framework to ammonium and carboxyl groups, further accelerating the hydrolysis of the –Si–O–Si– bonds in the silica backbone, degrading the nanocarriers to fragment residues for rapid clearance [59].

2.2. Other components-doped b-MSNs

MSNs are becoming an increasingly attractive drug delivery platform in cancer therapy because of their unique advantages. However, due to the highly stable Si–O–Si structure, the poor biodegradability of MSNs may lead to toxic bioaccumulation in the body, which would limit clinical applications. Therefore, in order to overcome the above mentioned limitations to further enhance the therapeutic efficiency, the following are some of the available strategies for adapting the framework of MSNs to improve biodegradability and enhance therapeutic efficacy.

2.2.1. Metal ions-doped b-MSNs

It is generally accepted that the main reason for the poor biodegradability of MSNs is the high stability of the Si–O–Si network structure, and the disruption of the stable network structure has been proved to be an effective strategy to enhance the biodegradability of MSNs [60]. Therefore, some measures have been taken to adjust the structure of the MSNs or to reduce the network stability of the MSNs to obtain b-MSNs. The most common method of accelerating the degradation of MSNs for tumor theranostics is to dope the silica framework with some metal ions. Such metal ions include calcium ions, copper ions, iron ions, zinc ions and manganese ions. For example, Chen *et al.* [61] constructed monodispersed zinc-containing b-MSNs (MSNPs-Zn), which were regarded as a tunable biodegradable nanoplatform for delivering therapeutic zinc ions into tumor cells. Besides, manganese ions could also be used for functioning in the MSNs framework to promote the degradation of the nanocarriers. For instance, Li *et al.* [62] prepared the Mn^{2+}-doped b-MSNs nanocarrier, which exhibited pH/redox dual-responsive degradation. However, the biocompatibility and biodegradability of these nanocomposites must be carefully monitored to ensure that they meet the requirements of clinical applications, as the use of these metal-doped nanocomposites *in vivo* may lead to potential risks.

2.2.2. HAP-doped b-MSNs

MSNs would bioaccumulate in the liver, spleen, and some other living organs, which may cause some side reactions such as cell necrosis and inflammation. Therefore, it is urgent to develop b-MSNs to obtain more efficient and safer drug delivery systems (DDSs). HAP (chemical formula $Ca_{10}(PO_4)_6(OH)_2$) is the main inorganic constituent of human bone and teeth, and is considered an excellent candidate for drug delivery carriers because of its excellent biodegradability, biocompatibility and bioactivity. By incorporating HAP into MSNs, the hybrid nanomaterials could achieve pH-responsive biodegradable behavior. For example, Song *et al.* [63] fabricated gold nanorods/mesoporous silica/HAP ($Au/SiO_2/HAP$) for multi-responsive drug delivery. The biodegradation of the hybrid NPs was accelerated by the dissolution of HAP from the hybrid backbone in the acid ambient of the tumor. Similarly, Hao *et al.* [64] prepared a heterogeneous drug carrier (MSNs/HAP) and obtained acid-responsive calcium release from the –Si–O–Ca– network in an acidic environment, thus the degradability of the MSNs/HAP was significantly improved. In contrast, even after 12 h of incubation at pH 5.0, the morphology of calcium-free MSNs remained unchanged.

2.2.3. CDs-doped b-MSNs

As a new type of fluorescent nanomaterials, CDs have the advantages of simple preparation, adjustable luminescence properties, high photostability, good biocompatibility and potential photodynamic therapy (PDT) and PTT functions. Therefore, combined with the unique advantages of MSNs and CDs, it is expected to realize the development of a multi-functional nano-diagnosis and treatment nanoplatform with low side effects. Recently, Qian *et al.* [23] introduced CDs into the framework of MSNs to obtain the CD@MSNs system, and the incorporation of CDs not only induced the framework expansion for biodegradation, but also enhanced the photothermal effect of the system and improved the intra-tumor accumulation and retention. Based on the superior functional properties of CDs, there has been an interest in combining them with silica nanomaterials for cancer immunotherapy. For example, Wang *et al.* [65] designed a biodegradable carbon-silica nanocomposite with immunoadjuvant properties, which could be biodegraded into small particles ($\sim$5 nm) to enable photoacoustic imaging (PAI)-guided PDT and PTT tumor immunotherapy.

3. The superiority of b-MSNs for enhanced theranostics

Compared with conventional MSNs, the more recently studied b-MSNs have the following advantages in addition to those mentioned above: (1) Improved biodegradability. Since the rich presence of silanol groups on the surface of MSNs, the extrinsic functional groups can be easily covalently attached and modified to improve the degradability of MSNs; (2) Controlled cargo release. These functional "gatekeepers" decorated around the mesopore openings could control the effective release of cargoes upon stimulation by TME triggers; (3) Multifunctional framework. The framework of the b-MSNs can be adjusted by introducing appropriate configurable/functional components, such as organic groups, metal ions, and active covalent bonds, which can provide many possibilities for functional diversification; (4) Nano-catalysis. Doping single atoms into b-MSNs could confer the nanomaterial catalytic function and promote b-MSNs degradation *in vivo*, enhancing the therapeutic effects; (5) Bio-imaging capabilities. Various therapeutic agents, contrast agents or other functional cargoes can be delivered to the target site by b-MSNs for precise bio-imaging of tumors; (6) Enhanced therapeutics. The increased biodegradation can facilitate b-MSNs-mediated nanodynamic therapy and improve efficacy.

3.1. Improved biodegradability

In general, the degree of coalescence of the –Si–O–Si– network structure has a significant effect on the biodegradability of the MSNs, and the high degree of condensation of the –Si–O–Si– network is an indication of their poor biodegradability [66]. The biodegradability of MSNs is a prerequisite to avoid potentially harmful effects when used in biological systems. Therefore, it is imperative to find suitable strategies to improve the biodegradability of MSNs to develop valuable carriers. Doping of metal ions and introduction of covalent bonds in the backbone of MSNs are reported to be effective strategies to promote degradation in response to TME. Metal ions, such as Mn^{2+}, Fe^{3+} and Ca^{2+}, are incorporated into the silica backbone to form –Si–O–M– (M = Mn, Fe, Ca, *etc.*) [67], which could greatly improve the biodegradability of b-MSNs because M–O bonds are more fragile than Si–O bonds in acidic environments [68]. For example, Tang *et al.* [69] prepared acid-responsive Cu-doped b-MSN, in which Cu^{2+} could replace part of the silica to form Si–O–Cu, resulting the acceleration of biodegradation by acid induced Cu–O bond destruction. Additionally, the introduction of covalent bonds can also improve the biodegradation of b-MSNs. For instance, Hu *et al.* [70] synthesized hollow MSNs (HMSNs) bridged with tetrasulfide bonds and demonstrated that HMSNs obtained initial degradation within 1 h and completed 100% fragmentation within 4 h after 10 mmol/L GSH treatment. In addition, Xia *et al.* [71] systematically compared the biodegradation of diselenide-bridged MONs (DSeMSNs) and ditelluride-bridged MONs (DTeMSNs). Typically, GSH and H_2O_2 levels are higher in cancer tissues than in normal tissues, and both DTeMSNs and DSeMSNs showed high degradation rates in media containing GSH and H_2O_2. However, DTeMSNs exhibited a higher degradation rate than DSeMSNs. This was because the bond energy of Te–Te (126 kJ/mol) was lower than that of Se–Se (bond energy 172 kJ/mol), which made the ditelluride bond more active and cleavable than the diselenide bond when exposed to GSH and H_2O_2 in TME.

3.2. Controlled cargo delivery

Controlled DDSs can improve the timeliness and accuracy of cargo release at the pathological sites and reduce the toxic side

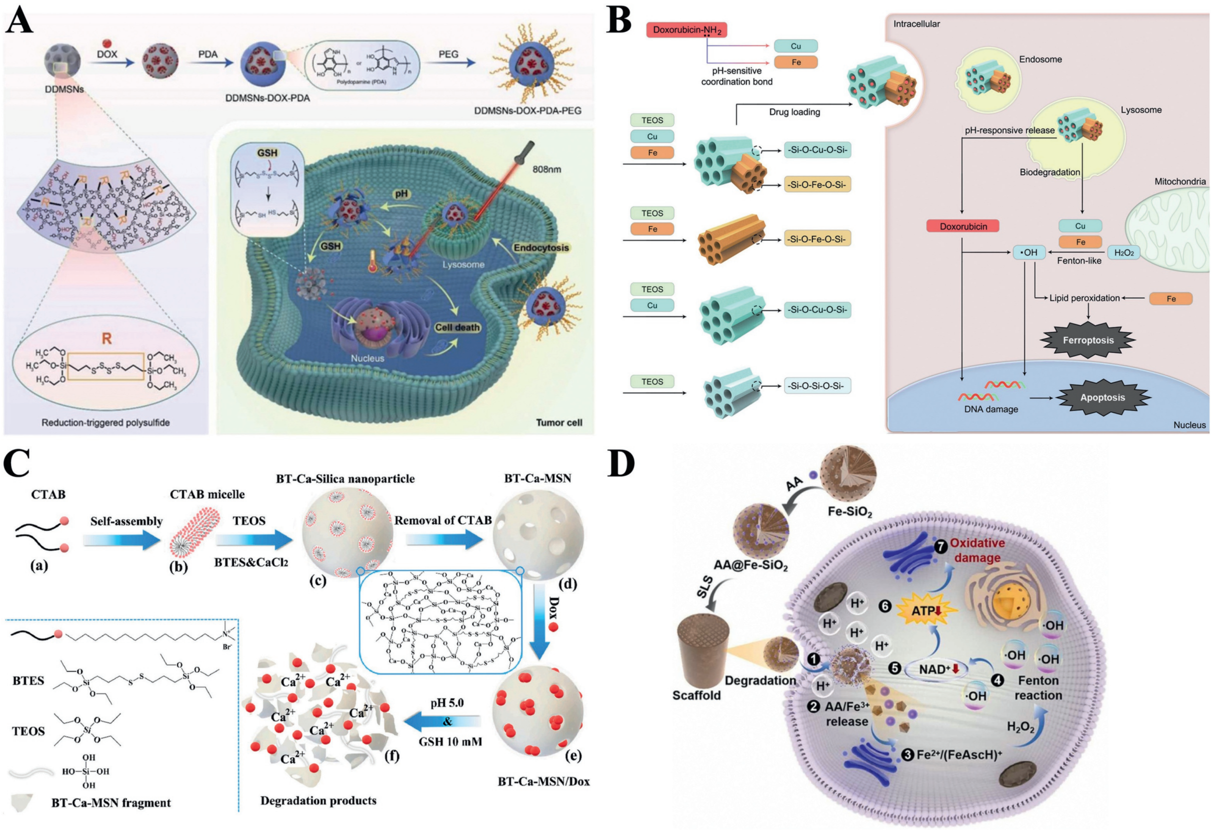

Fig. 3. (A) The DDMSNs-DOX-PDA-PEG preparation and the mechanism of drug release in the tumor cells. Reproduced with permission [81]. Copyright 2022, Elsevier B.V. (B) Synthesis of different metal-doped MSNs architectures, elucidating the arrangement of transition metals within the silica wall, internalization of metal-doped MSNs into cancer cells and the mechanistic of tumor ablation pathway. Reproduced with permission [83]. Copyright 2019, Elsevier B.V. (C) The synthesis of the biodegradable BT-Ca-MSNs with dual redox/pH response as a drug delivery vehicle. Reproduced with permission [20]. Copyright 2020, Elsevier Ltd. and Techna Group S.r.l. (D) AA@Fe-SiO$_2$ in the antitumor mechanism. Reproduced with permission [82]. Copyright 2023, Elsevier B.V.

effects [72]. However, many cargoes have high cytotoxicity and can seriously damage normal cells while killing tumor cells. Therefore, the ideal controlled DDSs should not only have good cell or tissue specificity, but are often required to achieve "zero release" without premature leakage before reaching the pathological site. In 2003, Lai *et al.* [13] creatively synthesized a stimuli-responsive DDS based on MSNs, which truly realized the controlled release of cargo. Since then, such DDSs have been intensively developed *via* utilizing various stimuli-responsive units as “gatekeepers” to respond to specific internal environments such as lower pH [73], higher GSH and ROS [74,75], enzymes [76], and external environments including light [77], temperature [78], and magnetic fields [79] to trigger the degradation or dissociation of b-MSNs nanocarriers to achieve the controlled release of cargoes. For example, conventional MSNs are bioaccumulative *in vivo* and may release the drug prematurely due to their low degradation rate and lack of protective gatekeepers in the systemic circulation. Chen *et al.* [80] doped Ca^{2+} and PO$_4^{3-}$ into the framework of MSNs and designed b-MSNs composite NPs capped with ZnO quantum dots. At pH 5.0, the ZnO cap dissociated, triggering the biodegradation of the b-MSNs backbone and achieving controlled DOX release behavior. In contrast, Lv *et al.* [81] constructed a nanoplatform (DDMSNs-DOX-PDA-PEG) with dual pH/GSH responsiveness by coating the surface of dendritic MSNs (DMSNs) with polyethylene glycol (PEG) and PDA (Fig. 3A). The PDA coating and the tetrasulfide bonds embedded within the DMSNs could be broken under an environment of low pH and high GSH concentration to promote the biodegradation of the DMSNs and to achieve the controlled release of DOX.

3.3. *Multifunctional framework*

The introduction of appropriate configurable/functional components to tune the framework composition of MSNs to promote biodegradation may satisfy different therapeutic purposes [84]. The first is the addition of bioactive organic groups such as amino acids [85], the lower bond energy of –Si–C– in amino acid functionalized b-MSNs compared to –Si–O– made b-MSNs susceptible to degradation. And oxamides could improve the biodegradation rate of b-MSNs in TME due to enzymatic reactivity [37]. Secondly, the introduction of metal ions into the framework of MSNs can significantly modulate the biodegradation properties of MSNs. For instance, Chen’s group [83] constructed pH-dependent b-MSNs by Cu^{2+} and Fe^{3+} bimetal doping (Fig. 3B). The bimetallic-doped b-MSN exhibited a large degree of degradability in pH 5.0 PBS, which was attributed to the ligand interaction between the silica molecules and the metal weakening the silica wall and allowing the mesoporous framework to degrade. Thirdly, to facilitate the biodegradation of MSNs, covalent bonds like disulfide bonds [86] and diselenide bonds [87] could also be designed into the framework of MSNs. Furthermore, disulfide bonding and calcium co-doped b-MSNs [20] exhibited rapid biodegradability in pH 5.0 + GSH 10 mmol/L (Fig. 3C). It can be seen that multifunctional frameworks offer a broad range of possibilities for diversifying the functions, which could further improve the biodegradation of b-MSNs-based nanomaterials.

3.4. Nano-catalysis

Based on the unique acidic physiological microenvironment of cancer tissues/cells and evolving nanotechnology, several promising nanotherapeutic measures have been extensively explored and developed for initiating local catalytic chemical reactions in TME to obtain attractive tumor therapeutic efficacy. Among the corresponding nanomaterials, b-MSNs with homogeneous mesopores and high specific surface area are essential for the improvement of metal dispersion and catalytic efficiency of metals. Different transition metal precursors can be easily introduced into the confined spaces of b-MSNs by grinding. And during subsequent calcination, single atoms are constructed in the form of –Si–O–M– (M = Cu, Co, Ni and Fe) by sacrificing the –Si–O–Si– to form –Si–O–M– framework [88,89]. Importantly, the incorporation of single atoms could impart lower condensation and bonding energy to the –Si–O–M– framework. Therefore, incorporating single atoms into b-MSNs may be very promising for tumor-specific nanocatalytic therapy. With this in mind, Shuai *et al.* [82] loaded ascorbic acid (AA) into Fe-doped mesoporous silica (called AA@Fe-SiO_2). The –Si–O–Fe– framework endowed AA@Fe-SiO_2 with excellent biodegradation and acid-catalytic properties. Due to the reaction of excess H^+ in an acidic environment with Fe atoms in the iron silicate backbone, the stability of the silica framework was weakened, resulting in the gradual disintegration of the skeleton, promoting the release of Fe^{3+} and accelerating the pro-oxidation reaction of AA (Fig. 3D).

3.5. Bio-imaging capabilities

Bio-imaging is a non-invasive diagnostic method that allows real-time dynamic monitoring of tumor tissue information including shape, size and location, and performing simultaneous treatment during cancer therapy [90,91]. The b-MSNs-based multifunctional nanoplatforms may offer potential opportunities for precise bio-imaging, therapeutic agent delivery, and simultaneous theranostic because of their unique advantages of loading various therapeutic agents, delivering these therapeutic agents to the desired sites, and releasing them in a controlled manner. For example, delivering contrast agents to tumor sites could improve the visualization of specific physiological regions, significantly improving the contrast between tumor tissue and normal tissue. The specific physiological state of tumor tissue would be emphasized [92-94], which has great diagnostic and prognostic implications for tumors. Thanks to the excellent features of b-MSNs, b-MSNs-supported imaging agents may be promising systems for designing targeted bio-imaging contrast agents with enhanced functionality and high structural stability. This property enables imaging in a variety of modes [95]. For example, Wu *et al.* [96] loaded indocyanine green (ICG) and perfluoropentane (PFP) by using disulfide-bonded HMON, while using paclitaxel (PTX) prodrugs as gatekeepers. The obtained nanotherapeutic agent (ICG/PFP@HMOP-PEG) could enable chemo-PTT and PA/ultrasound (US) bimodal imaging due to the cleavage of the HMON framework triggered by the GSH in TME.

3.6. Enhanced therapeutic

The b-MSNs offer irreplaceable advantages in cargo release. Moreover, b-MSNs are an ideal nanocarrier for enhanced therapeutics due to their adjustable pore size, ease of modification, and biocompatibility. Researchers have proposed redox-responsive b-MSNs containing disulfide bonds [97]. When exposed to reducing agents, the b-MSNs could be degraded to increase local release of active substances, and reduce potential toxic side effects while enhancing therapeutic efficacy. On the other hand, multimodal combination therapeutic delivery systems based on b-MSNs with controlled release and targeting properties can improve drug stability and bioavailability compared to conventional single therapeutic tools, which are of great significance for enhancing cancer therapeutic efficacy. For example, by co-loading the near-infrared (NIR) dye ML 880 and the chemotherapeutic drug GSH-*S*-transferase inhibitor (NBDHEX) into degradable MONs, a versatile and photothermal/ROS dual-responsive degradable DDS could be constructed. This innovative DDS could be timely degraded to release ML808 and NBDHEX for an enhanced tri-modal combination therapy of PDT/PTT/chemotherapy for liver cancer [98].

4. b-MSNs for enhanced tumor theranostics

Nanoplatforms based on b-MSNs have a variety of unique intrinsic properties, including improved biodegradability, controlled cargo delivery, multifunctional frameworks, nano-catalysis, bio-imaging capabilities and enhanced therapeutic efficacy. Therefore, b-MSNs have shown great promise in biomedicine in recent decades, becoming one of the nanomaterials of interest in tumor theranostics. In this section, our focus is firstly on the stimuli-responsive release of b-MSNs nanoplatforms for enhanced chemotherapy. Furthermore, we highlight recent advances in the delivery of various nanosensitizers (*e.g.*, photothermal agents (PTAs), photosensitizers (PSs), Fenton/Fenton-like agents and sonosensitizers) by b-MSNs-based nanoplatforms, as well as the wide range of applications in the delivery of gaseous molecules, biomacromolecules and the initiation of immunotherapy. Finally, we also present the diagnostic and therapeutic capabilities of b-MSNs in tumor theranostics. These latest findings may offer a broader prospect for the application of b-MSNs nanoplatforms in biomedicine and provide new ideas and options for future clinical tumor theranostics.

4.1. Stimuli-responsive release for enhanced chemotherapy

The b-MSNs-based therapeutic nanoplatforms have emerged as a key opportunity for the development of next-generation cancer nanomedicine owing to their unique advantages. Typically, b-MSNs materials are modified using active fractions for stimuli-responsive cancer nanotherapies, where these functional active fractions around the mesoporous openings could act as “gatekeepers” in response to stimuli from internal/external triggers, causing the accelerated degradation of b-MSNs backbone and the improved release of therapeutic agents to achieve the desired treatment. In this section, we will further describe how these viable “smart” therapeutic nanoplatforms interact with internal/external triggers and elucidate the potential mechanisms of b-MSNs-based nanoplatforms for enhanced chemotherapy. We expect these well-designed b-MSNs-based nanoplatforms with intelligent responsiveness to provide more effective solutions for tumor treatment.

4.1.1. Internal stimuli for drug release

The energy metabolism of tumor cells is dysregulated compared to most normal cells. This would lead to abnormal changes in many biochemical parameters in tumor cells, such as lower pH [99], high concentration of GSH [100], overproduction of H_2O_2 [101], overexpression of specific surface receptors [102], hypoxic environments [103], and abnormal expression of certain specific enzymes [104]. Therefore, these internal biochemical changes in TME described above are widely used as promising signals to trigger the release of therapeutic agents from b-MSNs-based nanoplatforms for precise cancer treatment. In this section, typical studies of b-MSNs in achieving internally stimulated drug release will be presented to reflect the impressive achievements of b-MSNs nanoplatforms designed by researchers in the field of tumor-specific therapeutics.

Due to the “Warburg” effect, there is a very dramatic difference in pH between tumor tissues and normal tissues, that is, the pH is around 7.4 in normal blood and tissue fluids, but the extracellular pH of tumor cells is about 6.5–6.9 and lysosomes have a pH of less than 5.4 [105]. Since Zink and his colleagues [106] reported pH-responsive cargo release using supramolecular nanovalve-linked MSNs, pH-responsive b-MSNs nanocarriers have gained considerable research attention in cancer therapy by introducing functional groups or molecules on the surface or within the framework to selectively trigger the release of therapeutic drugs for precision therapy [107]. For example, Kang *et al.* [108] incorporated acid-responsive HAP into the framework of b-MSNs and reduced DOX release to just below 15% in a neutral environment, while at pH 6.5, 6 and 5.5 the b-MSNs skeleton degraded and DOX release increased dramatically to 50%, 76% and 81%, respectively. (Fig. S1A in Supporting information). The pH-induced degradability of b-MSNs nanocarriers could not only perform responsive drug delivery, but also avoid premature drug leakage and exhibit efficient tumor aggregation, which may provide a more effective and reliable solution for tumor therapy.

In addition to lower pH, tumor tissues have higher redox conditions. In general, the intracellular GSH (2–10 mmol/L) of cancer tissues is approximately 100–1000 fold higher than that of normal tissues (2–10 μmol/L) [109]. Therefore, it is quite reasonable to exploit the considerable redox potential difference to develop redox-responsive nano-delivery systems. Redox-induced biodegradation behavior can be achieved by introducing redox-active chemical bonds (*e.g.*, disulfide, tetrasulfide, ditelluride bonds) into the MSNs framework. For example, Xia *et al.* [71] designed degradable and self-fluorescent ditelluride-bridged degradable MONs (DTeMSNs)/REG-curcumin (PEG-CCM) nanocomposite for drug release and cancer therapy (Fig. S3B in Supporting information). This nanocomposite enabled controlled biodegradation and sustained release of DOX under redox stimulation to enhance chemotherapy, as redox agents (GSH or H_2O_2) in the TME could effectively react with the Te–Te bond, leading to the breakdown of the intrinsic backbone of DTeMSNs. Therefore, the emergence of b-MSNs may provide an opportunity to overcome the low degradation rate and bioaccumulation of traditional MSNs *in vivo*.

From the above discussion, it is evident that the introduction of bioactive components on the surface or within the framework of MSNs could achieve pH-responsive and redox-responsive degradability and effectively facilitate the sensitive release of payloads for tumor-specific therapies with improved biosafety. Furthermore, many researchers have extensively investigated the use of proteins as endogenous triggers to further serve b-MSNs-based nanoplatforms to enhance tumor therapeutic efficacy. For example, Wang *et al.* [110] prepared functional DOX@/PEG/Fe-HMSN NPs by doping the framework of HMSNs with Fe ions and then PEGylated the surface of HMSNs (Fig. S1C in Supporting information). The Fe component of the HMSNs framework could be ligated by transferrin expressed on cancer cells, which accelerated the biodegradation of the silica matrix and caused the fast release of DOX. Mice treated with DOX-loaded Fe-HMSNs showed a significant reduction in tumor growth compared to mice treated with free DOX or saline, suggesting that protein-sensitive and degradable silica-based nanoplatforms may have promising applications for efficient cancer therapy.

To sum up, the use of biochemical changes within TME as response signals to enhance the controlled release of b-MSNs nanoplatforms is of great importance in tumor theranostics. However, despite the progress that has been made, there may be some biological parameters within the TME that have not yet been fully explored. With the continuous development of the biomedical field, it is expected that more response signals in TME will be further explored in the future, thus expanding the application of b-MSNs in tumor theranostics and achieving more precise therapeutic effects.

4.1.2. External stimuli for drug release

The b-MSN therapeutic nanoplatforms have made great progress in the internal response to therapeutic drugs release. However, the TME is a relatively complex system, and biochemical parameters such as acidity, redox and enzymatic activity are internal drivers of drug release, which may undergo spatio-temporal dynamic fluctuations. In addition, some internal responses in TME may be spontaneous and uncontrollable. Therefore, there may be uncertainty in relying on internal responses alone for tumor therapy. Therapeutic agent release triggered by external triggers may be more controllable and safer than internal responses. Hence, to further enhance the controllability of therapeutic agent release, there is a strong need to rationally manipulate b-MSNs nanoplatforms with the help of external triggers (*e.g.* light, X-ray, US and magnetic fields) to ensure that the manufactured b-MSNs therapeutic nanoplatforms are able to release payloads in response to external stimuli, thereby improving the efficacy of cancer treatment.

Compared to the stimuli provided by specific substances in TME, light as an external stimulus has less impact on the patient’s physiological condition, and photosensitive b-MSNs-based nanocarriers can better control the dose and timing of release of therapeutic drugs, while being able to respond quickly and sensitively to on-demand degradation. Therefore, the design and fabrication of novel photosensitive b-MSNs nanodelivery systems could offer safer and more effective drug therapeutics for tumors. For example, Fan *et al.* [111] fabricated the photo-responsive HMONs@GOQDs nanoplatform, which was based on $^1O_2$-reacted bridged organoalkoxysilanes and encapsulated graphene oxide quantum dots (GOQDs). During light exposure, GOQDs produced $^1O_2$ at significantly high quantum yields, leading to the cleavage of the $^1O_2$-reactive bridge and degradation of the nanoplatform (Fig. S2A in Supporting information). The release of DOX exceeded 80% within 3 h due to photo-induced degradation. It is noteworthy that once HMONs had completed drug delivery, they were safely cleared from the body, avoiding long-term toxicity.

The b-MSNs nanoplatform can achieve light-controlled drug release properties through light-stimulated degradation, making b-MSNs potential candidates for anticancer therapeutics delivery. However, conventional light would suffer from the disadvantage that short wavelengths of light (365 nm) cannot easily penetrate the thick skin of the human body, which may limit the effectiveness of light-responsive b-MSNs in clinical applications. As a result, conventional light-responsive b-MSNs nanosystems may no longer be adequate for therapeutic needs. In contrast, NIR light can penetrate deep into biological tissues, both as an induced light source and as a heat source for local thermal effects, and is expected to be able to act as a promising external trigger [112]. For instance, Peng *et al.* [113] assembled a nanotransformer named ID@M-N by using diselenide bonds to bridge MONs, with an ICG-hybridized *N*-isopropyl acrylamide (NIPAM) layer as a thermosensitive outer layer (Fig. S2D in Supporting information). Under the irradiation of NIR light, the ICG loading thermosensitive layer was dissociated. Simultaneously, the ROS generated by the ICG cleaved the diselenide bonds, leading to rapid degradation of the silica matrix and the production of smaller fragments containing DOX. This NIR light-induced drug release behavior promoted deep tumor penetration and improved adequate chemotherapy.

Besides, X-rays have emerged as one of the promising external stimuli for solid tumor therapy due to their high penetration depth and good spatial specificity. Recently, Shao *et al.* [21] developed a mimetic MONs drug carrier with diselenide bridge and cancer cell membrane coating by exploiting the sensitivity of diselenide bonds to X-ray radiation/ROS. In the experiments, the organosilica framework collapsed into irregular aggregates within 24 h under low-dose X-ray radiation (1 Gy) and completely disintegrated within 3 days in a medium containing H_2O_2, achieving good drug release (Fig. S2B in Supporting information).

In recent years, a growing number of studies are focusing on the use of external stimuli to trigger degradation and cargo release from b-MSNs delivery vehicles. Because of the inherent advantages of exogenous stimulation, more b-MSNs-based nanosystems that can respond to external stimuli are expected to emerge in the future, and these novel stimulus-responsive NPs may play an important role in clinical therapy through different design and functionalization strategies for precision tumor therapy.

4.1.3. Inhibiting metastasis

Metastatic cancer delineates the progression by which cancer cells travel from their primary site to infiltrate and colonize distant organs or tissues in the body. Approximately 90% of cancer-related deaths resulted from tumor metastasis [114]. Therefore, anti-metastatic therapy has become crucial for curing cancer [115]. The high loading and degradable properties of b-MSNs make them a potential solution for the effective treatment of postoperative malignant metastases. Generally, the presence of circulating tumor cells in cancer survivors is believed to be the underlying cause of cancer metastasis. To prevent the initiation of a destructive metastatic cascade, b-MSNs nanomaterials loaded with mifepristone and coupled with antibodies to epithelial cell adhesion molecules have been reported to prevent cancer metastasis by targeting the inhibition of circulating tumor cells activity and their adhesive invasion to the vascular endothelium [116]. Furthermore, regulation of the TME may also play a major role in tumor growth and metastasis. For example, Yu *et al.* [117] constructed DOX-encapsulated and $KMnO_4$-doped b-MSNs (MMPs) and applied them to modulate TME (GSH-depleting, ROS-producing, oxygenating, cytotoxic and immune-activating) (Fig. S2C in Supporting information). In addition to inhibiting the growth and metastatic spread of primary and distal non-treated cancers, MMPs achieved a 100% tumor clearance rate at distal non-treated sites in mice.

Although there are no methods to completely inhibit tumor metastasis and recurrence, with the development of nanotechnology, considering the ways and means of tumor spread, it is believed that more and more therapeutic strategies will emerge in the near future, such as delivering vascular materials through b-MSNs to pinch off the proliferation around solid tumors and block the nutrient supply. By delivering certain therapeutic cargoes, the body's immune system can be enhanced and immune evasion can be minimized to the greatest extent possible. Alternatively, b-MSNs may also assist in transporting cargoes that can track tumor cells in the lymphatic system, improving the ability to control cancer cell metastasis and inhibit tumor recurrence.

4.2. Delivery of nanosensitizers

The b-MSNs nanomaterials are ideal nanodrug carriers due to their high tunability, and play a vital role in tumor theranostics, especially in delivering nanosensitizers [118]. Li *et al.* [119] reported that through different structural and surface functionalization designs, silica materials can be engineered to respond to external stimuli, triggering the release of therapeutic agents and enhancing the therapeutic effect to inhibit tumor growth and metastasis. In recent years, researchers have started employing b-MSNs as transporters for delivering diverse kinds of nanosensitizers to tumor sites to facilitate nanodynamic therapies. The main therapeutic approaches include PTT, PDT, sonodynamic therapy (SDT) and chemodynamic therapy (CDT). Among them, PTT uses NIR light to activate the photothermal conversion ability of PTAs loaded in the b-MSNs to achieve an excellent photothermal effect and induce tumor cell death. PDT and SDT use optical or acoustic activation of PSs/sonosensitizers loaded in b-MSNs to achieve the therapeutic effect. CDT induces tumor cell death through Fenton/Fenton-like reactions mediated by metal-loaded b-MSNs. In addition, multiple nanosensitizers can be co-loaded into b-MSNs nanomaterials to enhance synergistic therapeutic effects. Here, we will describe the application of these nanodynamic therapies in the field of tumor theranostics.

4.2.1. PTAs

PTT is a therapeutic modality that introduces PTAs with high photothermal conversion efficiency and uses NIR irradiation to activate the PTAs, converting light energy into thermal energy for local tumor cell ablation without causing systemic toxicity [120]. Among the various existing nanomaterials, b-MSNs are promising candidates for integrating PTAs for PTT due to their easily modified surface structure, good PTAs loading ability and *in vivo* safety. For example, Qian *et al.* [121] constructed degradable PMOs with double sulfur bond hybridization (disulfide and tetrasulfide bonds) to encapsulate both aloe-emodin and IR820 for chemo-PTT against tumors. Similarly, Wang *et al.* [122] reported a degradable MONs nanosystem (DOX@(MONs-Azo)@PDA) bridged with diselenide and decorated with double-gated Azo/PDA for synergistic PTT and chemotherapy to treat breast cancer. Once at the tumor site, the PDA corona exhibited a heightened susceptibility to the acidic pH of the TME, while the diselenide bridge demonstrated swift responsivity to the GSH of the TME. This allowed the degradable MONs to dissociate rapidly and efficiently release the encapsulated DOX into the tumor cells (Fig. 4A). By capitalizing on the synergistic interplay between PTT and chemotherapy, the formulation was able to completely eradicate tumors in BALB/c mice bearing 4T1 tumors with negligible systemic toxicity. PTT exists for about half a century and has become a promising tool for diagnosing and treating cancer cells. However, PTT still faces significant challenges, such as the limited depth of tissue penetration and the potential for thermal damage to normal tissue. Therefore, it is imperative to develop new therapeutic approaches to overcome these limitations.

4.2.2. PSs

PDT as a non-invasive method of tumor ablation has gained much interest in the last decade and has been clinically approved for cancer treatment [127]. During PDT, PSs, laser light and molecular oxygen are the three indispensable elements for antitumor effects. When laser light of a specific wavelength is applied to the tissue where the PSs are located, PSs would interact with the surrounding oxygen to generate ROS and induce tumor cell apoptosis or necrosis. However. upon entering the bloodstream, PSs tend to accumulate in aqueous environments and the skin. Therefore, the design of ideal DDSs to precisely deliver PSs to target tumor tissues and exert lasting therapeutic effects is crucial to achieving effective PDT. Notably, the rich mesoporosity and surface functionalization of b-MSNs can provide great advantages for the loading and protection of PSs. By enabling the timely degradation and fragmentation of b-MSNs in PDT, the loss of ROS in the internal pores is reduced and the killing power of ROS on cancer cells is amplified. This unique property will greatly enhance the efficacy of b-MSNs in cancer therapy. For instance, Yang *et al.* [126] developed red light-induced self-destructing diselenide bond-bridged b-MSNs for PDT to promote anti-tumor immune responses (Fig. 4E). By utilizing ROS-mediated diselenide bond cleavage, the silica matrix could degrade 58.2% after one day of light exposure,

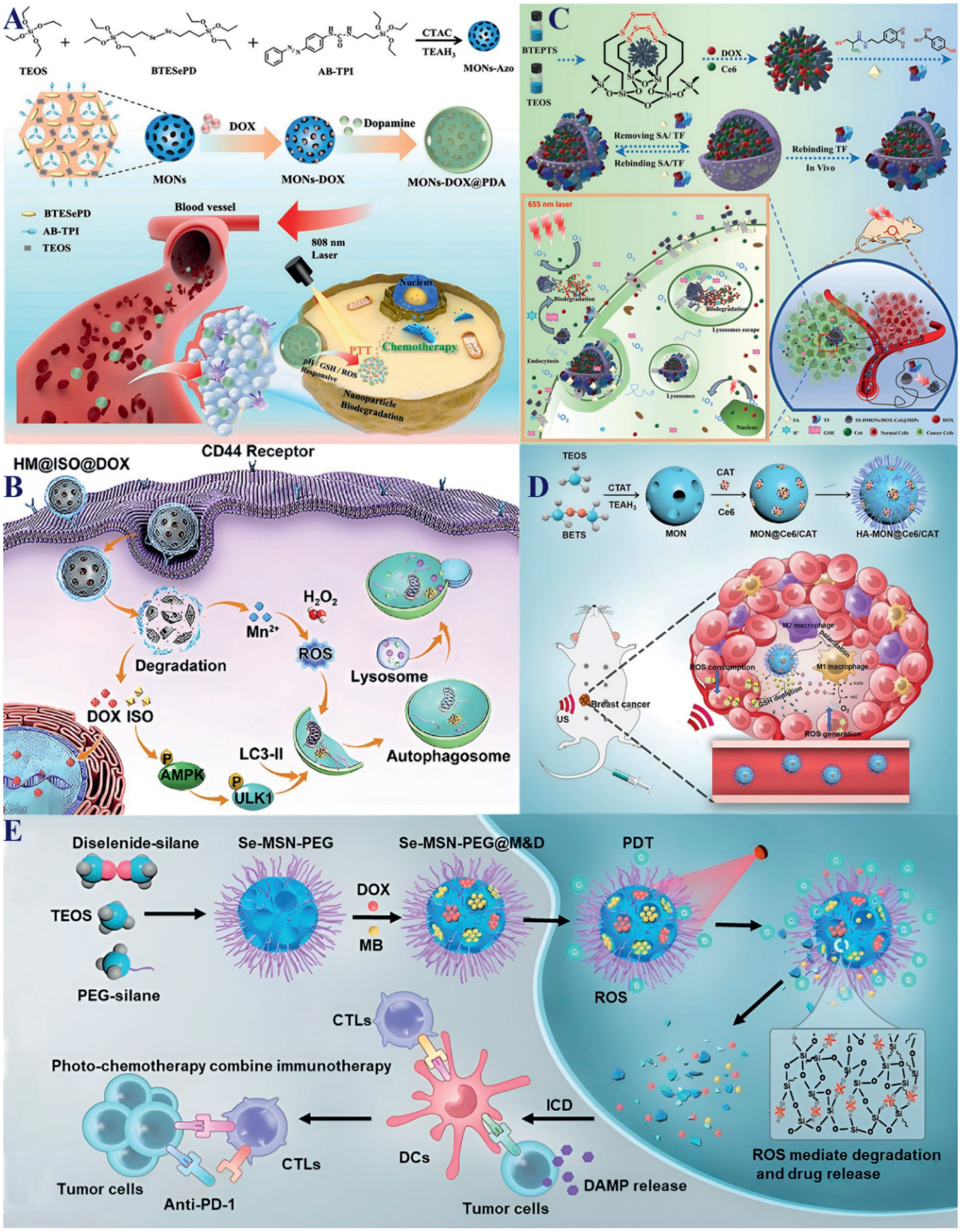

Fig. 4. (A) Schematic illustration of the combined therapy of photothermal-enhanced chemotherapy using DOX@(MONs-Azo3)@PDA. Reproduced with permission [122]. Copyright 2023, Elsevier Inc. (B) Explanation of mechanisms underlying HM@ISO@DOX mediated antitumor effects. Reproduced with permission [123]. Copyright 2022, Elsevier Ltd. (C) Schematics of fabrication of SS-DMONs/DOX-Ce6@MIPs and *in vivo* targeting and PDT. Reproduced with permission [124]. Copyright 2023, Wiley-VCH. (D) The synthesis process of the mesoporous organosilica nanoplatform and its application in the multimodal modulation of TME to enhance SDT. Reproduced with permission [125]. Copyright 2021, Dove Medical Press Ltd. (E) The synthesis process of Se-MSNs-PEG with cascade drug release and amplified ICD modality and the application in efficient and cancer chemotherapy-phototherapy-immunotherapy. Reproduced with permission [126]. Copyright 2022, Elsevier Ltd.

ultimately promoting the release of DOX and ROS. The degradability of the b-MSNs backbone ensured *in vivo* safety while enabling controlled drug release. Thus, the excellent properties of b-MSNs make them promising candidates for loading nanosensitizers. In addition, the introduction of targeting molecules may allow b-MSNs to target tumor cells more precisely and improve the biodistribution and efficacy of the cargo. For example, Liu *et al.* [124] prepared a disulfide-bridged degradable dendritic MONs (DMONs) DDS (SS-DMONS/DOX-Ce6@MIPs) imprinted with silicone sialic acid and transferrin (TF). The DDS possessed excellent tumor-targeting and dual-responsive drug-release capabilities. Under laser irradiation, the loaded chlorin e6 (Ce6) generated toxic ROS, which combined with DOX to achieve synergistic chemical/photodynamic anticancer effects (Fig. 4C).

4.2.3. *Fenton/Fenton-like agents*

Despite PDT has made great progress in tumor theranostics, its limitation lies in the insufficient depth of light penetration [128].

Therefore, a new therapeutic strategy has been proposed, namely CDT, which uses transition metal elements to catalyze H_2O_2 through Fenton/Fenton-like reactions in tumor cells *in situ* to induce apoptosis [129]. However, the mildly acidic pH, limited H_2O_2 content and overexpression of reducing substances in the TME could severely inhibit the efficiency of CDT [130]. With the rapid development of nanotechnology, certain nanomaterials with improved CDT efficiency have been used. And b-MSNs nanomaterials have been proven to be an ideal carrier for CDT due to their modifiable physical and chemical features. Inorganic components such as metal ions can be incorporated into the framework of MSNs to catalyze CDT initiation [131]. For example, Wang *et al.* [123] fabricated a co-delivery system for the treatment of hepatocellular carcinoma by incorporating DOX and isoginkgetin (ISO) into the mesoporous channels of manganese-doped MSNs, and then conjugated with hyaluronic acid (HA) to form HM@ISO@DOX (Fig. 4B). After being phagocytosed by the tumor cells, HM@ISO@DOX was biodegraded by the action of hyaluronidase. Furthermore, endogenous GSH, H_2O_2 and acidic pH in tumor cells would further facilitate the biodegradation process of HM@ISO@DOX by reducing the high-valent manganese ions (Mn^{3+} and Mn^{4+}) to Mn^{2+}. This would release the encapsulated chemotherapy drug and trigger the Mn^{2+}-mediated Fenton-like reaction to produce ROS for CDT. In addition, covalent bonds can be introduced into b-MSNs to enhance their application in CDT. For example, Liu *et al.* [132] designed a tetrasulfide bond-rich degradable MONs nanoplatform to regulate redox homeostasis and increase Fe^{2+}-triggered ROS generation by integrating GSH consumption, H_2S generation, self-provisioning of H_2O_2, and co-delivery of DOX and Fenton reagent Fe^{2+}.

4.2.4. Sonosensitizers

Low intensity US triggered SDT is a cancer treatment method with high tissue penetration and non-invasive properties [133]. By activating sonosensitizers to generate ROS, SDT can destroy tumor cells and vascular epithelial cells [134]. The generation of ROS is primarily initiated by the energy produced during cavitation and bubble collapse induced by US [135]. Currently, sonosensitizers can be classified into two major categories, organic sonosensitizers and inorganic sonosensitizers. However, the low accumulation of organic sonosensitizers at the tumor may limit the efficacy of SDT due to their hydrophobicity, high phototoxicity and low bioavailability [136]. In this regard, the efficacy of SDT can be effectively enhanced by b-MSNs-based nanoplatforms because of their ability to increase the water solubility and reduce the phototoxicity of sonosensitizers. Typically, the efficacy of SDT is limited by the unique microenvironment of solid cancers, which is characterized by hypoxia, GSH overexpression and high accumulation of anti-inflammatory tumor-associated macrophages. To address this issue, Zhou *et al.* [125] encapsulated sonosensitizers (Ce6) and peroxidase (CTA) in disulfide-bond-modified MONs to modulate the TME for efficient SDT treatment (Fig. 4D). Additionally, Zhu *et al.* [137] developed biodegradable HMSNs with MnO_x components integrated and conjugated to protoporphyrin. It was found that silica-based nanocarriers could degrade rapidly in the TME, and the MnO_x components acted as a nanoenzyme to catalyze the production of O_2 from H_2O_2, which helped alleviate tumor hypoxia and deplete GSH, and provided a rich oxygen source for SDT-induced ROS generation, thus greatly enhancing the efficacy of SDT.

4.3. Gaseous molecule delivery

Gas therapy is a new type of tumor theranostics that uses laser irradiation to produce a brief high-temperature gas, which causes a dramatic increase in pressure, resulting in the instantaneous expansion of bubbles within the gas, thus destroying tumor cells and blood vessels and achieving a therapeutic effect [138]. Compared to conventional chemotherapy or radiotherapy, gas therapy has the advantage of low toxicity and good local efficacy [139]. It has been found that gas molecules such as NO [140], CO [141], H_2 [142], H_2S [143] and SO_2 [144] have a modulating effect on the development of cancer. However, the off-target phenomenon of gas molecules often leads to poor tumor accumulation and weakens the therapeutic efficiency. Notably, b-MSNs have emerged as an ideal stimuli-responsive gas release nanoplatform due to their excellent properties to release gas molecules in a controlled manner, effectively preventing premature gas release and avoiding potential toxicity and side effects. Recently, Wu *et al.* [145] constructed RG-Mn@H nanocatalysts by surface engineering with RGD through the simultaneous integration of MnCO and GOD into biodegradable HMONs. In TME, the GOD gatekeeper was removed by GSH-induced disulfide bond cleavage and pH-induced imine bond hydrolysis, resulting in the release of loaded MnCO, which further reacted with the endogenous H_2O_2 and H^+ to achieve CO gas release and promote the efficacy of CO therapy.

4.4. Biomacromolecules delivery

Protein therapy is an effective means of intervening in cancer because of the highly specific targeting effect. However, proteins are susceptible to degradation and denaturation by proteases accompanied by the difficulties of the controlled release [146]. Moreover, the low stability and large size of proteins often result in a loss of therapeutic efficacy. Current protein delivery vehicles suffer from many problems, such as low loading efficiency, poor stability in serum, and lack of delivery versatility for different proteins [147]. At this point, b-MSNs offer a new route for delivering proteins. Proteins encapsulated in b-MSNs can be protected and the stability and bioavailability *in vivo* will be improved. For example, Yuan *et al.* [148] recently reported a novel approach to deliver a range of genetic material, including oligonucleotides, plasmids and siRNAs, using GSH-responsive biodegradable silica nanocapsules (BS-NPs) and successfully used this strategy for the intracellular co-delivery of siRNA/cetuximab (also known as Erbitux^{TM}) for the combination treatment of cancer cells overexpressing the epidermal growth factor receptor (Fig. S3A in Supporting information). The results indicated a significant reduction in tumor volume in mice treated with cetuximab and siAKT co-encapsulated with BS-NPs compared to negative controls, with 65.5% tumor inhibition over 28 days of treatment. Therefore, the use of b-MSNs to transport proteins can overcome the shortcomings of proteins that are prone to degradation and inactivation, and achieve controlled release of proteins for better therapeutic effects.

4.5. Initiation of immune response

The b-MSNs are considered to be effective carriers for enhancing tumor immunotherapy due to their degradability, stability and biocompatibility, and may play an important role in tumor immunotherapy. For example, the functionalized degradable MONs could co-deliver antigenic proteins (ovalbumin) and Toll-like receptor 9 agonists to antigen-presenting cells and induce endosomal escape [149]. Besides, Li *et al.* [150] prepared GSH-responsive degradable PEGylated HMONs as a nanocarrier to load hydroxycamptothecin (HCPT) and siRNA that could inhibit the monocarboxylate transporter (MCT-4). This nanocomplex was able to increase intracellular lactate accumulation by silencing MCT-4 expression, while promoting the phenotypic polarization of tumor-associated macrophages and the induction of apoptosis in tumor cells. In addition, the nanocomplex induced the secretion of pro-immune factors and activated an immune response to inhibit lung metastasis (Fig. S3B in Supporting information).

Therefore, by regulating the surface modification and functionalization of b-MSNs, the immune response can be activated, thereby enhancing the efficacy of immunotherapy. In addition, b-MSNs can also improve the efficacy of immunotherapy by carrying immunomodulators and specific antigens (*e.g.*, tumor neovascularisation-associated antigens, cell proliferation and apoptosis protein antigens). Overall, b-MSNs-based nanocarriers have broad and promising applications in tumor immunotherapy, but many challenges need to be addressed in future research, such as how to reduce the immune escape of tumors and how to improve the controlled release of drugs in the TME.

4.6. The synergistic therapy

In the context of the limitations of current single treatment strategies in inhibiting tumor growth, researchers are working to combine different therapeutic approaches to compensate for the shortcomings of single treatment strategies and expect to achieve more optimal treatment outcomes. Chemotherapy-related synergistic therapeutic strategies such as chemo-PTT, chemo-PDT, chemo-SDT and chemo-immunotherapy utilize b-MSNs to deliver PTAs, PSs and sonosensitizers. Once b-MSNs are ingested into tumor cells, these encapsulated cargoes can be released through biodegradation of the silica carrier to maximize the therapeutic effect on tumor cells, achieving multiple therapeutic benefits, including promoting apoptosis and destroying tumor cells. In addition, synergistic therapies based on nanodynamic therapy strategies include PTT-PDT, PDT-gas therapy and CDT-PTT, offering a more effective approach for tumor theranostics. These synergistic therapies can take advantage of the unique strengths of PTT, PDT and CDT to improve the effectiveness of tumor theranostics, expanding the scope and depth of cancer treatment and providing new ideas for developing more effective tumor treatment strategies.

4.6.1. Chemo-related synergistic therapy

For most tumors, chemotherapy is the mainstay of treatment. However, chemotherapy is less effective than expected and has been associated with significant side effects and drug resistance problems in numerous clinical and preclinical studies [151]. In contrast, in addition to the direct death of cancer cells, PTT may improve chemotherapy efficacy because the heat produced could facilitate drug release at the tumor site and improve the sensitivity of tumor cells to drugs [152]. In addition, PTT mainly targets the local tumor cells rather than the cells that have metastasized, whereas chemotherapy is a systemic treatment. Synergizing the two methods can achieve both local and distant effects, which can have a positive effect on the treatment of tumors. The application of b-MSNs for targeted delivery of drugs and PTAs to tumors can exert synergistic chemotherapy and PTT. For example, Qian *et al.* [153] fabricated a disulfide-bonded biodegradable HMONs nanosystem (PTX/IR820@HMONs-PEG) for the simultaneous delivery of PTX and IR820 and showed a significant increase in cell mortality exposed to NIR light, confirming the strong tumor-inhibiting effect of photothermal-assisted chemotherapy. In another example, Zhang *et al.* [154] co-loaded CuS NPs and molecular drug DSF into biodegradable HMONs to construct DSF@HCu nanomedicine, which achieved the synergistic effect of PTT and *in-situ* tumor chemotherapy under NIR light irradiation (Fig. 5A).

The combined use of chemotherapy and PDT regimens effectively compensates for the low efficacy of tumor monotherapy. On the one hand, PDT can reduce chemotherapy-induced drug resistance by inhibiting the expression of key drug resistance proteins like P-glycoprotein, improving cancer cell chemosensitivity and reducing chemotherapy drug doses [158]. On the other hand, chemotherapy can compensate the disadvantages of PDT, such as limited light penetration, eradicating tumor cells from different sites and deep tissues, and enabling complementary treatment of tumors. Moreover, after PDT, the number of actively dividing cancer cells in the PDT-treated tumor area decreases, resulting in a reduction of tissue growth rate, making it easier for chemotherapeutic drugs to enter tumor cells and obtain a longer residence time. Therefore, by co-delivering PSs and chemotherapeutic drugs, synergistic effects between the two can be realized and better therapeutic efficacy can be achieved. Based on the advantages of b-MSNs, Li’s group [159] designed a smart nanoplatform (UCSSDH) for on-demand burst drug release using diselenide-bridged mesoporous silica (Se-Se-mSiO_2) structures. The up-converted 650 nm emission light activated the Ce6 to produce $^1O_2$ for PDT when irradiated with 980 nm NIR light. The generated $^1O_2$ further cleaved the diselenide bond, driving the degradation of Se-Se-mSiO_2 and the associated bursting release of DOX. As a result, UCSSDH achieved effective chemo-PDT synergistic anti-tumor effects.

In addition to alleviating TME hypoxia, combining SDT and chemotherapy has been shown to have a synergistic effect in killing cancer cells with fewer side effects and overcoming drug resistance than monotherapy. On the one hand, SDT can induce bubble cavitation, which can partially damage tumor blood vessels and help improve the tumor vascular network, making it easier for chemotherapy drugs to penetrate tumor tissue and reach the target site, increasing the concentration of drugs in tumor tissue and improving the penetration and efficacy of chemotherapy [160,161]. On the other hand, SDT would lead to membrane disruption and tissue necrosis, which may increase the permeability of tumor cell membranes and promote the absorption of chemotherapeutic drugs by tumor cells [136]. For example, curcumin (Cur) is both a natural drug with good anti-cancer activity and a potent sonosensitizer capable of producing ROS to kill tumor cells upon stimulation by US. Based on this, Tian *et al.* [162] constructed Cur@Gd-HMSNs-CMD nanocomposites for synergistic SDT and chemotherapy by loading Cur into Gd-HMSNs and modifying the surface with carboxymethyl dextran (CMD). The Gd@HMSNs-CMD backbone was able to degrade in a mild acidic microenvironment and under US irradiation due to the presence of Gd elements in the silica backbone, promoting the release of loaded Cur and producing ROS, which could destroy tumor cells and achieve synergistic therapeutic effects of chemo-SDT.

Chemotherapy and immunotherapy are the two main directions in the current field of tumor theranostics. However, each of these treatments has its limitations. Chemotherapy drugs can cause a range of side effects and tumor cells can gradually become resistant to the drugs. The effectiveness of immunotherapy is also influenced by factors such as tumor immune escape and the immunosuppressive environment. In order to treat tumors more effectively, new strategies of chemotherapy in conjunction with immunotherapy have emerged in recent years. For example, to enable chemo-immunotherapy for cancer, Zhang *et al.* [156] tailored an ICD nanoamplifier with diselenide-bridged biodegradable MONs and a chemotherapeutic ruthenium compound (KP1339). The GSH response of KP1339-loaded MONs resulted in controlled drug release and matrix biodegradation. High concentrations of MONs selectively induced GSH depletion, ROS generation, and endoplasmic reticulum stress in cancer cells, thereby enhancing the ICD of KP1339 and promoting a robust anti-tumor immune response, synergistically enhancing therapeutic efficacy (Fig. 5C).

4.6.2. Nanosensitizers-based synergetic therapies

Photoactivated therapeutic strategies (PTT and PDT) are widely used and recognized in the field of tumor theranostics due to their low toxicity, non-invasiveness and high efficiency. The increase in local temperature induced by PTT can enhance tissue blood flow, increase tumor site O_2 levels and promote PSs release and uptake, thus enhancing the therapeutic effect of PDT [163]. Furthermore,

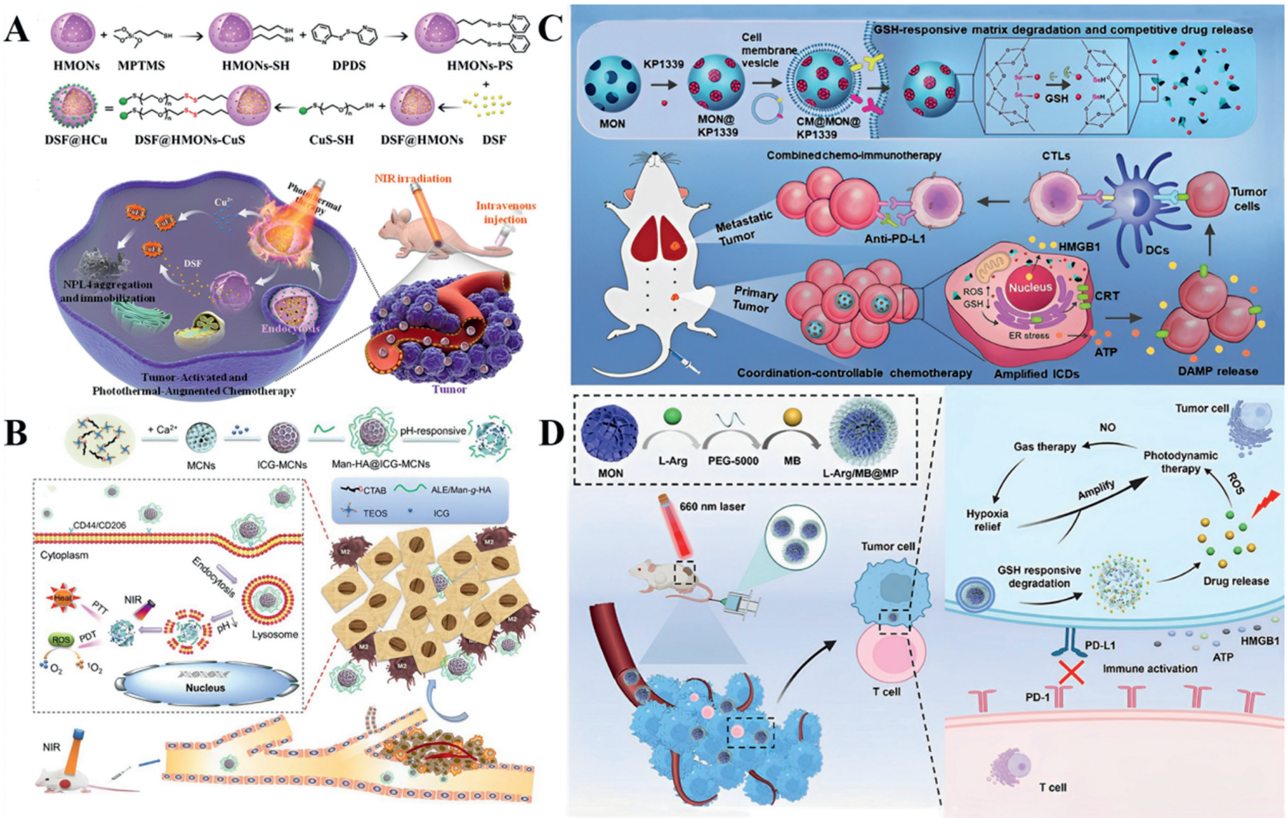

Fig. 5. (A) Schematic illustration of preparation of DSF@HCu nanosystem and efficient cancer cell killing and tumor growth inhibition by PTT-induced *in situ* Cu^{2+} release-activated DSF chemotherapy. Reproduced with permission [154]. Copyright 2021, BMC. (B) Schematic illustration of the fabrication of Man-HA@ICG-MCNs and synergistic tumor growth inhibition *in vivo* by PDT/PTT. Reproduced with permission [155]. Copyright 2021, Elsevier B.V. (C) Schematic diagram of the synthesis of diselenide bond-bridged MONs to enhance immunogenic cell death for the chemo-immunotherapy of cancer. Reproduced with permission [156]. Copyright 2021, Wiley-VCH GmbH. (D) Schematic synthesis of the L-Arg/MB@MP nanotherapeutic system and the mechanism of L-Arg/MB@MP-mediated synergistic PDT and gas therapy for treating tumor. Reproduced with permission [157]. Copyright 2022, Elsevier Ltd.

tumor cells may become more sensitive to thermotherapy due to the ROS generated by PDT, further enhancing the therapeutic effect of PTT [164]. Therefore, it is of great biomedical application to construct multifunctional nanocomposites using b-MSNs as carriers to combine chemotherapeutic drugs, PSs and PTAs to maximize the synergistic killing effect on tumor cells. For instance, Gao *et al.* [155] added calcium ions during the formation of MSNs to confer pH-responsive degradation behavior to the silica backbone, resulting in mesoporous calcium silicate nanocomposites (MCNs), then mannosylated HA was modified on the surface of ICG-loaded MCNs to obtain a nanoplatform named Man-HA@ICG-MCNs (Fig. 5B). Once the tumor site was irradiated with 808 nm NIR light, the nanoplatform absorbed the light energy and converted it into thermal energy to achieve the PTT effect, and triggered the generation of $^1O_2$ for PDT. Ultimately, the synergistic therapy of PDT and PTT showed significant efficacy in inducing cancer cell death and tumor ablation, independent of oxygen availability.

PDT can be used synergistically not only with PTT but also with gas therapy to treat tumors. Specifically, the use of gas therapeutics to influence TME can improve the efficacy of PDT. In addition, this synergistic therapy strategy can improve the sensitivity of cancer cells to PSs and reduce side effects such as angiogenesis due to hypoxia. However, the precise release of gas therapeutics into the TME remains a challenge. Recently, Feng *et al.* [157] prepared a GSH-responsive PEG-coated degradable MONs to encapsulate L-arginine (L-Arg) and methylene blue (MB) to form L-Arg/MB@MP for PDT synergistic gas therapy for tumor treatment. When L-Arg/MB@MP accumulated in the TME, the disulfide bonds in the MONs backbone were broken in the presence of the GSH, resulting in the structural collapse of the MONs and the release of the loaded MB and L-Arg. After exposure to the laser, L-Arg/MB@MP directly generated abundant ROS for PDT, while a fraction of ROS participated in oxidizing L-Arg to produce NO, which could be used for gas therapy as well as a biomessenger to modulate vasodilation and alleviate hypoxia in tumor. In addition to this, the biodegradation of L-Arg/MB@MP induced GSH depletion in tumor tissues and amplified the therapeutic effect of PDT in synergy with gas therapy (Fig. 5D). Overall, the use of b-MSNs to combine gas therapeutics with PDT allowed for the precise release of gas therapeutics, thereby improving the efficacy of PDT and avoiding damage to normal cells.

In CDT synergistic PTT, b-MSNs play a key role. First, b-MSNs deliver Fenton or Fenton-like agents (*e.g.*, metal ions) to the tumor tissue by drug loading. Once the b-MSNs enter the tumor tissue, these Fenton or Fenton-like agents will be released and affect the tumor cells in various ways, including interfering with the metabolism or DNA replication of the tumor cells and disrupting the cell structure. Subsequently, NIR light is used to activate the b-MSNs loaded with PSs, generating a localized photothermal effect to destroy the tumor cells and further enhance the therapeutic effect. This local thermal effect can destroy the structure and function of tumor cells, causing them to be damaged or even die. At the same time, PTT can enhance the effect of Fenton or Fenton-like agents as they have been released into the tumor tissue, resulting in a better therapeutic effect. Typically, the Fe-mediated Fenton reaction converts cytoplasmic H_2O_2 to a broad range of highly toxic ·OH, leading to irreversible mitochondrial damage for tumor cell clearance. Unfortunately, intracellular overexpression of GSH is always effective in scavenging ·OH, resulting in a significant reduction in CDT efficacy. In order to overcome this drawback and ameliorate cytoplasmic oxidative stress, Li *et al.* [165] constructed Fe_3O_4 ultra-small NPs-encapsulated and ICG-loaded degradable organic MSNs (omSN@Fe-ICG). Upon internalization of the omSN@Fe-ICG, the tetrasulfide bonds in the silica backbone could easily collapse with the consumption of GSH, resulting in the biodegradability of the silica-based framework. In this way, omSN@Fe-ICG could amplify the generation of toxic ROS through the selective conversion of H_2O_2 to ·OH by the released iron-based NPs. In addition, the rate of Fenton reaction could be further enhanced by NIR laser-induced PTT. Consequently, tumor eradication could be significantly improved by GSH depletion and PTT-assisted CDT.

To summary, although synergistic treatment with nanosensitizers has shown some potential to effectively kill deep-seated tumors, new strategies need to be developed to further promote the application of nanosensitizers in tumor theranostics. These strategies include exploring the mechanisms of action of nanosensitizers in depth, developing more efficient PSs, alleviating the problem of insufficient H_2O_2 in the TME and increasing the penetration depth of the excitation light.

4.7. Tumor theranostics

Nano-theranostic integration is a comprehensive nanoplatform that integrates the two separate processes and functions of diagnosis and therapy into a single nanocarrier through the rational design and synthesis of nanomaterials [166]. This platform enables effective imaging of focal tissues, simultaneous detection, localization, and treatment of tumor tissues. Additionally, treatment efficacy can be continuously monitored to tailor drug delivery for optimal therapeutic effect while minimizing toxic side effects. For this reason, a number of bio-imaging techniques have been used to help determine the optimal time for therapy and to monitor subsequent treatments. These bio-imaging techniques include PAI, ultrasound imaging (USI), magnetic resonance imaging (MRI), fluorescence imaging (FL), and multimodal imaging. By delivering contrast agents to the tumor site *via* b-MSNs nanoplatforms, these techniques can enhance the visualization of specific physiological regions [167]. In addition, many researchers have also focused on the integration of these bio-imaging techniques with therapeutic modalities on b-MSNs-based nanoplatforms for more effective tumor theranostics. These approaches not only provide accurate tumor diagnostic information, but also allow for some degree of therapeutic efficacy and real-time monitoring with feedback on the treatment process to optimize treatment options and improve outcomes. Specific information is shown in Supporting information.

5. Conclusion and outlook

The rapid advancement of nanotechnology has facilitated the development of numerous MSNs-based nanocarriers for efficient drug delivery, as MSNs have demonstrated exceptional characteristics including high drug loading, large specific surface area, flexible surface modification and tunable size and morphology, making them promising delivery systems for various applications.

The poor biodegradability of MSNs often results in severe bioaccumulation, which is a major barrier to biomedical application and clinical translation. Therefore, this review summarized various strategies to improve the biodegradability of MSNs for effective tumor theranostics, such as the incorporation of various substances, including organic groups, metal ions, covalent bonds, HAPs and CDs into the b-MSNs-based nanocarrier frameworks. And thanks to the enhanced biodegradability of b-MSNs, this review described the application of b-MSNs-based nanocarriers for enhanced tumor theranostics, including improved tumor chemotherapy, nanodynamic therapy (PTT/PDT/CTD/SDT), gas therapy, biomacromolecules delivery, initiation of immune responses, multimodal synergistic therapy, and bioimaging-mediated tumor therapy. The emergence of these therapeutic strategies may provide new ideas, opportunities and challenges for cancer treatment.

We summarized many strategies to increase the biodegradability of MSNs, including the incorporation of metal ions or chemical bonds, but it is worth noting that not all metal doping could improve the biodegradability of MSNs. Shi *et al.* [60] pointed out that although a moderate amount of strontium doping could confer improved biodegradability to MSNs, an excessive amount of strontium doping would hinder the biodegradability of MSNs by forming some unknown insoluble substances. Similarly, not all covalent bonds could accelerate the biodegradability of MSNs. The work of Wang *et al.* [168] broke the common perception that all thioether bond-bridged MONs could be excellent biodegradable carriers. It is also worth mentioning that PEG as a steric stabilizer could also inhibit the biodegradability of MSNs [169] because of the reduction of silanol groups on the surface of MSNs after PEGylation, which reduced hydrolysis-dependent degradation.

Therefore, it is important to acknowledge that although significant progress has been made in the preparation of b-MSNs biomaterials, several challenges still need to be addressed to further promote the b-MSNs for clinical translation. Some of these challenges include:

(1) The degradation properties of b-MSNs. Understanding the behavior of b-MSNs in complex biological environments such as blood or cellular compartments is essential to ensure their stability, prevent aggregation and control degradation rates. To ensure that b-MSNs can exert a therapeutic effect at the tumor site, researchers often construct TME-responsive b-MSNs to achieve biodegradation and controlled drug release behavior. However, TME is complex and heterogeneous, which may lead to insensitive and difficult biodegradation of b-MSNs. Although external triggers such as light, temperature, US, magnetic field, *etc.* have been explored to achieve stimuli-responsive biodegradation of b-MSNs for cargo release, these external stimuli may lead to untimely degradation of b-MSNs, triggering potential toxic side effects. Therefore, it is necessary to thoroughly investigate the degradation properties of b-MSNs *in vivo* and explore other triggering factors to improve the biodegradation of b-MSNs. For example, bio-enzyme catalysis can be designed to improve the biodegradation of b-MSNs since bio-enzymes can recognize and degrade specific chemical bonds or molecular structures modified on b-MSNs. In addition, the use of specific microorganisms *in vivo* may also mediate the biodegradation of b-MSNs for controlled drug release. Besides, surface functionalization by introducing specific functional components, such as enzymes or biodegradable ligands, can improve the biodegradability of b-MSNs and promote their further application in biomedical fields.

(2) The biodegradation mechanisms of b-MSNs. Factors like morphology, specific surface area, pore size and particle size may also have an important influence on the degradation of b-MSNs. For example, different morphologies of b-MSNs, such as spherical, rod-shaped or flaky, may exhibit different behaviors in the biodegradation process [170]. Larger specific surface areas are often associated with faster biodegradation rates, and larger pore and particle diameters may lead to faster biodegradation. In addition, morphology may also affect the rate of diffusion and transport of substances, which in turn affects the biodegradation of b-MSNs [171]. These factors may be interrelated and have complex effects on the biodegradation of b-MSNs. Therefore, it is necessary to thoroughly investigate the effects of

these factors on the biodegradation of b-MSNs. To study the effects of these factors in detail, b-MSNs with different morphologies, specific surface areas, pore sizes and particle sizes can be prepared by modulating the synthesis method and subsequent functionalization, and their biodegradation behavior can be demonstrated by *in vitro* and *in vivo* experiments. In addition, the relationship between these factors and the biodegradation of b-MSNs can be explored through further theoretical simulations and computational methods. *In vivo* kinetic studies could be studied in depth to follow the distribution, degradation rate and drug release behavior of b-MSNs with different pore sizes, particle sizes, morphologies and specific surface areas in organisms. This will help to optimize the design and synthesis of b-MSNs for more precise control of biodegradation and improve their safety and efficacy in tumor theranostics.

(3) The behavior of b-MSNs *in vivo*. Future studies should focus on the following aspects: (a) *In vivo* biodistribution: understanding how b-MSNs behave in different biological conditions, including their localization after injection and their accumulation in target tissues or cells, can optimize targeted therapies and minimize adverse effects on non-targeted tissues. (b) Metabolic pathways: studying the metabolic pathways of b-MSNs *in vivo* can reveal their metabolites and metabolite toxicity. This is important for evaluating the safety and potential toxicity of b-MSNs, and contributes to rational design and optimization. (c) Long-term residual properties: the study of long-term residuals of b-MSNs *in vivo* is essential to assess their persistence and potential bioaccumulative effects. This includes studies of the rate of degradation of b-MSNs, the rate of clearance of metabolites, and the long-term effects of residues on the organism. These studies will enable better understanding of the controllability and safety of b-MSNs, as well as risk assessment and monitoring of their clinical application. (d) *In vivo* toxicity assessment: currently, the biodegradability of b-MSNs is mainly dependent on *in vitro* experimental data, and further assessments of their acute and long-term toxicity *in vivo*, as well as bioaccumulation and elimination are needed. Such an assessment can be accomplished by using animal models and performing *in vivo* translational experiments to ensure the safety of b-MSNs and the feasibility of potential clinical translation.

(4) The safety evaluation of b-MSNs. In order to ensure the safety of b-MSNs, a comprehensive evaluation system needs to be established. Firstly, toxicity studies are one of the key aspects in evaluating the safety of b-MSNs. This includes studies on acute toxicity, chronic toxicity and reproductive toxicity of b-MSNs nanomaterials. The effects of b-MSNs on cellular, tissue and physiological functions could be assessed through *in vivo* and *in vitro* experiments at different doses and time scales to determine their potential toxic effects and safety boundaries. In addition, properties such as biocompatibility and immunogenicity of b-MSNs need to be investigated to assess their tolerance and interactions in organisms. Therefore, the establishment of a comprehensive evaluation system is the key to ensuring the safety of b-MSNs. The toxicity studies, biodistribution and evaluation of metabolic pathways can provide a comprehensive understanding of the behavior of b-MSNs *in vivo* and potential safety issues. Meanwhile, solving the industrialization and commercialization issues of b-MSNs can assure their sustainable development and commercial application. This requires collaboration between academia, industry and regulatory agencies to jointly promote the safety evaluation and application of b-MSNs.

In conclusion, it is crucial for researchers to acknowledge the limitations of b-MSNs and work towards finding solutions that are better adapted to clinical needs. To accelerate the development of b-MSNs nanotechnology, an interdisciplinary approach that integrates the fields of pharmacology, molecular biology, artificial intelligence, statistics and computer imaging in the design of drug delivery therapies is needed. By addressing these challenges, b-MSNs nanocarriers hold the promise of becoming the next generation of nanomedicines, capable of treating many currently incurable diseases and significantly improving human well-being.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Mengwei Ye: Writing – original draft, Software, Methodology, Investigation, Formal analysis, Conceptualization. **Qingqing Xu:** Writing – original draft, Data curation. **Huanhuan Jian:** Visualization, Investigation. **Yiduo Ding:** Investigation. **Wenpeng Zhao:** Software. **Chenxiao Wang:** Software, Resources. **Junya Lu:** Validation, Supervision. **Shuaipeng Feng:** Visualization, Software. **Siling Wang:** Visualization, Supervision. **Qinfu Zhao:** Writing – review & editing.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cclet.2024.110221.

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