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Redox-responsive theranostic nanoplatforms based on inorganic nanomaterials

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ABSTRACT

Spurred on by advances in materials chemistry and nanotechnology, scientists have developed many novel nanopreparations for cancer diagnosis and therapy. To treat complex malignant tumors effectively, multifunctional nanomedicines with targeting ability, imaging properties and controlled drug release behavior should be designed and exploited. The therapeutic efficiency of loaded drugs can be dramatically improved using redox-responsive nanoplatforms which can sense the differences in the redox status of tumor tissues and healthy ones. Redox-sensitive nanocarriers can be constructed from both organic and inorganic nanomaterials; however, at present, drug delivery nanovectors progressively lean towards inorganic nanomaterials because of their facile synthesis/modification and their unique physicochemical properties. In this review, we focus specifically on the preparation and application of redox-sensitive nanosystems based on mesoporous silica nanoparticles (MSNs), carbon nanomaterials, magnetic nanoparticles, gold nanomaterials and other inorganic nanomaterials. We discuss relevant examples of redox-sensitive nanosystems in each category. Finally, we discuss current challenges and future strategies from the aspect of material design and practical application.

1. Introduction

Advanced nanoplatforms for cancer diagnosis and therapy, with unique properties such as nanoscale size, large surfaces with high area-to-volume ratio and favorable physicochemical characteristics, have been extensively designed and explored. Nevertheless, significant limitations remain, including leakage of the loaded drug during the circulation process and slow drug release at the diseased sites, which will dramatically compromise the effectiveness of the treatment [1–3]. Therefore, tremendous efforts have been devoted to developing controlled release nanosystems, e.g. bio-responsive nanocarriers [4–6]. Variations in endogenous stimuli, including pH [7], redox potential [8] and the concentration of enzymes [9] or specific analytes, have been exploited to control the release of drugs. Among the bio-responsive nanocarriers that have been developed, redox-sensitive nanocarriers have attracted particular attention in recent years [10,11].

Redox potential is a property that differs between cancerous and healthy tissues, as well as between the extra-cellular and intra-cellular compartments. It has been reported that the level of the glutathione tripeptide (γ-glutamyl-cysteinyl-glycine) (GSH) is much higher in tumor tissues than healthy ones. In addition, the concentration of GSH in the cytosol and subcellular compartments (e.g. lysosomes and endosomes) is approximately 2–10 mM, about 100–1000 times higher than that in cellular exterior, which is about 2–10 μM [12]. Taking advantage of this physiological difference, scientists have constructed various redox-sensitive nanocarriers, which demonstrate excellent stability during blood circulation but rapidly degrade and effectively trigger drug release in tumor cells [13].

Nanosystems responding to the redox environment can be prepared by integrating reduction- or oxidation-sensitive bonds. Disulfide bonds, prone to rapid cleavage by GSH, can be broadly applied to develop reduction-responsive nanovehicles. The energies of diselenide (Se—Se) and carbon-selenium (C—Se) bonds (172 and 244 kJ·mol^{-1}, respectively) are lower than the energy of disulfide bonds, which makes them more sensitive to reducing agents, e.g. intracellular GSH [14]. Additionally, oxidation-responsive groups containing ferrocene [15], boronic ester [16] and tetrathiafulvalene [17] are hydrophilic in the oxidized form, but are hydrophobic in the reduced form. Thus, polymers containing these groups can self-assemble into nanoparticles in reducing conditions and disassemble in oxidizing conditions, allowing site-specific drug release.

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Generally, liposomes, micelles, dendrimers and polymer- or protein-based nanomaterials can be employed to develop redox-sensitive nanocarriers for drug delivery. Some of these nanocarriers have been approved by the Food and Drug Administration (FDA) and are used in the clinic. However, the requirement for multiple functionalities including targeting ability, redox responsiveness and longevity in circulation, makes their preparation a complex and tedious multi-step process. Hence, manufacturing reproducibility, mass production and the pre-leakage of drugs under harsh environmental conditions remain major challenges for clinical translation of these conventional nanocarriers. Recently, the focus has been on novel redox-reponsive nanosystems based on inorganic nanocarriers because of their facile synthesis/modification and their unique physicochemical properties. Moreover, the size, shape and surface functionalization of the nanoparticles can be easily controlled, and the production processes can be scaled up.

In this review, we will focus separately on the preparation and application of mesoporous silica nanoparticles (MSNs), carbon nanomaterials, magnetic nanoparticles, gold nanomaterials and other inorganic nanomaterials to construct redox-responsive theranostic nanoplatforms. In particular, we evaluate MSNs-based redox-sensitive nanosystems. In addition, current challenges and future strategies are also discussed from the aspect of material design and practical application.

2. Redox-responsive nanoplatforms based on mesoporous silica nanoparticles

Although only a few nanomedicines based on inorganic nanoparticles have been received FDA approval, their novel design and formulations are influencing conventional medicine and show potential for use in diagnosis and/or treatment. MSNs have the advantages of excellent biocompatibility [18], uniform cylindrical mesopores, tunable pore sizes and volumes [19], different shapes ranging from spheres to rods and high surface areas [20]. In addition, their surfaces can be easily functionalized [21]. Currently, the family of MSNs including MCM-41, MCM-48 and MCM-50 has been utilized for redox nanosystems, because sufficient silanol groups (Si—OH) on the surfaces of these MSNs are available for further modifications. As described in the following sections, drugs can be loaded onto MSNs-based nanopreparations by means of covalent conjugation or physical loading.

2.1. Covalent conjugation

Therapeutic molecules including chemical- and gene-based drugs can be covalently conjugated onto the surfaces and mesopores of MSNs by redox-sensitive bonds. Fluorescent compounds including cyanine 5 (Cy5) and fluorescein isothiocyanate (FITC) are usually used to trace the location of MSNs and loaded drugs. Yan-Li Zhao et al. [22] employed Cy5 to label antisense peptide nucleic acid (PNA), an analogue of DNA and RNA [23]. PNA (Cy5) was then covalently conjugated onto fluorescent mesoporous silica nanoparticles (FMSN) through a disulfide linkage to yield FMSN-SS-PNA (Cy5) (Fig. 1A). It was demonstrated that cellular endocytosis of PNA was facilitated by anchoring it onto the surface of the FMSN, and the intracellular release of PNA (Cy5) occurred due to cleavage of the disulfide bonds by a natural reducing agent, i.e. GSH (Fig. 1B). Additionally, Zhao et al. found that expression of the B-cell lymphoma 2 (Bcl-2) protein was efficiently silenced by FMSN-SS-PNA (Bcl-2) (Fig. 1C). It follows that the toxicity of conjugated drugs can be reduced and their delivery efficiency can be enhanced by linking the drugs to MSNs via redox-responsive bonds. This approach provides new insights into the development of MSNs-based pharmaceuticals.

2.2. Physical loading

Chemotherapeutics or gene-silencing drugs can also be encapsulated into the mesopores of MSNs, which are capped by redox-sensitive molecular gates to control cargo release. These sealing agents, which include cyclodextrin [2] rotaxanes [24,25] or pseudorotaxanes [26,27], bio-macromolecules [28,29], inorganic nanoparticles and so forth, behave as molecular nanovalve to “switch off” and “switch on” the mesopores.

2.2.1. Cyclodextrin as a capping agent

Switchable [2]rotaxanes or pseudorotaxanes that are used as gates are usually composed of the following components: (a) linear stalks, which anchor the rotaxanes to the surfaces of MSNs; (b) gating rings, such as cyclodextrins, crown ethers, cyclophanes and cucurbiturils, which encircle the stalks and trap the cargo; (c) cleavable stimulus-responsive bonds, which can control the movement of macrorings, thus leading to opening or closure of the mesopores; and (d) stoppers at the termini of the stalks [30]. Yan-Li Zhao et al. [25] modified [2]rotaxanes on MSNs using a disulfide bond as a linker. They immobilized a tetraethylene glycol (TEG) derivative onto MSNs. α-cyclodextrin (α-CD) rings were then attached to the TEG units using the high affinity between -$(CH_2$-$CH_2O)_4$- of TEG and the hydrophobic cavity of α-CD. The α-CD rings act as a molecular gate to block and release the loaded drugs because of its unique three dimensional structure [26,27]. Folic acid (FA) was finally anchored onto the termini of the TEG chains. The FA molecule is able to prevent shedding of the α-CD rings because of its 2-amino 4-hydroxyl pteridin structure and three -NH- groups. Thus, FA units behaved both as both the stoppers of [2]rotaxanes and as tumor-targeting agents [28]. More interestingly, Xian-Zheng Zhang et al. [26] fabricated a novel class of multifunctional envelope-type mesoporous silica nanoparticles (MEMSN) in a “programmed packing” manner. As illustrated in Fig. 2A, doxorubicin (DOX) was loaded into the mesopores of MSNs, the surface of which was linked to β-CD through disulfide bonding. The MSNs were decorated with the Arg-Gly-Asp (RGD) motif, the matrix metalloproteinase (MMP) substrate peptide, i.e. Pro-Leu-Gly-Val-Arg (PLGVR), and poly(aspartic acid) (PASP). After the MEMSN arrives at tumor sites, the PASP protection layer can be removed via hydrolysis of the PLGVR peptide by MMP, leading to exposure of the targeting peptide RGD (Fig. 2C). Subsequently, the nanoparticles would be endocytosed by tumor cells (Fig. 2D). The loaded drugs would then be released quickly because the gatekeeper β-CD would be eliminated owing to breakage of the disulfide bonds by GSH within the tumor cells (Fig. 2E). In vitro results [26] indicated that the efficiency of inhibition of tumor cell growth was dramatically enhanced by the MEMSN.

2.2.2. Macromolecules as capping agents

Biomacromolecules [31–35] are also often exploited as sealing agents for the mesopores of MSNs. Kai-Yong Cai and co-workers [36] fabricated a biocompatible redox-sensitive nanocontainer, in which cytochrome *c* (CytC) was immobilized onto MSNs as a gatekeeper via disulfide bonds. The AS1411 aptamer was further conjugated to the surfaces of the MSNs for cell/tumor targeting (Fig. 3A). This novel nanosystem can achieve three therapeutic effects: (i) the breakage of —S—S— for release of loaded DOX (therapy I); (ii) binding of AS1411 molecules to nucleolin, leading to loss of the ability to repair DNA damage (therapy II); and (iii) interaction of CytC with apoptotic protease activating factor (Apaf-1), resulting in cell apoptosis (therapy III) (Fig. 3B). In vivo investigation indicated that tumor growth was effectively inhibited by the triplex therapeutic nanosystem due to the synergistic effects of combining therapies I, II and III, as shown in Fig. 3C. In 2011, Cai et al. also reported redox-responsive nanoreservoirs with collagen as the molecular cap for orifices of the MSNs and lactobionic acid (LA) as the targeting moiety [35]. Xian-Zheng Zhang et al. [32] immobilized an RGD-containing peptide onto MSNs using disulfide bonds. The RGD-containing peptide behaved not only as an intracellular reductant-responsive gatekeeper, but also as a target molecule for $\alpha_v\beta_3$-integrin on tumor cells. In 2013, Zhang et al. constructed a dual-responsive drug carrier, based on MSNs, with pH- and redox-sensitivity [33].

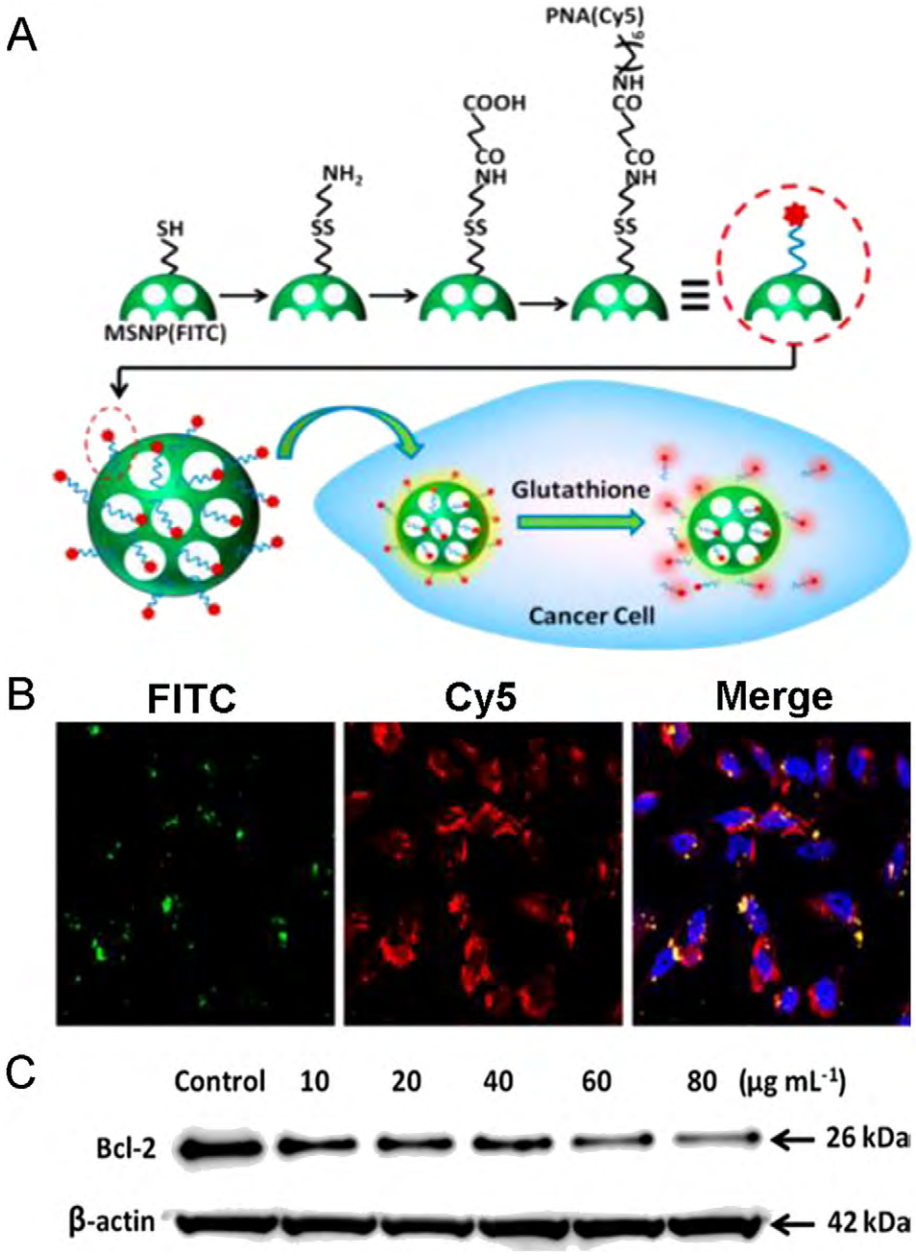


Fig.1. A. Illustration of FMSN-SS-PNA (Cy5) conjugates and intracellular release behavior of PNA (Cy5) from the conjugates in presence of GSH. B. CLSM images of HeLa cells treated with FMSN-SS-PNA (Cy5) for 24 h, indicating that almost all of the PNA (Cy5) is released from the conjugate in HeLa cells. C. When HeLa cells were incubated with FMSN-SS-PNA (Bcl-2) at different concentrations and the expression level of Bcl-2 protein was detected by the western blotting method. Adapted with permission from reference [22].

Monomethoxypolyethylene (MPEG) was connected with the peptide RGDFFFFC via a pH-sensitive bond, i.e. benzoic-imine. In the acidic pH conditions of tumor tissues, the MPEG was shed, and the DOX-loaded nanosystem was then easily "swallowed" by tumor cells via receptor-mediated endocytosis. Subsequently, the intracellular GSH induces rapid DOX release by cleaving the disulfide bonds.

Natural macromolecules [29,37–39], e.g. heparin (HP), polyethylene glycol (PEG) and poly(acrylic acid) (PAA), can also be applied as sealants. Kai-Yong Cai et al. [29] exploited HP as a capping agent and immobilized HP on MSNs via disulfide bonds. They further coupled LA to HP for cell targeting. Yong-Yong Li and De-Ping Wang et al. [37] reported a unique redox-sensitive nanocontainer in which PEG chains were conjugated onto MSNs via disulfide bonds and served as efficient gatekeepers to control the release of loaded drugs. Similarly, Dong Yang et al. [38] developed a reduction-responsive drug carrier in which poly(acrylic acid) (PAA), linked to MSNs via disulfide linkage, acted as a molecular valve. Interestingly, Itamar Willner et al. [39] fabricated another novel redox-triggered drug delivery system, in which MSNs were modified with chloronaphthoquinone units to trap drugs by use of donor-acceptor interactions. In this system, 2-amino-3-chloronaphthoquinone behaved as an electron acceptor and the π bonds of the entrapped substances acted as electron donors. Biological reducing agents, such as nicotinamide adenine dinucleotide (phosphate) (NAD(P)H) and ascorbic acid, can reduce the quinone units to the hydroquinone state (Fig. 4A). Following reduction, 2-amino-3-chloronaphthoquinone exhibited hydrophilicity and turned toward the aqueous phase, leading to opening of the pores and release of the trapped drugs. When the hydroquinone units were oxidized to quinone in the presence of oxidants, reloading of model drugs also occurred (Fig. 4B).

Redox-sensitive bonds are not only used to anchor molecular valves onto MSNs, as described above, but are also employed to

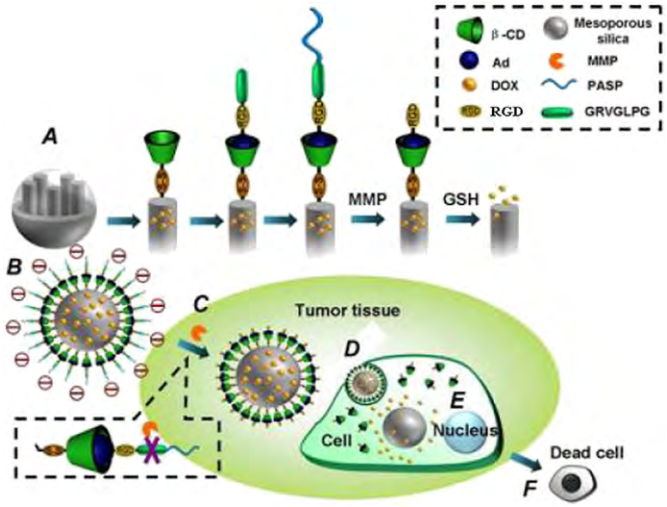


Fig.2. A. Functionalization protocol for MEMSN and the release behavior of MEMSN at tumor sites; B. encapsulation of DOX within the MEMSN under physiological condition; C. removal of the PASP layer in response to MMP in the tumor tissues; D. cellular uptake via RGD-mediated endocytosis; E. glutathione-triggered DOX release inside tumor cells; F. apoptosis of tumor cells. Adapted with permission from reference [26].

form cross-linked polymer shells to act as gatekeepers. Feng and co-workers [40] firstly synthesized cystamine-cross-linked poly(*N*-(acryloxy)succinimide) (PNAS)-coated MSNs. However, the process of immobilizing cross-linked polymeric networks on the surface of MSNs is restricted by the two-step method of PNAS polymerization and cross-linking. In 2013, Chun-Yan Hong et al. [41] developed one-pot synthesis of cross-linked poly(oligo(ethylene glycol)) acrylate-co-N,N′-cystaminebismethacrylamide) (poly(OEGA-*co*-CBMA))-capped MSNs via reversible addition-fragmentation chain transfer (RAFT) polymerization. Similarly, Shi-Yong Liu et al. [42] copolymerized *N*-(acryloxy)succinimide (NAS), oligo(ethylene glycol) monomethyl ether methacrylate (OEGMA) and 1,8-naphthalimide (NaphMA), forming P(NAS-co-OEGMA-co-NaphMA) brushes on the surface of MSNs. The brushes were further cross-linked with cystamine to block the mesopores to entrap guest molecules, i.e. rhodamine B (RhB).

2.2.3. Inorganic nanoparticles as capping agents

Inorganic nanostructures have unique physicochemical properties. When inorganic nanomaterials are used as sealing agents for the mesopores of MSNs, the coated MSNs can be further modified for an enormous diversity of application. For example, quantum dots (QDs)-functionalized MSNs were able to facilitate intracellular drug delivery and simultaneous cell imaging. In addition, magnetic nanoparticles (Fe_3O_4 NPs), if modified onto MSNs, can also be used to guide MSNs-based systems to the target disease site under the control of an external magnetic field.

Brian G. Trewyn's group [43] modified the mesopores of MSNs with gold nanoparticles (Au NPs) through disulfide linkage, thus physically preventing the encapsulated luciferin from leaching out. Luciferase is adsorbed onto PEGylated MSNs through electrostatic interactions. When the luciferase-luciferin Au-MSNs were endocytosed by cells, the trapped luciferin was released due to breakage of the disulfide bonds

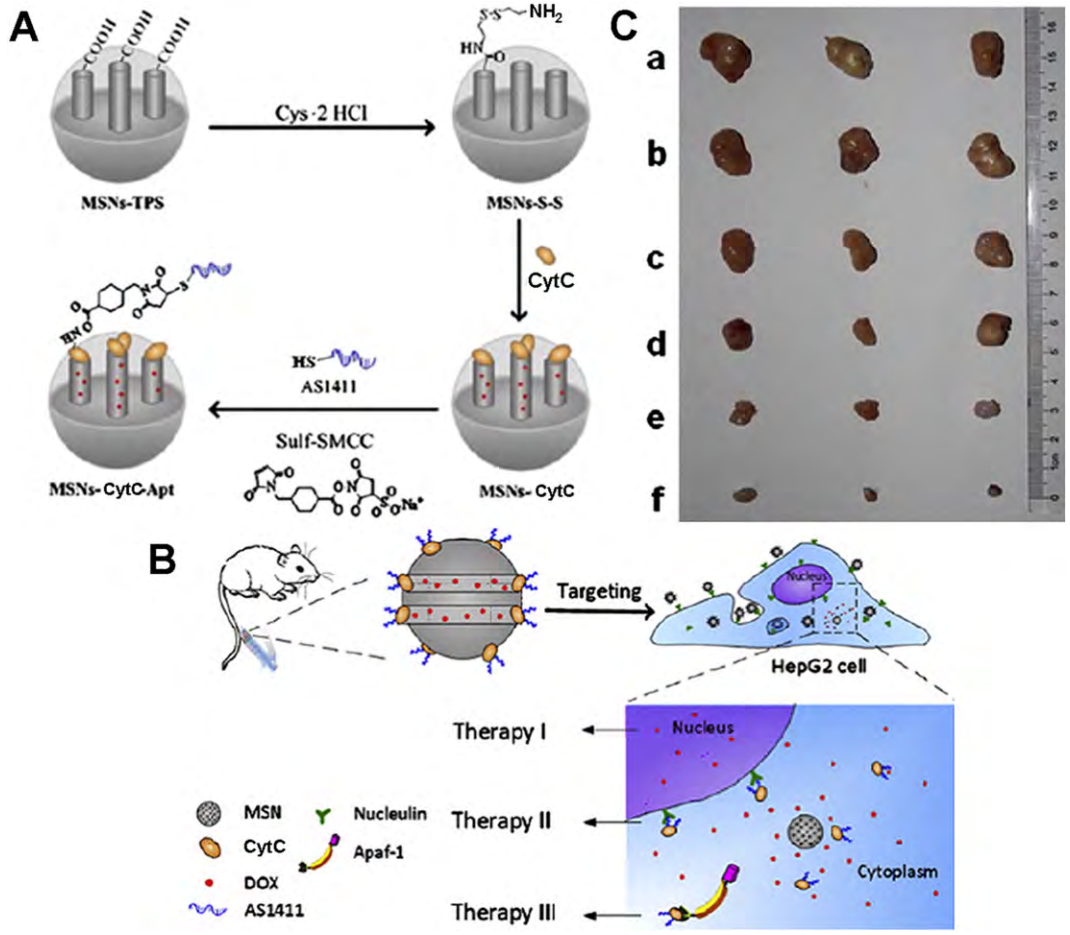


Fig.3. A. Synthetic route of MSNs-CytC-Apt. B. Scheme showing triplex therapy effects due to the release of loaded DOX (therapy I), coupling of AS1411 molecules with nucleolin (therapy II) and cell apoptosis induced by binding of CytC to Apaf-1 (therapy III). C. Photographs of tumors treated with saline (a), MSNs (b), MSNs-CytC-Apt (c), DOX (d), MSNs@DOX (e) and MSNs-CytC-Apt@DOX (f). Adapted with permission from reference [36].

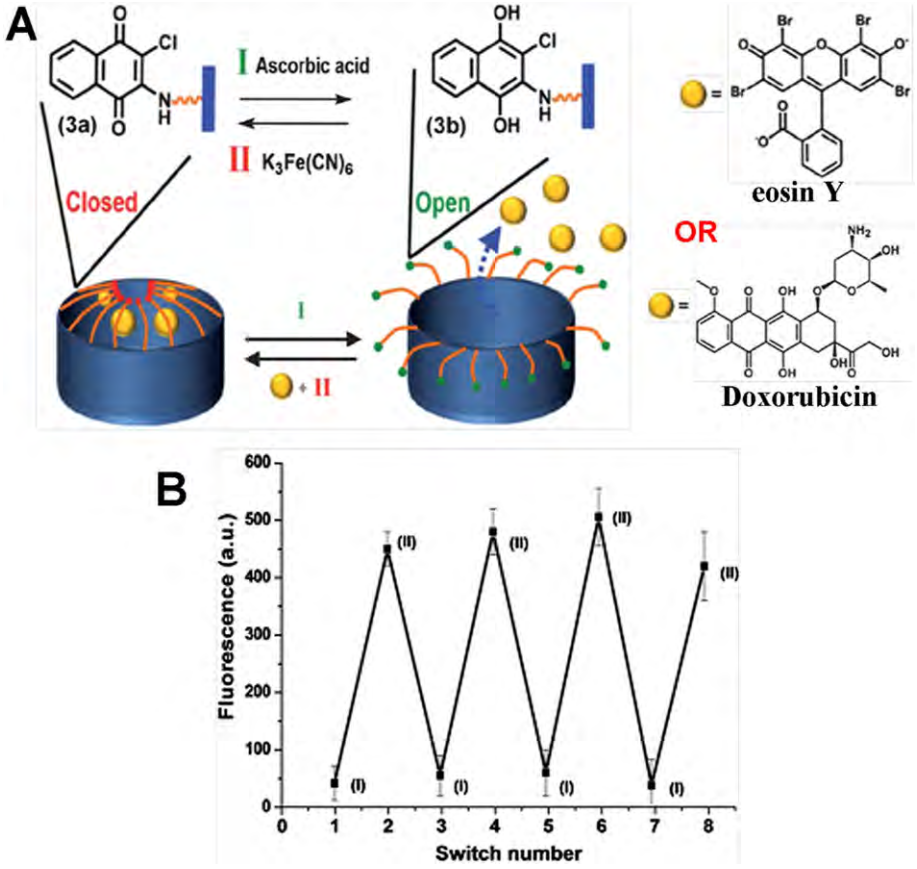


Fig.4. A. Schematic diagram of MSNs mesopores functionalized with 2,3-dichloro-1,4- naphthoquinone units, illustrating the loading/release behavior of model drugs, i.e. eosin Y or doxorubicin, using ascorbic acid and $K_3Fe(CN)_6$ as the redox triggers. B. Cyclic switching of the fluorescence of eosin Y corresponding to its loading/release from the MSNs mesopores along with oxidation of hydroquinone to quinone using $K_3Fe(CN)_6$ (I) and reduction of quinone to hydroquinone using ascorbic acid (II). Adapted with permission from reference [39].

by intracellular GSH or cysteine. The co-delivered luciferase converted the discharged luciferin to oxyluciferin in the presence of intracellular ATP and Mg^{2+}, leading to luminescence. Therefore, the luciferase-luciferin Au-MSNs nanosystem demonstrated the potential to image tumor growth and metastasis. Guang-Shan Zhu et al. [44] took advantage of the regenerative antioxidant property of cerium oxide nanoparticles (CeO_2 NPs) as capping agents for MSNs, and generated redox-responsive CeO_2@MSNs. The CeO_2 NPs were rapidly eroded when exposed to biologically prevalent antioxidants (vitamin C and glutathione), leading to controlled release of therapeutic camptothecin from the mesopores of the MSNs.

3. Redox-responsive nanoplatforms based on carbon nanomaterials

Carbonaceous nanomaterials including graphene oxide [45–48], carbon nanotubes [49,50] and fullerene [51–53] have been widely used as vectors for cancer theranostic applications over the past decades due to their versatile functionalization chemistry and biological compatibility. Moreover, their unique mechanical, thermal and optical properties make them rising stars for improving therapeutic outputs [54]. For instance, most carbon-based nanomaterials can absorb light in the infrared (IR) or near infrared (NIR) regions and transform photons to thermal energy, which is useful for the destruction of cancer cells by the photothermal effect [55,56].

Carbon nanomaterials have a unique sp^2 structure and an inherently hydrophobic nature, which means that they can interact with chemotherapeutic cancer drugs via either covalent conjugation, non-covalent absorption, hydrophobic interactions or π-π stacking [54]. As is known, surrounding a nanovector with a PEG shell can endow the vector with high physiological solubility and stability in the circulation. However, the release of loaded drugs is adversely affected by the significant diffusion barrier of the PEG shell. Considering this, the groups of Yong-Yong Li and Dong-Lu Shi functionalized nanographene oxide (NGO) with detachable PEG via cleavable disulfide bonds, i.e. NGO-SS-mPEG. Very similar results were also reported by Yan-Hong Ji's group [45]. Sung Young Park et al. [48] utilized quaternized 2-chloro-poly(ethylene glycol) (QC-PEG) to reduce graphene oxide. The obtained rGO/QC-PEG exhibited excellent solubility in the aqueous phase. The rGO/QC-PEG matrix was then surrounded by thiolated pluronic (Plu-SH) to form a network via disulfide bonds, thus achieving the goal of high DOX loading.

Carbonaceous nanomaterials are able to emit intrinsic Raman vibration signals, which provide a method to monitor their in vivo distribution, metabolism and excretion [57–59]. Yi-Ping Cui's group [59] modified NGO with polyethylenimine (PEI) through an amidization reaction. DOX was then covalently conjugated with PEI via disulfide bonds, as shown in Fig. 5B. Subsequently, Ag nanoparticles were attached to the surface of NGO via an in situ reduction process, which further enhanced the Raman signals of NGO. As indicated in Fig. 5C, the distribution of the redox-responsive Ag/NGO-PEI-DOX nanocomposite can be tracked by the surface enhanced Raman scattering (SERS) signals of NGO throughout the whole process. The release dynamics of the loaded drug can be tracked using the powerful technique of combined SERS-fluorescence spectroscopy. Additionally, some carbon-based nanomaterials such as carbon nanotubes [60], nanodots [61] and GO [62] can also produce fluorescence over a broad range of wavelengths for bio-imaging applications. More interestingly, although GO is itself fluorescent, it also efficiently quenches the fluorescence of fluorescent dyes [63], quantum dots [64] and conjugated polymers [65]. Yongdoo Choi and Youngnam Cho [47] linked a second-generation

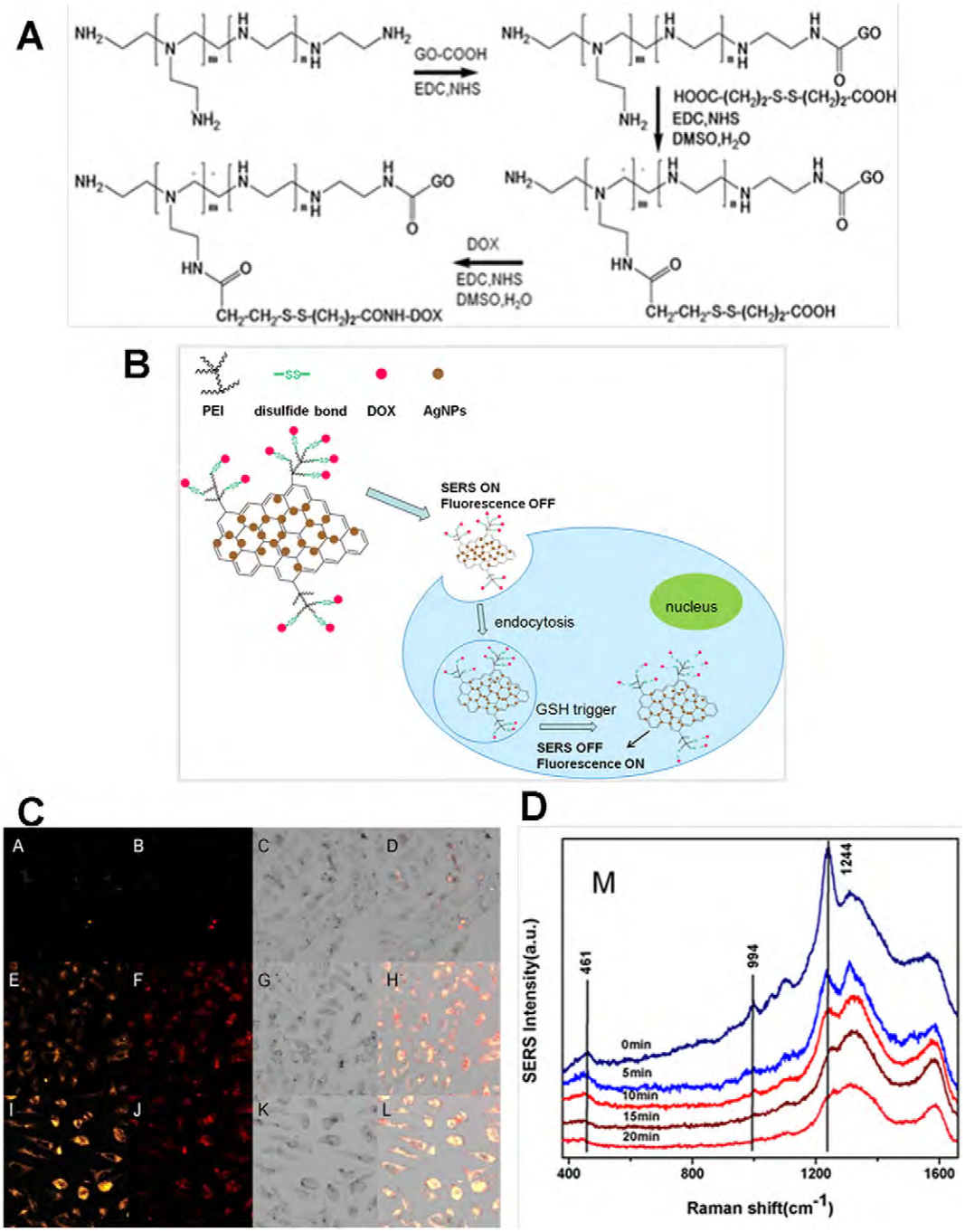


Fig.5. A. Synthetic pathway of the disulfide-containing Ag/NGO-PEI-DOX nanocomposite. B. Intracellular delivery of DOX by the redox-responsive NGO-based carrier. The distribution of the nanocarrier and the dynamic release behavior of DOX were investigated by SERS and fluorescence signals, respectively; C. Fluorescence (A, E and I), SERS (B, F and J), bright field (C, G and K) and merged (D, H and L) images of HeLa cells exposed to Ag/NGO-PEI-DOX for 2 h(A–D), 4 h (E–H), and 8 h (I–L). SERS images were produced by the 1590 cm^{-1} Raman band of NGO and the fluorescence images of DOX were obtained from 540 to 600 nm. D. Average SERS spectra were acquired from HeLa cells incubated with DOX-loaded Ag/NGO composites for different times ($n = 10$). Adapted with permission from reference [59].

photosensitizer, i.e. chlorine6 (Ce6), to GO via disulfide bonds. After the GO-SS-Ce6 conjugates were engulfed by cancer cells, the disufide bonds were broken by intracellular GSH, leading to the release of Ce6. The dissociated Ce6 becomes highly fluorescent and phototoxic, can be used for fluorescence imaging and photodynamic therapy.

4. Redox-responsive nanoplatforms based on magnetic nanoparticles

MNPs include nanoparticles based on ferrous or ferric oxide, cobalt or nickel. The unique feature of MNPs is their responses to an external magnetic field. This property means that they have applications in targeted drug delivery [66], as contrast agents for magnetic resonance imaging (MRI) [67], as heating mediators for cancer therapy (hyperthermia) [68] and in magnetically-assisted cell transfection [69]. In particular, MNPs have been extensively utilized as drug delivery vectors. However, the key problem with MNPs is how to load drugs in vitro and release drugs in vivo in response to physiological stimuli [70,71].

Recently, MNPs have been modified with β-CD [72], mesoporous silica shells [73], amorphous layered hydroxides [74], glycerol monooleate [75], etc. to load therapeutic drugs via hydrophobic interactions and electrostatic interactions. Also, PEG [76], dextran [77], chitosan [78],

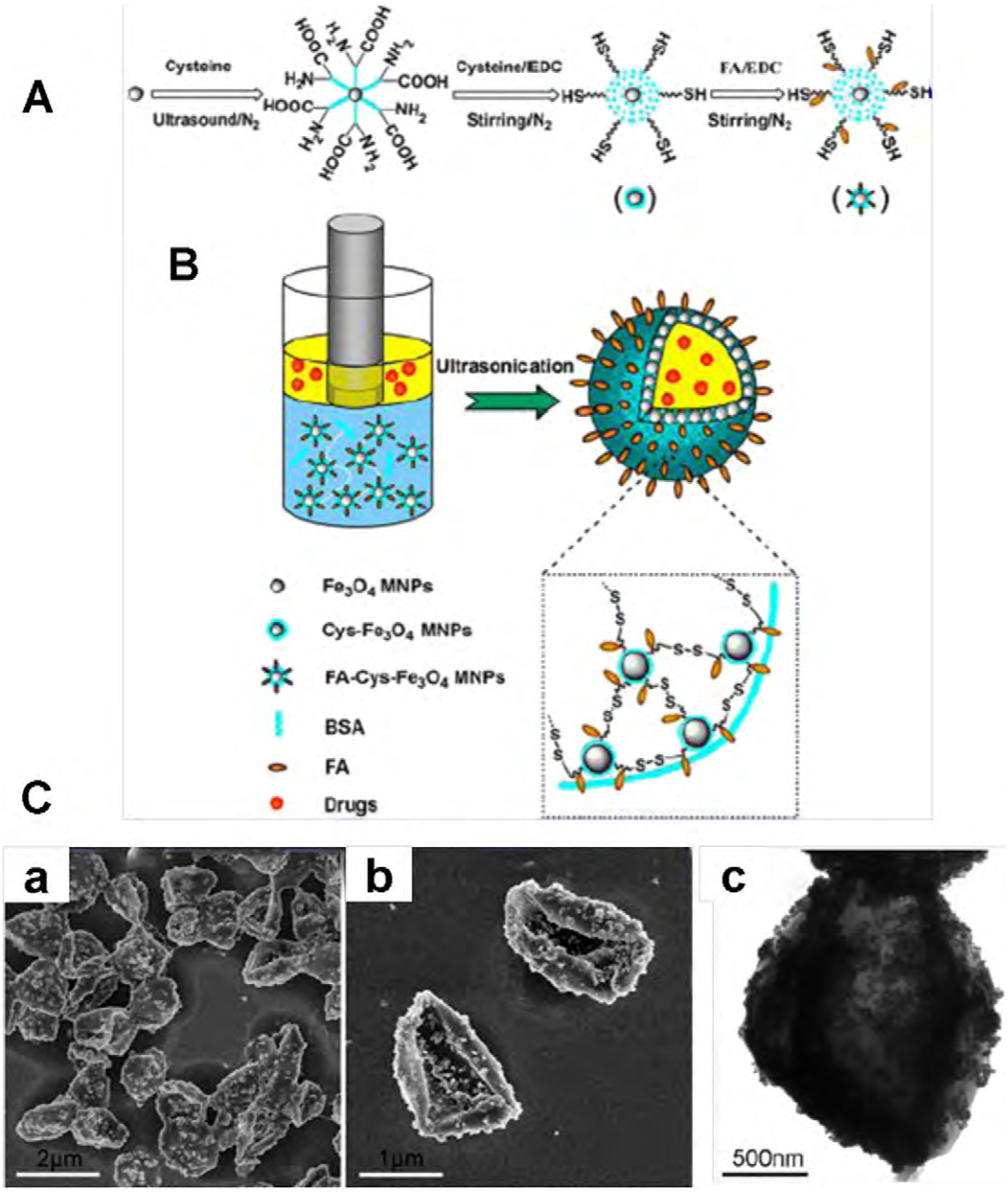
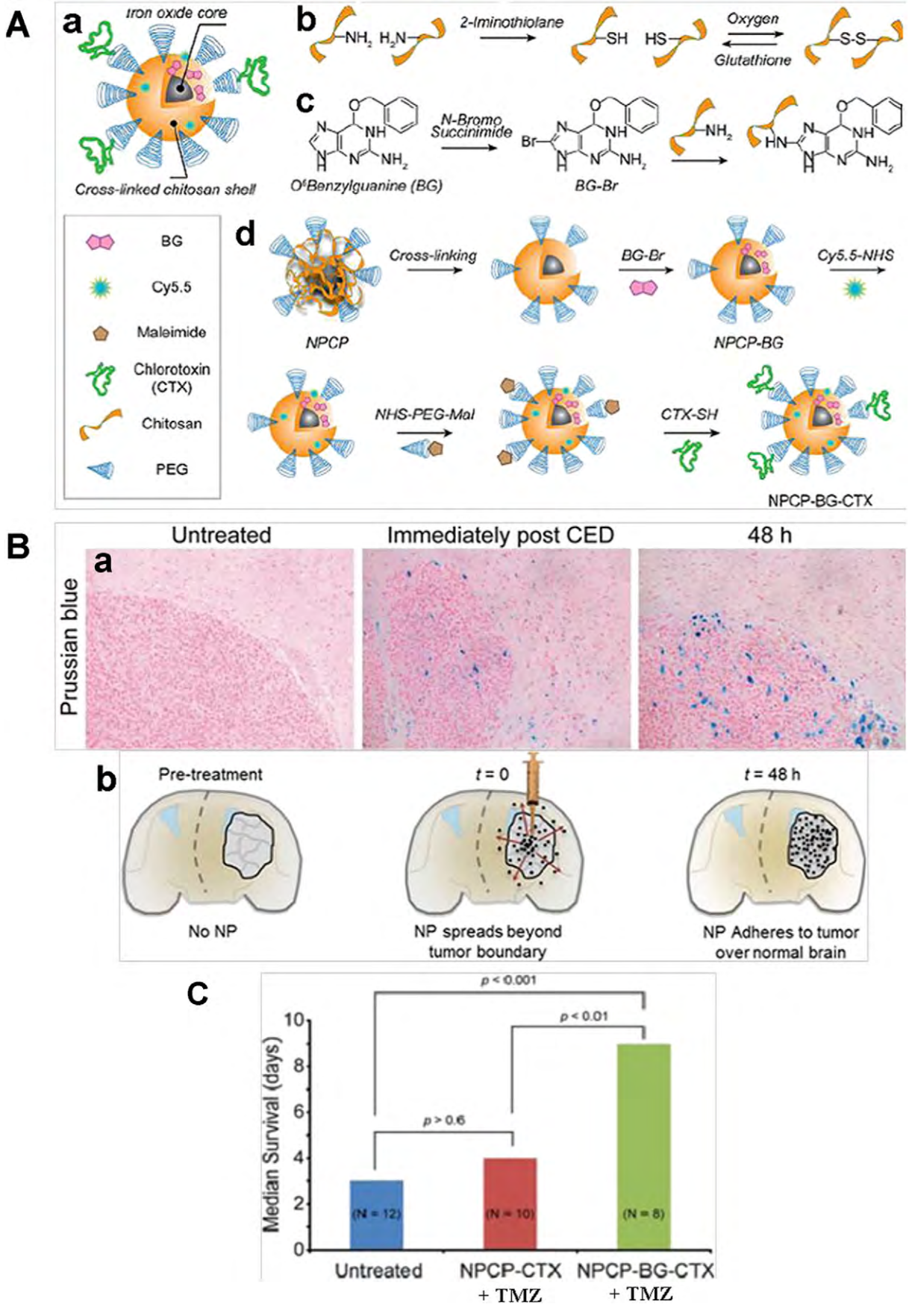


Fig.6. A. Synthetic route of FA-Cys-Fe_3O_4 MNPs; B. Schema of FA-Cys-Fe_3O_4 MC_s prepared using the sonochemical fabrication method; C. SEM (a, b) and TEM (c) images of FA-Cys-Fe_3O_4 MC_s. Adapted with permission from reference [84].

PEI [79] and phospholipids [80] can be immobilized on the surfaces of MNPs for the conjugation of drug molecules. Moreover, a number of novel MNPs-based systems have been constructed for controlled release of the drug payload in the presence of external stimuli such as redox environment [72], pH [81], enzymes [82] and magnetic fields [83]. Kai-Yong Cai and his group [72] synthesized PEI/β-CD, which acts as a nanoreservoir for drug loading, and conjugated it onto the surface of MNPs through disulfide linkers to create MNP-S-S-PEI/β-CD. The fabricated redox-sensitive vehicle efficiently delivered anticancer drugs into tumor cells due to its ability to escape form endosomes and release the loaded drugs in response to intracellular reductants. In addition, targeted drug delivery was also achieved. Xue-Jun Cui et al. [84] further introduced FA onto Fe_3O_4 nanoparticles via cysteine. Thus the synthesized nanosystem possessed both biological and magnetic targeting activities, as shown in Fig. 6A. Drug-loaded microcapsules (MCs) was then formed from the nanoparticles by ultrasonication (Fig. 6B). Formation of the MCs was ascribed to cross-linking between the sulfhydryl groups in the cysteine layers. The Fe_3O_4 MNPs were densely loaded on the creasy and scraggle surfaces of the FA-Cys-Fe_3O_4 MCs (Fig. 6C), thus conferring a superior magnetic response on the microcapsules. In this work, FA-Cys-Fe_3O_4 MCs were able to selectively target folate receptor-positive cells and controllably release loaded hydrophobic drugs.

Fig.7. A. Graphical illustration of NPCP-BG-CTX (a), Chitosan was cross-linked via disulfide bonds (b), the chitosan molecules were modified with BG (c) and NPCP-BG-CTX was prepared by covalently attaching BG and CTX to NPCP (d). B. Representative Prussian blue staining of GBM tumor sections obtained from untreated and NPCP-BG-CTX treated mice immediately post CED and 48 h post CED (a) and scheme showing time-dependent location of NPCP-BG-CTX before and after CED (b). C. Median survival of untreated, NPCP-CTX/TMZ-treated and NPCP-BG-CTX/TMZ-treated mice. Adapted with permission from reference [89].


A
a
Iron oxide core
Cross-linked chitosan shell
b
2-Iminothiolane
Oxygen
Glutathione
c
N-Bromo Succinimide
O⁶Benzylguanine (BG)
BG-Br
BG
Cy5.5
Maleimide
Chlorotoxin (CTX)
Chitosan
PEG
d
Cross-linking
BG-Br
Cy5.5-NHS
NPCP
NPCP-BG
NHS-PEG-Mal
CTX-SH
NPCP-BG-CTX
B
Untreated
Immediately post CED
48 h
Prussian blue
a
b
Pre-treatment
t = 0
t = 48 h
No NP
NP spreads beyond tumor boundary
NP Adheres to tumor over normal brain
C
p < 0.001
p < 0.01
p > 0.6
Median Survival (days)
(N = 12)
(N = 10)
(N = 8)
Untreated
NPCP-CTX + TMZ
NPCP-BG-CTX + TMZ

In addition, the magnetic hyperthermia effects of MNPs have also been employed to improve the therapeutic efficacy of cytotoxic drugs. MNPs are usually combined with redox-sensitive drug delivery platforms to synergistically combine targeted drug delivery and controlled drug release along with a site-specific rise in temperature [85,86]. For example, MNPs were embedded in poly(methacrylic acid) (PMAA) microspheres containing disulfide bonds to create PMAAs-s microcontainers, which had an efficient magnetic response and controlled collapse in a highly reducing environment [86].

Superparamagnetic iron oxide nanoparticles (SPIONs) are one kind of MNPs [70]. The particle cores of SPIONs is usually magnetite (Fe_3O_4), which can be oxidized to maghemite (γ-Fe_2O_3). SPIONs have been the focus of much more attention owing to their excellent biocompatibility, superparamagnetism, high-field magnetic irreversibility and high-field saturation [71,87]. Currently, several formulations based on SPIONs have been approved for clinical use, e.g. Ferumoxytol® for iron replacement therapy [88]. Mi-Qin Zhang's group [89] synthesized a biocompatible chitosan-g-PEG copolymer that was then coated onto the surfaces of SPIONs (Fig. 7A). The primary amines in chitosan were partially converted to sulfhydryl groups, which were then oxidized to formed disulfide bonds, yielding a redox-sensitive polymer shell surrounding the SPIONs (Fig. $7A_b$). O^6-benzylguanine (BG) and the tumor-targeting peptide chlorotoxin (CTX) were covalently attached to the chitosan and PEG, respectively (Fig. $7A_c$ and A_d). Zhang et al. found that the NPCP-BG-CTX remained around the tumor boundary immediately following convection-enhanced delivery (CED) and then diffused into the tumor by 48 h (Fig. 7B). In vivo studies revealed that mice treated with NPCP-BG-CTX in combination with temozolomide (TMZ) had a median survival time of 9 days, which is three times longer than the survival time for untreated animals (3 days; Fig. 7C).

Polymers containing redox-sensitive bonds can also be coated onto the surfaces of SPIONs to load therapeutic drugs by a hydrophobic-hydrophobic mechanism [90,91] or electrostatic interaction and covalent conjugation [92]. Malcolm M.Q. Xing et al. [90] incorporated SPIONs into reducible polyamidoamine (rPAA) graft poly(ethylene glycol) (PEG)/dodecyl amine copolymers, by virtue of intercalation of the oleic acid layers on SPIONs with the alkyl chains of the copolymers. The intercalating areas provided reservoirs for hydrophobic drugs, e.g. DOX.

5. Redox-responsive nanoplatforms based on gold nanomaterials

Gold nanoparticles (GNPs) with different sizes and diverse shapes have found wide applications in the biomedical field, ranging from diagnostic tests to therapeutic treatments [93]. GNPs can be used in photothermal therapy (PTT) because they are capable of absorbing light in the visible or NIR region and then transforming the optical energy into thermal energy, leading to “burning” of the diseased cells. In addition, during the photo-to-thermal conversion process, photochemically-generated singlet oxygen and highly active radicals can induce necrosis and apoptosis of tumor cells. This means that GNPs can be used as photodynamic therapy (PDT) substances to treat oncological diseases or infectious diseases.

GNPs also have the advantages of superior biocompatibility and easy surface modification through gold-sulfur or gold-nitrogen bonds, which can be ruptured in response to reducible constituents, e.g. GSH or photothermal reactions. Generally, remedial drugs or genes can be loaded onto GNPs by the methods of simple physical adsorption [94,95] or by using thiol-containing molecules as linkers, e.g. alkanethiol [96,97] and PEG-SH [98,99]. Vincent M. Rotello's group [100] created a drug delivery system using a core consisting of 2 nm of GNPs and a shell consisting of a mixed layer of a cationic quaternary ammoniated (11-mercaptoundecyl)tetra (ethylene glycol) (TTMA) and a fluorescent thiolated molecule (Bobdipy dye, HSBDP). The system can be utilized for dual-loading of hydrophobic drugs and therapeutic genetic materials. Huan-Yu Dou et al. [101] first synthesized thiol-terminated pluronic block copolymers (PFs), i.e. F127-SH and P123-SH, which self-assembled into PF micelles while simultaneously encapsulating paclitaxel (PTX). Then, GNPs were added onto the surfaces of PF-PTX micelles through gold-sulfur bonds. Ja-an Annie Ho and his co-authors [102] attached 5 nm GNPs as gatekeepers onto amino-modified MSNs through gold-nitrogen coordination linkages. When the obtained nanohybrids were endocytosed by cells, GNPs were detached from the surface of the MSNs because of the formation of gold-sulfur bonds between GNPs and GSH. Thus, GSH was heavily consumed, resulting in elevated oxidative stress in the cancer cells. Furthermore, the dissociated GNPs in cells also elicited elevated levels of reactive oxygen species (ROS). Therefore, the redox-responsive nanohybrids loaded with chemotherapeutics possessed synergistic therapeutic effects.

Non-spherical gold nanoparticles such as cubes, nanocages, rods and shells, as well as other exotic structures, are known for their appealing optical properties [103–105]. Particularly, their surface plasmon resonance (SPR) absorption always occurs in the NIR region, which is advantageous because NIR light can penetrate a few centimeters into living tissues and then be converted into heat energy by the GNPs. Thus, photothermal therapy for cancer can be achieved. Xiao-Gang Qu's group [106] developed a novel dual-responsive system based on gold nanocages (Au NCs) to deliver a metal chelator, i.e. clioquinol (CQ) for the treatment of Alzheimer's disease (AD). Specifically, the Au NCs were functionalized with oxidation- [107] and thermal-sensitive [24] phenylboronic acid (PBA) to create Au NCs-PBA. Human IgG, which acts as the nanoscopic cap of Au NCs, was then linked to Au NCs-PBA via boronate ester bonds, during which CQ was simultaneously entrapped within the pores of the Au NCs. It was reported that H_2O_2 can oxidize arylboronic esters to phenols [107,108], leading to the detachment of IgG and then the release of encapsulated CQ. At the same time, breakage of the boronic ester bonds can also occur due to the plasmonic heating of Au NCs [24]. Using this system, amyloid-β peptide (Aβ) aggregation was effectively inhibited by the released CQ in response to H_2O_2 and thermal energy. This dual-responsive system provided a new treatment option for AD.

6. Redox-responsive nanoplatforms based on other inorganic nanomaterials

Other inorganic nanomaterials including quantum dots (QDs) [109], mesoporous hydroxyapatite (MHAp) nanoparticles [110] and layered double hydroxides (LDHs) [111] have also been widely used to fabricate redox-responsive nanoscale devices for theranostics. Duqiao Ding group [109] found that the fluorescence of selenium doped graphene quantum dots (Se-GQDs) could be reversibly quenched and recovered by oxidative hydroxyl radical (•OH) and GSH. This result indicated that, the therapeutic agents can be tracked by means of the fluorescence of Se-GQDs when they are employed as nanovectors. Yu-Dong Huang et al. [110] innovatively developed a redox-sensitive nanovector, namely LA-Col-S-S-MHAp, based on MHAp nanoparticles. Lactobionic acid-conjugated collagen (LA-Col), which acted as both a cap and a targeting moiety, was covalently attached onto the surfaces of MHAp nanoparticles for drug loading and controlled release.

Engineering multifunctional nanosystems with redox-responsive performance is a highly desirable strategy for successful treatment of cancer. More than one kind of inorganic nanomaterial can be integrated into a single nanoplatform so that the resulting particles have multiple functionalities including drug loading, controlled release behavior, diagnostic imaging and disease therapeutics [7,112,113]. Jian-Lin Shi and his group [114] prepared a triple-functional nanosystem by integrating paramagnetic MnO_x and superparamagnetic Fe_3O_4 nanoparticles onto exfoliated graphene oxide nanosheets, i.e. FeMn-GO NPs. Mn(III)and Mn (IV) in MnO_x NPs were reduced to Mn^{2+} in the reducing environment, thus facilitating T_1-weighted MRI, while the Fe_3O_4 NPs function as T_2-weighted MRI contrast agents (CAs). The authors founded that Dox-loaded FeMn-GO can induce higher cytotoxicity against Dox-

resistance breast cancer cells (MCF-1/ADR) than free Dox. This was mostly attributed to magnetic field-induced hyperthermia from the MnO_x and Fe_3O_4 NPs. Zhu-Yuan Wang et al. [115] presented a SERS-traceable nanocarrier with a core-shell structure, in which Raman molecule-tagged Au@Ag nanorods and mesoporous silica (MS) behaved as the SERS core and the drug-containing shell, respectively. Drug molecules were attached to the MS through disulfide bonds. This fabricated system can be located by SERS signals and the drugs can be released in a controlled manner by virtue of the GSH-responsive behavior.

7. Redox-responsive nanoplatforms based on inorganic/organic hybrid nanomaterials

Nanostructured organic/inorganic hybrid materials exhibit drastically enhanced drug delivery efficacy for disease treatment. Biocompatible polymers have the ability to encapsulate therapeutics and protect active molecules, and can be easily modified in order to introduce other functional molecules. Inorganic nanoparticles have unique physicochemical properties. Thus, multiple functionalities, including targeting ability, controlled release behavior, and tracking of pharmacokinetics and biodistribution, can be incorporated within a single inorganic/organic hybrid nanoplatform. Wei-Zhong Yuan et al. [8] synthesized a temperature- and redox-sensitive magnetic complex micelle for controlled drug release. Oleic acid-modified Fe_3O_4 nanoparticles were self-assembled into the hydrophobic cores of nanosized micelles formed from the amphiphilic copolymer PCL-SS-PDMAEMA. The loaded hydrophobic Dox was controllably released by changing the temperature and the DTT concentration. These release behaviors were attributed to the PDMAEMA polymer and disulfide bonds, respectively. Pablo Botella and his colleagues [116] reported a novel hybrid nanocarrier using PLGA nanoparticles as a core and a redox-responsive amorphous organosilica as a shell, i.e. PLGA-Organosilica hybrid nanoparticles (POSN). The outer layer was built with a silsesquioxane framework containing a number of disulfide bridges (Fig. 8A). Hydrophobic molecules, e.g. pyrene, incorporated within the PLGA cores can be released due to cleavage of the disulfide chemical doors in the presence of DTT (Fig. 8B). POSN showed better controlled release behavior of pyrene because the molecular gates formed by the organic-inorganic silica shell can be opened by reducing compounds (Fig. 8C).

Redox-active agents including tetrathiafulvalene (TTF) [117], ferrocene (Fc) [118], and conducting polymers [119] can be reversibly oxidized into their corresponding radical cations [6]. Interestingly, these reagents are hydrophobic in the reduced state, whereas they become hydrophilic in the presence of oxidants. Thus, block copolymers containing these moieties can self-assemble into micelles with hydrophobic cores and disassemble in response to oxidizers, which is especially useful for potential applications in redox-controllable release of encapsulated compounds [117]. Jin-Suck Suh and his colleagues [118] designed bi-functional magnetic polyaniline (PANi) nanohybrids (MPNHs) which were capable of magnetic resonance imaging and redox-sensing of the tumor microenvironment. Suh et al. founded that a green color appeared in tumor cells following treatment with targeting peptide-conjugated MPNHs (MPNHm-P). This suggests that the metabolites in cancer cells, e.g. oxidative species and H^+ ions, converted PANi from the emeraldine base (EB, blue) state to the emeraldine salt (ES, green) state.

More interestingly, the redox status of Fc groups and their interaction with host molecules, i.e. β-cyclodextrin (β-CD), can be regulated by external potential, a phenomenon which can be applied to construct electrochemically-controlled drug release systems [119–123]. Compared to redox reagents, electrochemical methods involve no redox contamination and can be conducted readily, thus making them especially favorable for use in biological systems. Jin-Ying Yuan's group [120] has modified the Fc and β-CD with poly(L-lactide) (PLLA) and

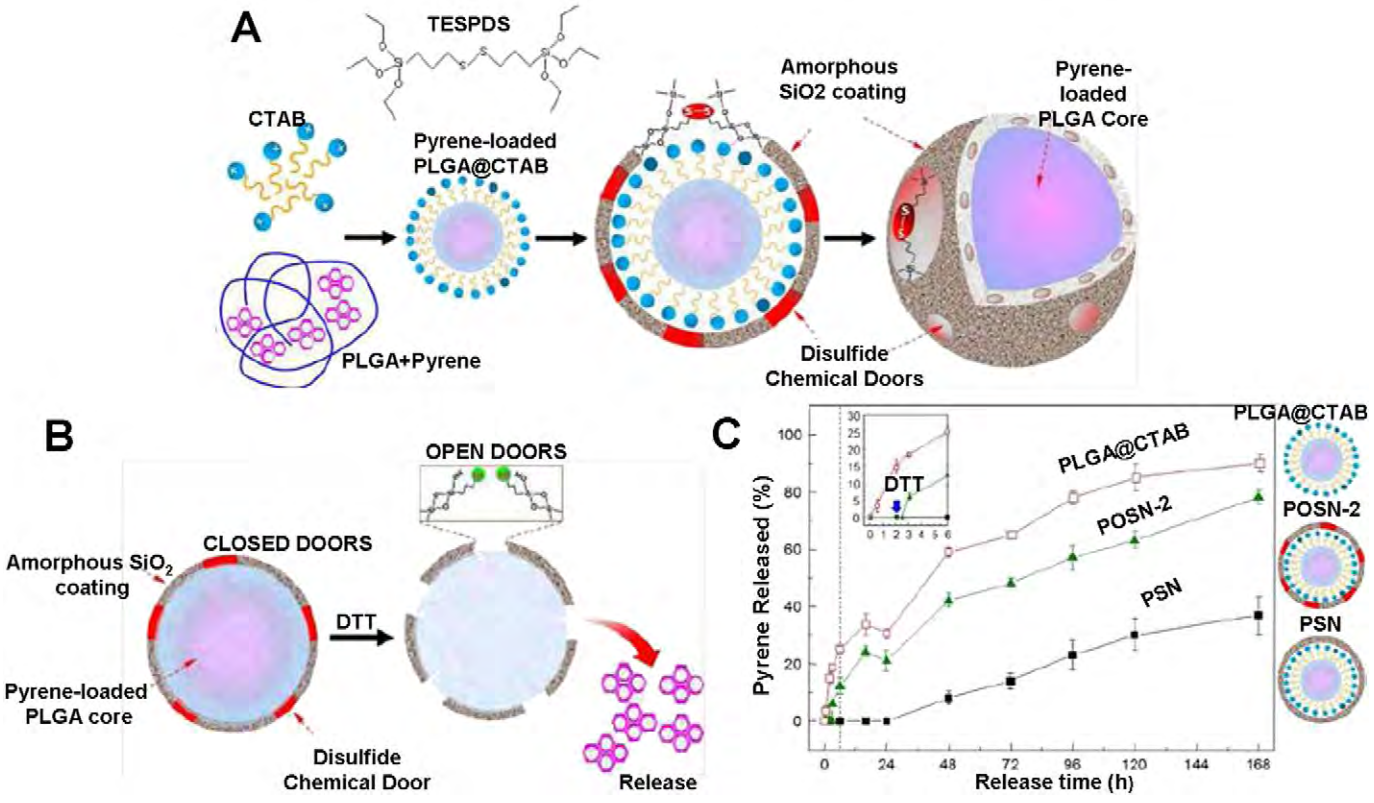


Fig.8. A. Synthesis of pyrene-encapsulated PLGA-Organosilica nanoparticles with disulfide chemical doors. B. Illustration of the release mechanism of pyrene from PLGA-Organosilica nanoparticles in response to DTT. C. Release curves of pyrene from bare PLGA nanoparticles (PLGA@CTAB), PLGA-Organosilica nanoparticles (POSN-2) and PLGA-Organosilica nanoparticles without redox-responsive disulfide bonds (PSN) in PBS at 37 °C. For POSN-2, 100 mM DTT was added at 2 h. The inset shows the release profile during the initial stage from 0 to 6 h. Adapted with permission from reference [116].

PEG, respectively. The resulting supramolecular block copolymer PEG-β-CD/Fc-PLLA can self-assemble in aqueous solution to form micelles. Therefore, reversible assembly and disassembly as well as the release of paclitaxel, can be realized by electrochemical regulation.

8. Concluding remarks and future perspectives

As described in the previous section, reduction- or oxidation-responsive bonds are introduced into inorganic nanomaterials to realize controllable release of drugs. Although inorganic nanoparticles are widely exploited for therapeutic and diagnostic purposes because of their unique features, very few of them have entered the clinic. Primarily, the biocompatibility of surface-modified inorganic nanoparticle platforms is vital for normal cells or tissues, but is very difficult to examine. It is well known that the toxicity of nanoparticles depends on quite a lot of different elements, e.g. chemical composition, administration method, size, shape and surface properties. Additionally, there are still challenges in eliminating the pre-leakage and gaining precise control over the spatial and temporal release of drugs from these redox-responsive delivery systems. Furthermore, the lack of optimal design criteria is also a challenge in fabricating nanoplatforms to obtain the best efficiency. Last but not the least, the manufacturing cost of redox-sensitive nanosystems based on inorganic nanomaterials has to be balanced against the actual efficacy for tumor diagnosis and treatment. Fortunately, the rapid development of both nanotechnology and biotechnology will help overcome these technological hurdles so that redox-responsive nanosystems have practical clinical applications in the future.

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