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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 $kJ \cdot mol^{-1}$, 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 -$(CH_2\text{-}CH_2O)_4$- 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].