Smart nanomedicine agents for cancer, triggered by pH, glutathione, H$_2$O$_2$, or H$_2$S

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Abstract: Effective tumor diagnosis and therapy have always been a significant but challenging issue. Although nanomedicine has shown great potential for improving the outcomes of tumor diagnosis and therapy, the nonspecial targeted distribution of nanomedicine agents in the whole body causes a low diagnosis signal-to-noise ratio and a potential risk of systemic toxicity. Recently, the development of smart nanomedicine agents with diagnosis and therapy functions that can only be activated by the tumor microenvironment (TME) is regarded as an effective strategy to improve the theranostic sensitivity and selectivity, as well as reduce the potential side effects during treatment. This article will introduce and summarize the latest achievements in the design and fabrication of TME-responsive smart nanomedicine agents, and highlight their prospects for enhancing tumor diagnosis and therapy.

Keywords: tumor microenvironment, smart nanomedicine agents, theranostic agents, smart nanoprobes, smart nanocarriers

Introduction
Malignant tumor is one of the key diseases leading to mortality around the world. Owing to the limited outcomes and undesirable side effects of conventional therapy (such as surgery and chemotherapy), many efforts from various fields have been devoted to exploring effective and safe therapeutic modalities and agents.$^{1-3}$ In the past two decades, a number of imaging technology and therapeutic modalities of minimally invasive nature have shown great promise toward this goal.$^{4-7}$ For example, photodynamic therapy, which employed a photosensitizer to generate cytotoxic singlet oxygen to kill tumor cells in the specified position irradiated by excitation light, displays high treat selectivity and leaves little or no scarring.$^{8,9}$ These promising imaging technologies and therapeutic modalities are boosted by the unceasing emergence of nanomedicine agents that possess versatile physio-chemical properties, such as fluorescence,$^{10}$ magnetism,$^{11}$ near-infrared (NIR) absorption,$^{12}$ and porous structures.$^{13}$ For instance, gold nanoparticles with strong NIR absorption can be utilized for photoacoustic imaging and photothermal therapy.$^{14}$ Porous silicon and metal–organic frameworks with high porosity and large surface area can be used as carriers for delivering anticancer drugs.$^{15,16}$

One of the major concerns for nanomedicine agents in practical application is their nonspecial targeted distribution in the body.$^{17}$ Although nanoparticles are preferred to accumulate in the tumor area (because of the EPR effect) and the accumulated benefits can be further improved through decorating tumor-specific targeting moieties (eg, peptides, aptamers, and antibodies) on the surface of the nanoparticles, still only a very small
### Table 1 Paradigms of smart nanomedicine agents for cancer

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**Abbreviations:** CAP, cellulose acetate phthalate; CDT, chemodynamic therapy; FL, fluorescence imaging; GSH, glutathione; MOF, metal–organic framework; MRI, magnetic resonance imaging; NP, nanoparticle; PAI, photoacoustic imaging; PDT, photodynamic therapy; PEG, polyethylene glycol; PTT, photothermal therapy; PU, polyurethane; DPP, diketopyrrolopyrrole; ZIF, Zeolitic imidazole frameworks; BPOx, benzoxazine; HAS, human serum albumin; DOX, doxorubicin; iNGR, CRNGRGPDC; Ara, Cytarabine; HA, hyaluronic acid; PU, polyurethane; AA, amino acid; Azo, azobenzene; EG₆, oligoethylene glycol; PBLA, poly(benzyl-L-aspartate); CA6, chlorin e6; SPB@PON, semiconducting polymer brush and polyoxometalate cluster; CTA, cyanine; RGD, a tumor-targeting unit; OEG, oligoethylene glycol; SN38, 7-ethyl-10-hydroxycamptothecin; HMSNs, hollow mesoporous silica nanoparticles; MSNs, mesoporous silica nanoparticles; HAOP NP, H₂O₂-activatable and O₂-evolving PDT nanoparticle; PCN-224, porous coordination network-224; MS, mesoporous silica; BODIPY, boron dipyrromethene; NIR-II, the second near-infrared window; BODIPA, semi-cyanine-BODIPY hybrid dyes.
amount (about 0.7%) of administered materials can reach the tumor.\textsuperscript{18} Indeed, most of the nanoparticles are sequestered by the reticuloendothelial system. As a result, the diagnosis signals and therapeutic functions can only be activated at the target site by special exogenous stimuli (e.g., light, magnetism, ultrasound) or endogenous stimuli (e.g., pH, redox, enzyme).\textsuperscript{17,21–24} Because of the abnormal growth and metabolism of the tumor cells, the tumor tissues are usually involved in a variety of unique physicochemical microenvironments, including acidic pH, hypoxia, high level of glutathione (GSH) and \( \text{H}_2\text{O}_2 \), as well as overexpressed enzymes and proteins, etc.\textsuperscript{25} These unique microenvironments are undesirable because they are usually beneficial for tumor proliferation, invasion, adhesion, and antitherapy.\textsuperscript{26,27} While, on the other hand, they can be regarded as endogenous stimuli for designing tumor-specific smart nanomedicine agents.\textsuperscript{17,28} Typically, the theranostic functions of these smart nanomedicine agents are in “closed” state in normal tissues, but become “on” state when taken up by tumor cells, giving high theranostic sensitive and selectivity, as well as low side effects.\textsuperscript{29} Furthermore, the diagnosis signals activated by the tumor microenvironment (TME) may in turn reflect the change of the physiological parameters of the tumor cells/tissues, providing valuable information for doctors to alter the theranostic strategy in real time.\textsuperscript{30}

Up to now, a great number of TME-responsive smart nanomedicine agents have been explored, and many of them showed great potential for application in tumor diagnosis and treatment.\textsuperscript{1,31} Based on the functions of these smart nanomedicine agents, they can be mainly divided into three types: 1) smart nanoprobes for specific tumor imaging and detection; 2) smart nanocarriers for antitumor drug delivery and controlling release; and 3) smart therapy/theranostic agents that possess functions of treatment or combine both functions of diagnosis and treatment. In this review article, we will introduce and discuss recent developments in the design and fabrication of smart nanomedicine agents for enhancing tumor diagnosis and treatment by exploiting the TME, including acidic pH and overexpressed GSH, \( \text{H}_2\text{O}_2 \), and \( \text{H}_2\text{S} \) (Table 1).

**pH-responsive nanomedicine agents**

In tumor tissues, because the growth rate of tumor cells is usually much faster than that of normal cells, the existing nutrients and blood oxygen content cannot meet the growth needs.\textsuperscript{32} As a result, tumor cells produce energy for survival through anaerobic glycolysis, which is different from that of oxidative phosphorylation for normal cells. With such metabolisms, tumor cells would generate a large amount of lactic acid and adenosine triphosphate hydrolyse, as well as some excess carbon dioxide and protons, which results in increased acidity of the tumor site and lower pH value than that of normal tissue.\textsuperscript{33} Generally, the pH value in the normal human tissue cells and normal cell lysosomes is about 7.4 and 5.0–6.5, respectively, while that of the tumor tissue and tumor cell lysosomes is about 6.0–7.0 and 4.0–5.0, respectively.\textsuperscript{34} To explore this special acidic TME for improving tumor diagnosis and treatment, a number of pH-sensitive nanomedicine agents have been developed.\textsuperscript{35}

**pH-responsive smart nanoprobes**

Many researchers have utilized the difference pH between tumor tissue and normal tissue to design smart nanoprobes, which display significantly different/varying signals in these two tissues, giving a high diagnosis signal-to-noise ratio.\textsuperscript{36,37} To date, a number of pH-responsive smart nanoprobes have been explored on the basis of various imaging techniques, including fluorescence imaging,\textsuperscript{38} photoacoustic imaging,\textsuperscript{39} and magnetic resonance imaging (MRI).\textsuperscript{40} For instance, Liu et al\textsuperscript{41} designed a pH-responsive nanoassembly based on DPP-thiophene-4 (diketopyrrolopyrrole) for fluorescent images of numbers of different malignant tumors (Figure 1A).\textsuperscript{41} With \( \text{pH}>7.0 \), the fluorescence molecules of DPP-thiophene-4 (diketopyrrolopyrrole) self-assemble into nanoassemblies with very weak fluorescent emission, while when the pH is lower than 6.8 the assemblies disassemble into individual fluorescence molecules, associating with strong fluorescent emission, as shown in Figure 1B. Besides, with every 0.2 pH unit change, the signal of fluorescent emission increased by about 10-fold, which makes this pH-responsive nanoassembly a promising probe for precisely imaging different malignant tumors in vivo (Figure 1C).

Lin et al\textsuperscript{42} developed a pH and GSH-responsive \( \text{T}_2-\text{T}_1 \) switching MRI contrast agent (\( \text{Fe}_3\text{O}_4\text{-ZIF-8} \) assembly) for highly sensitive tumor imaging (Figure 1D).\textsuperscript{42} The \( \text{Fe}_3\text{O}_4\text{-ZIF-8} \) assembly was built using the zeolitic-imidazole framework (ZIF-8) as a matrix to assemble the small \( \text{Fe}_3\text{O}_4 \) nanoparticles (\( \text{T}_1 \) contrast agent) into \( \text{Fe}_3\text{O}_4 \) aggregation (\( \text{T}_2 \) contrast agent). In the acidic environment and the presence of GSH, the ZIF-8 matrix is unstable, resulting in disassembly of the \( \text{Fe}_3\text{O}_4\text{-ZIF-8} \) assembly and release of \( \text{Fe}_3\text{O}_4 \)...
Figure 1 (A) Schematic illustration of the pH-switchable DPP-thiophene-4-based probe for fluorescence imaging of malignant tumor. (B) TEM images of DPP-thiophene-4 at either pH 6.8 or 7.0. (C) Fluorescence imaging and corresponding signal changes of six malignant tumor-bearing mice before and after injection of DPP-thiophene-4 (10 μg/mL) at tumor tissue (red dotted cycle) and nontumor area (blue dotted cycle). Figures A to C reprinted with permission from Liu Y, Qu Z, Cao H, et al. pH switchable nanoassembly for imaging a broad range of malignant tumors. ACS Nano. 2017;11(12):12446–12452. Copyright © 2017, American Chemical Society. (D) Illustration of the Fe₃O₄@ZIF-8 assembly as pH and glutathione (GSH)-responsive T₂–T₁ switching magnetic resonance imaging (MRI) contrast agent. (E) Relaxivity of Fe₃O₄@ZIF-8 after incubation with different pH and concentrations of GSH in PBS for 3 h. (F) In vivo T₁ MRI images and (G) corresponding T₁ signals of 4T1 tumor-bearing mice before and after intravenous injection of Fe₃O₄@ZIF-8. Figures D to G are reprinted with permission from Lin J, Xin P, An L, et al. Fe₃O₄@ZIF-8 assemblies as pH and glutathione responsive T₂–T₁ switching magnetic resonance imaging contrast agent for sensitive tumor imaging in vivo. Chem Commun. 2019;55(4):478–481. Copyright © 2019, The Royal Society of Chemistry.

Abbreviations: DPP, diketopyrrolopyrrole; ZIF, Zeolitic imidazole frameworks; GSH, glutathione.
nanoparticles, consequently leading to the T₂–T₁ switching contrast (Figure 1E). In vivo T₁-weighted images of mice-bearing 4T1 tumor showed that Fe₃O₄@ZIF-8 was able to provide darkening contrast enhancement for the liver site and darkening to brightening contrast enhancement for the tumor site (Figure 1F and G), giving remarkably different MRI signals for improving the distinction between normal tissue and tumor tissue.

Using the ratio method or code equation to analyze the imaging signal of the responsive probe at different pH, correspondence between the imaging signal and the pH value can be established, which can in turn be used to detect the tumor pH in real time. For example, Chen et al.⁴³ reported a pH-responsive nanoprobe (C–HSA–BOPx–IR825) for detecting the pH of the TME. The nanoprobe was designed on the basis of the pH-inert NIR dye IR-825 (as internal reference) and the pH-responsive NIR dye benzo[a]phenoxazine (BOPx, as indicator) with photoacoustic imaging analysis; the ratios of signal intensity for C–HSA–BOPx–IR825 at 680 nm (from BOPx) and 825 nm (from IR825) were decreased with the increase of pH value, and exhibited a linear relationship in the pH range of 4.5–7.0, making this nanoprobe have great potential for application in the detection of tumor pH.

**pH-responsive smart nanocarriers**

Because traditional molecule antitumor drugs have significant side effects for normal organs, enormous interest has been focused on the development of a smart nanocarrier that can deliver and control the release of molecular drug.⁴⁴ The low pH value of the TME makes it possible to design a pH-responsive smart nanocarrier for tumor-specific chemotherapy. Theoretically, a pH-sensitive nanocarrier would deliver and control the release of the antitumor drug upon encountering the acid microenvironment of tumor, while exhibiting very low or zero drug release in the normal tissue, thus reducing the damage to normal tissue during treatment.⁴⁵ Ye et al.⁴⁶ designed a pH-sensitive lipid-poly-peptide hybrid nanoparticle (iNGR-IPNs) loaded with the antitumor drug doxorubicin (DOX) to address cellular uptake and intracellular drug release for tumor treatment. Likely a pH-sensitive switch, this smart nanoparticle undergoes a first phase transition at pH 7.0–6.5 with the surface potential transformed from negative charge to neutral charge for increasing cellular uptake, and a second phase transition at pH 6.5–4.5 with disassembly of the skeleton to induce endolysosome escape and release the DOX into the cytoplasm. In vitro and in vivo studies demonstrated that this two-step pH-responsive delivery can promote cell uptake and control the release of drug in the acidic environment, consequently leading to more potent antitumor efficacy and less systemic toxicity.

For the design of smart nanocarriers, metal–organic frameworks have attracted great attention because of their designable structures and unique porous frameworks for high drug loading. Zhou et al. reported one-pot synthesis of a metal–organic framework (ZIF-8) with high encapsulation of DOX (Figure 2A).⁴⁷ Because the ZIF-8 is stable in the neutral condition, but decomposes in the acid environment, the release of DOX molecules that loaded in the ZIF-8 matrix can be controlled by pH (Figure 2B and C). Zhang et al.⁴⁸ developed a versatile prodrug strategy to further increase the amount of drug loading within the pH-responsive metal–organic framework carrier (ZIF-8) (Figure 2D).⁴⁸ As a proof of concept, a drug molecule (cytarabine, Ara) was bonded to a fluorescence molecule (indocyanine green, Ara-IR820) to form a prodrug Ara-IR820 (Figure 2E), which was then embedded into the ZIF-8 matrix (Ara-IR820@ZIF-8) with high loading owing to the strong interaction between sulfonic groups (from IR820) and ZIF-8. At the same time, a tumor targeting molecular HA was bound to the ZIF-8 to improve the tumor targeting ability. Upon entering the tumor tissues/cells, the low pH triggered the HA/Ara-IR820@ZIF-8 to disassemble and release Ara-IR820, which subsequently hydrolyzed (the amide bond) to form the individual molecule of IR820 for fluorescence imaging and Ara for chemotherapy. In vitro and in vivo experiments demonstrated that this pH-sensitive HA/Ara-IR820@ZIF-8 with good tumor targeting capability exhibited excellent pH-triggered fluorescence imaging-guided chemotherapy and photodynamic dual treatment against cancers (Figure 2F).

Because of their unique viscoelastic and biomimetic properties, hydrogels assembled by small-molecular or polymeric networks/fibers are also promising materials for designing smart drug delivery.⁴⁹,⁵⁰ For instance, Hua et al.⁵¹ designed pH-responsive core-hell nanofibers for intravaginal drug delivery. The core-hell nanofibers composed of polyurethane (PU) and cellulose acetate phthalate (CAP) exhibited significantly improved tensile strength compared with the existing CAP. These coaxial fibers were stable in the acidic environment (pH 4.2), while dissolving very rapidly in the neutral environment and released the loading rhodamine fluorescent molecules. Besides, they exhibited low cytotoxicity, giving great potential for use as pH-responsive drug delivery. Xiong et al.⁵² reported a novel multiresponsive hydrogel assembled by an amine acid gelator AA-Azo-

Abbreviations: DOX, doxorubicin; ZIF, Zeolitic imidazole frameworks; Ara, Cytarabine; HA, hyaluronic acid; TEM, transmission electron microscopy.
EG∞. Owing to the coexistence of different functional groups (including amino acid head, azobenzene, and oligoethylene glycol), this hydrogel has responsive behavior upon triggering by pH, ultraviolet–visible light, and temperature, showing great potential use in tissue engineering and drug delivery.

**pH-responsive nanotheranostic agents**

By utilizing the low pH in the TME, it is possible to design smart nanodiagnostics agents with diagnosis and treatment functions simultaneously activated by the change of pH values.53 For example, Ling et al54 developed a pH-responsive magnetic nanotherapeutic agent (termed pH-sensitive magnetic nanogranules, PMNs) for MRI imaging and fluorescence imaging guiding photodynamic therapy of resistant heterogenous tumors (Figure 3A). This nanotherapeutic agent was built by self-assembly of Ce6-grafted-poly(ethylene glycol)-poly(β-benzyl-L-aspartate) (PEG-PBLA-Ce6) and ultra-small iron oxide nanoparticles. In a neutral environment (pH 7.4), the surface charge of the PMN is negative, and the Ce6 encapsulated in the PMN loses its fluorescence because of the fluorescence resonance energy transfer. Once it reaches a slightly acidic environment, the whole body of the PMN becomes positively charged and expands to promote cell uptake. When the pH is below 6.5, excessive H+ in the solution causes the monomers in the PMN to repel each other, leading to cracking of the PMN and the release of iron oxide nanoparticles for T1-weighted contrast and Ce6 for fluorescent imaging and generation of O2. In vivo experiments with colon cancer tumors have shown that PMNs exhibited excellent activated dual-mode imaging and photodynamic therapy effects (Figure 3B), demonstrating that such pH-responsive PMNs have great potential for early tumor detection and specific treatment.

Yang et al55 designed an acidity/reducibility dual-responsive assembly (SPB@POM) contained a semiconducting polymer brush (SPB) and a polyoxometalate cluster (POM) (Figure 3C). In the acidic microenvironment, the small assembly will self-assemble into big aggregate through proton-induced hydrogen bonding self-assembly. This self-assembly could not only enhance the retention and accumulation of assembly in the tumor, but also enhance the NIR absorption of the assembly, consequently leading to remarkable improvement in the contrast of photoacoustic imaging and the efficacy of photothermal therapy.

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**Figure 3** (A) pH-induced structural transformation of pH-sensitive magnetic nanogranules (PMNs) and change of magnetism and photoactivity. (B) In vivo near-infrared (NIR) fluorescent imaging of HCT116 tumor-bearing mice before and after intravenous injection of different materials. Figures A and B reprinted with permission from Ling D, Park W, Park SJ, et al. Multifunctional tumor pH-sensitive self-assembled nanoparticles for bimodal imaging and treatment of resistant heterogeneous tumors. J Am Chem Soc. 2014;136(15):5647–5655.54 Copyright © 2014, American Chemical Society. (C) Schematic of the structure of semiconducting polymer brush (SPB) and a polyoxometalate cluster (POM), as well as mechanism for the acidity-triggered aggregation of SPB@POM. (D) Photoacoustic intensities of SPB and SPB@POM under different conditions. Figures C to E reprinted with permission from Yang Z, Fan W, Tang W, et al. Near-infrared semiconducting polymer brush and pH/GSH-responsive polyoxometalate cluster hybrid platform for enhanced tumor-specific phototheranostics. Angew Chem-Int Edit. 2018; 57(43):14101–14105.53 Copyright © WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim. **Abbreviations:** GSH, glutathione; PMNs, pH sensitive magnetic nanogranules; SPB@POM, semiconducting polymer brush and polyoxometalate cluster.
Yang et al. chose to combine pH-sensitive polyaniline polymer with polyethylene glycol (PEG) to synthesize a biocompatible pH-responsive agent for photothermal therapy of tumors. In a neutral environment, polyaniline with the structure of an emeraldine base exhibited the main absorbance peak at about 580 nm, while in the acidic environment its structure was changed to emeraldine salt with absorbance red-shifted to the NIR region, which could be used as NIR photothermal therapy.

**GSH-responsive nanomedicine agents**

Due to the different potential between the internal and external environments of tumor cells, tumor cells can overproduce some reducing substances. One of the typical overexpressed reducing substances is GSH. Generally, the concentration of GSH in tumor cytoplasm can reach 2–10 mmol/L, which is 100–1000 times higher than that of the extracellular fluid and blood. Therefore, GSH has been identified as an ideal stimulating element for designing tumor-specific smart nanomedicine agents.

**GSH-responsive smart nanoprobes**

For the design of a GSH-responsive organic molecule probe or nanoprobe, several reducible bonds, including the disulfide bond, diselenium bond, and nitroazo-aryl-ether, have attracted great attention. In the presence of GSH, these reducible bonds can be cleaved, thus leading to the activation of the probe. For example, Yuan et al. reported a GSH turn-on NIR fluorescent probe (CyA-cRGD), composed of a NIR fluorescence unit (CyA) binding with a fluorescence quenching unit (nitroazo aryl ether group) and a tumor-targeting unit (cRGD) (Figure 4A). With the presence of GSH, the nitroazo aryl ether group connecting the fluorescence unit and the fluorescence quenching unit will be cleaved, leading to the turn-on of the

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**Figure 4** (A) Proposed glutathione (GSH)-mediated activation mechanism of CyA-cRGD probe. (B) Fluorescence spectra of CyA-cRGD probe with and without NEM or GSH. (C) Relative fluorescence (FL) intensity ratios of CyA-cRGD in the presence of different amino acids or metal ions. (D) Fluorescence images of CyA-cRGD in the presence of different amino acids and metal ions detected by the near-infrared (NIR) fluorescence imaging system. Figures A to D reprinted with permission from Yuan Z, Gui L, Zheng J, et al. GSH-activated light-up near-infrared fluorescent probe with high affinity to αvβ3 integrin for precise early tumor identification. ACS Appl Mater Interfaces. 2018;10(37):30994–31007. Copyright © 2018, American Chemical Society.

**Abbreviations:** CYA, cyanine; RGD, a tumor-targeting unit; GSH, glutathione.
fluorescence (Figure 4B). Competition experiments revealed that this GSH-responsive CyA-cRGD probe has high selectivity along different amino acids and metal ions (Figure 4C and D). Moreover, with excellent tumor targeting capability, this probe displays a high fluorescence signal-to-noise ratio for distinguishing the tumor tissue and normal tissue, making it highly promising for application in early tumor diagnosis.

Besides organic materials, many inorganic materials, such as MnO$_2$, gold nanoparticles, and polyoxometalate cluster, have also been widely used for designing GSH-responsive nanoprobes. For instance, Yuan et al.$^{64}$ developed a GSH-responsive probe combining fluorescence and MRI dual imaging on the basis of MnO$_2$ nanosheets. The fluorescence unit of aptamer was bound to the MnO$_2$ nanosheets, which serves as a fluorescence quencher. Upon endocytosing by tumor cells, the MnO$_2$ nanosheets react with the overexpressed GSH to generate abundant Mn$^{2+}$ ions and release the primers, consequently leading to simultaneous turn-on of the signals for MRI and fluorescence imaging, which in turn can be used to detect the cellular GSH.

**GSH-responsive smart nanocarriers**

For the design of GSH-responsive drug nanocarriers, two common strategies have been widely used. The first strategy is directly connecting the drug molecule to another molecule or polymer through clearable bonds (such as a disulfide bond), and then self-assembly into a nanoparticle or liposome.$^{65}$ The second strategy is loading the drug molecule into GSH-responsive or non-GSH-responsive porous matrixes such as mesoporous silicon and metal–organic frameworks.$^{66}$ For the porous matrixes without GSH-responsive ability, their aperture can be sealed after the adsorption of the drug using small molecules that contain clearable bonds or using nanoparticles that can be degraded by GSH.$^{67}$ For example, Wang et al.$^{68}$ designed a GSH and ROS heterogeneity-responsive produg nanocapsule (OEG-2S-SN38) through self-assembly of a polymer, composed of a chemotherapy drug SN38 and an oligo(ethylene glycol) (OEG) chain linked by a thioether chain with ester groups (Figure 5A). Upon encountering GSH/ROS, the nanoparticle would be disassembled owing to the thiolysis triggered by GSH (Figure 5B) and enhanced hydrolysis of the linker triggered by the ROX oxidation, leading to the release of the parent drug SN38 for anticancer therapy (Figure 5C).

Recently, Yu et al.$^{69}$ reported a “manganese extraction” strategy for design of GSH/acid-responsive mesoporous silica drug carrier (PEG/Mn-HMSNs) with good biodegradation and theranostic functions (Figure 5D). The doping of Mn ions into the mesoporous silica means the introduction of the –Mn–O– bonds into the –Si–O–Si– skeleton. Because –Mn–O– bonds can be easily broken in the reducing or acidic conditions, the –Mn–O– bond-doped skeleton of the mesoporous silica exhibited fast disintegration and biodegradation in the TME (Figure 5E). Besides, the degradation of the Mn-doped mesoporous silica nanoparticles trigged by GSH led to activation of the release of abundant Mn$^{2+}$ ions for MRI and drug for chemotherapy (Figure 5F and G).

**GSH-responsive nanotheranostic agents**

Besides smart probes and drug carriers, the design of GSH-responsive smart nanotheranostic agents that combine both functions of diagnosis and therapy is also a hot research topic in the field of nanomaterial and nanomedicine.$^{70}$ To date, many kinds of nanomaterials, including organic polymer,$^{71}$ metal oxide,$^{72}$ gold nanoparticles,$^{73}$ and polyoxometalate clusters,$^{74}$ have been utilized to design GSH-responsive nanotheranostic agents. For example, Gong et al.$^{75}$ successfully synthesized a bimetallic oxide MnMoO$_5$ nanorod as a GSH-responsive smart nanotheranostic agent (Figure 6A). The original PEG-modified MnMoO$_5$ nanorods exhibited almost no NIR absorption. However, once interacted with GSH, the Mo$^{VI}$ ions in MnMoO$_5$ were reduced to Mo$^{V}$ ions, making the nanorods possess strong NIR absorption that can be utilized for photoacoustic imaging and photothermal therapy (Figure 6B and C). Besides, the change of the charge of Mn ions leads to increased $r_1$ relaxivity with improved MRI (Figure 6D). In vivo experiments demonstrated that this MnMoO$_5$ nanorod possessed good biodegradability and excellent GSH-triggered photoacoustic imaging and MRI for guiding photothermal therapy (Figure 6E–G).

Recently, Liu et al.$^{76}$ designed a GSH-responsive magnetic gold nanowreath by layer-by-layer self-assembly of gold nanowreath-coated SiO$_2$ with small magnetic iron oxide nanoparticles. In the TME, the overproduced GSH would trigger disassembly of iron oxide nanoparticles, resulting in turn-on of $T_1$-weighted MRI for determining the best time point for therapy. Besides, the gold nanowreath in this agent also endows it with excellent functions of photoacoustic imaging and photothermal therapy of tumor. Therefore, combining turn-on $T_1$ contrast imaging and innate photothermal imaging can effectively guide photothermal therapy.

**H$_2$O$_2$-responsive nanomedicine agents**

Hydrogen peroxide ($\text{H}_2\text{O}_2$) is another overproducing metabolite in most common tumors.$^{77}$ Accumulating evidence suggests that $\text{H}_2\text{O}_2$ in normal tissues is usually at a low level, while
Figure 5 (A) The self-assembly and redox triggered the SN38 releasing mechanism of the OEG-2S-SN38 nanocapsule. (B) SN38 releasing curves in PBS with or without glutathione (GSH) (10 mM) at pH 7.4 or 4 at 37 °C. (C) The changes of tumor volume for different treatment groups. Figures A to C reprinted with permission from Wang J, Sun X, Mao W, et al. Tumor redox heterogeneity-responsive prodrug nanocapsules for cancer chemotherapy. Adv Mater. 2013;25(27):3670–3676. Copyright © WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim. (D) Schematic illustration of the GSH/acid-responsive polyethylene glycol (PEG)/Mn-HMSN drug carrier designed through a “manganese extraction” strategy for enhancing theranostic functions. (E) Accumulated releasing curves of Mn elements in the neutral SBF with GSH concentrations of 0, 5.0, and 10.0 mM. (F) T1-weighted magnetic resonance imaging (MRI) of tumor-bearing mice and corresponding T1 signal intensity of the tumor and liver sites before and after intravenous injection of PEG/Mn-HMSNs with a dose of 5 mg/kg. (G) Tumor-growth inhibition effect for different treatment groups. Figures D to G reprinted with permission from Yu L, Chen Y, Wu M, et al. “Manganese extraction” strategy enables tumor-sensitive biodegradability and theranostics of nanoparticles. J Am Chem Soc. 2016; 138(31):9881–9894. Copyright © 2016, American Chemical Society.

Abbreviations: DOX, doxorubicin; i.v., intravenous; OEG, oligo(ethylene glycol); SN38, 7-ethyl-10-hydroxyl-camptothecin; PBS, phosphate-buffered saline; GSH, glutathione; HMSNs, Hollow mesoporous silica nanoparticles; PEG, polyethylene glycol; MR, magnetic resonance.
that in the tumor tissues is much higher at 100 μM–1 mM,\(^\text{76}\) which may attributed to the overproduction of oxide dismutase (SOD) for catalyzing the conversion of superoxide anion radicals to H\(_2\)O\(_2\) and O\(_2\).\(^\text{79-81}\) An increased level of H\(_2\)O\(_2\) may play a significant role, directly or indirectly, in the development of the cancer cells, but can also induce apoptosis of cancer cells when increased to a much higher level. For chemists, the characteristic high level of H\(_2\)O\(_2\) for the tumor environment can be explored to design H\(_2\)O\(_2\)-responsive drug carriers,\(^\text{77}\) endogenous O\(_2\) producers,\(^\text{82}\) and chemodynamic therapy agents\(^\text{83}\) for tumor-specific diagnosis and treatment.\(^\text{84}\)

**H\(_2\)O\(_2\)**-responsive smart nanocarriers

For the design of H\(_2\)O\(_2\)-responsive drug nanocarriers, oxidation-responsive polymers have attracted considerable attention. For example, poly(propylene sulfide) is a hydrophobic polymer, but it can transform to a hydrophilic polymer (poly(propylene sulphphone)) upon oxidative conversion.\(^\text{85}\) The hydrophobic poly(propylene sulfide) can self-assemble into nanoparticles with a hydrophilic block such as poly(ethylene glycol) and a hydrophobic drug molecule such as DOX. Upon encountering H\(_2\)O\(_2\), the hydrophobic poly(propylene sulfide) would be oxidized into hydrophilic poly(propylene sulfphone), resulting in disassembly of the nanoparticles and release of the DOX molecule for chemotherapy.

Ma et al\(^\text{86}\) reported a redox dual-responsive assembly containing diselenide block copolymers as a potential drug carrier (Figure 7A). The diselenide bonds (Se-Se) in the block copolymers can be cleaved and oxidized into selenenic acid in the oxidation environment and reduced into selenol in the presence of reductants. Therefore, the micelles formed by such diselenide block copolymers will disassemble upon encountering oxidants such as H\(_2\)O\(_2\) or reductants such as GSH, and simultaneously release the cargo loading in the micelles (Figure 7B–D).

Besides blocking copolymer micelles, porous materials such as mesoporous silica have also been widely utilized to design H\(_2\)O\(_2\)-responsive drug carriers. Using H\(_2\)O\(_2\)-responsive ultrasmall Ag nanoparticles as nanolids for sealing the drug in the channel of mesoporous silica nanoparticles, Muhammad et al\(^\text{87}\) developed a H\(_2\)O\(_2\)-responsive silica-based drug delivery system (Figure 7E). In the TME, overexpressed H\(_2\)O\(_2\) triggered the Ag nanoparticles to leave from the cap of the channel of mesoporous silica and to aggregate, followed by release of the therapeutic drug (Figure 7F–H).

**In situ O\(_2\)** producer for improving photodynamic therapy

Hypoxia is a state referring to the low level of oxygen, which is a typical characteristic of most solid tumors.\(^\text{88}\) The origins of tumor hypoxia can be mainly traced to abnormal vascularization raised by the fast growth of the tumor. Compared with the
The hypoxia not only provides an environment to continue...
Figure 8 (A) Schematic illustration of the mechanism of $\text{H}_2\text{O}_2$-triggered $\text{O}_2$ generation and photosensitizer release for enhanced photodynamic therapy (PDT). (B) Releasing curves for MB from HAOP nanoparticles (NPs) with and without $\text{H}_2\text{O}_2$ (100 μM). (C) Tumor growth curves of mice upon different treatments. (D) H&E staining of tumors for different groups at 24 h post treatment. Figures A to D reprinted with permission from Chen H, Tian J, He W, et al. $\text{H}_2\text{O}_2$-activatable and $\text{O}_2$-evolving nanoparticles for highly efficient and selective photodynamic therapy against hypoxic tumor cells. J Am Chem Soc. 2015;137(4):1539–1547. Copyright © 2015, American Chemical Society. (E) Schematic illustration of the fabrication of PCN-224-Pt. (F) Ultraviolet–visible spectra of remaining $\text{H}_2\text{O}_2$ after catalysis by PCN-224-Pt for different times at pH 7.4. (G) Degradation rates of DPBF after treatment with PCN-224 or PCN-224-Pt in the absence and presence of $\text{H}_2\text{O}_2$ under light irradiation in a N$_2$ atmosphere at pH 7.4. (H) Photographs of mice bearing H22 tumor before and on day 14 after various treatments. (I) Relative tumor volume for different treatment groups. Figures E to I reprinted with permission from Zhang Y, Wang F, Liu C, et al. Nanozyme decorated metal–organic frameworks for enhanced photodynamic therapy. ACS Nano. 2018;12(1):651–661. Copyright © 2018, American Chemical Society.
a Fenton-like reaction in the presence of Fenton agents and H$_2$O$_2$, as a toxic reactive oxygen species to kill tumor cells.$^{94}$ This therapeutic strategy was recently proposed by Bu et al.$^{45}$ Because it is activated via two endogenous stimulating elements, including sufficient H$_2$O$_2$ and mildly acidic conditions (to dissolve ferrous ions from the nanoparticles), chemodynamic therapy has advantages of high logicality and selectivity, as compared with many other therapy methods such as chemotherapy, photodynamic therapy, and radiotherapy. Up to now, a number of inorganic and inorganic–organic hybrid nanomaterials, including Fe$_3$O$_4$, FeS$_2$, $^{96}$ and Cu/Fe complex nanoparticles, $^{97}$ have been explored as H$_2$O$_2$ catalysts for chemodynamic therapy on the basic principles of the Fenton reaction.

Utilizing the high content of H$_2$O$_2$ in the tumor, Tang et al.$^{96}$ designed an antiferromagnetic pyrite nanocube decorated with polyethylene glycol (FeS$_2$-PEG) for self-enhanced MRI and chemodynamic therapy. In the tumor site, the FeS$_2$-PEG catalyzed the endogenous H$_2$O$_2$ to generate OH effectively through the Fenton reaction (Figure 9A). Besides, the localized heat from the photothermal properties of the pyrite can accelerate the Fenton reaction, making it more effective for chemodynamic therapy (Figure 9B and C). Furthermore, upon surface oxidation by H$_2$O$_2$, the valence state of the ferrous ion was changed, leading to enhancement of the T$_1$ and T$_2$ MRI signals for guiding chemodynamic therapy (Figure 9D).

Liu et al.$^{98}$ reported photothermal-enhanced chemodynamic therapy using ultrasmall WO$_{3-x}$@-poly-L-glutamic acid nanoparticles (Figure 9E). Upon encountering H$_2$O$_2$, the WO$_{3-x}$@-poly-L-glutamic acid nanoparticles exhibit a Fenton-like reaction to generate OH, and the generated rate can be effectively enhanced by increasing the surrounding reaction temperature through effective photothermal conversion (Figure 9F and G). Besides, the good photoacoustic performance can be used to guide this synergistic treatment (Figure 9H), making WO$_{3-x}$@-poly-L-glutamic acid nanoparticles promising H$_2$O$_2$-responsive theranostic agents.

In the TME, there is not only H$_2$O$_2$ but also a large amount of the reducing substance GSH, which can significantly deteriorate the diagnosis and treatment effect of H$_2$O$_2$-responsive theranostic agents. To overcome this obstacle, Lin et al.$^{99}$ designed a MnO$_2$-based nanoagent with simultaneous Fenton-like Mn$^{2+}$ ion delivery and GSH depletion for enhanced chemodynamic therapy. After being taken up by cancer cells, the MnO$_2$ decorating the mesoporous silica nanoparticles (MS@MnO$_2$ NPs) reacts with the GSH in the acidic TME to generate glutathione disulfide and Mn$^{2+}$ ions. The resulting Mn$^{2+}$ ions serve as Fenton-like ions to trigger the H$_2$O$_2$ to form OH for killing cancer cells, and simultaneously as activity T$_1$-weighted contrast agents for MRI. The properties of simultaneous acid-controlled Mn$^{2+}$ ion release and GSH depletion endow

![Figure 9](https://example.com/figure9.png)
MS@MnO2 NPs with intensified chemodynamic therapy and activatable MRI functions for monitoring therapy, demonstrating the great potential of MnO2 as a TME-responsive multifunctional theranostic agent.

H2S responsiveness
Hydrogen sulfide (H2S) is a key signal molecule in the human body and plays an important role in health and disease. Accordingly, in mammalian systems, endogenous H2S is primarily synthesized from cysteine or cysteine derivatives in the presence of enzyme catalyst, such as cystathionine-β-synthase (CBS), cystathionine-γ-lyase (CSE), and 3-mercaptopropionate thiotransferase (3-MST). It has been suggested that many diseases such as Down syndrome, Alzheimer’s disease, cirrhosis, diabetes, and cancer are associated with an abnormal concentration of endogenous H2S. Therefore, research on endogenous H2S, including the detection of H2S and utilizing H2S to develop specific nanotheranostic agents, has attracted considerable interest in the areas of medical, nanomaterial, and chemical science.

H2S-responsive smart nanoprobes
Given the key role of the H2S molecule in vivo, detection of this signaling molecule accurately is of great importance. To date, many interests have been focused on the design of intelligent nanoprobes owing to their high sensitivity, high signal-to-noise ratio, real-time imaging, and simple operation features. Particularly, smart fluorescent probes with high sensitivity have attracted great attention. Generally, intelligent fluorescent probes were designed based on fluorescent molecules that can react with the H2S molecule, leading to the change of the fluorescent emission. Nevertheless, because of the low concentration of endogenous H2S and large amounts of interference molecules such as GSH and cysteine (Cys) in the complex biological systems, the design of H2S-responsive fluorescent probes with high sensitivity and chemical selectivity still remains a formidable challenge.

Zhao et al developed a boron dipyrromethene (BODIPY)-based fluorescence micelle as an H2S-responsive probe for detecting H2S. This probe micelle contained a semicyanine-BODIPY dye (BODInD-Cl) as the H2S interaction molecule, and BODIPY as a complementary energy donor of BODIPY. The main feature of this nanoprobe is that the absorption of the energy acceptor BODInD-Cl will shift from 540 nm to 738 nm after the H2S trigger to reduce the efficiency of Förster resonance energy transfer, leading to the simultaneous “turn-on” of the fluorescent signal of energy donor BODIPY1 and “turn-off” of the fluorescent signal of energy acceptor BODInD-Cl. As a result, this probe can be used to quickly detect and track H2S using a fluorescence ratio. Besides, competition experiments showed that the red shift of the absorption peak of BODInD-Cl can only be mainly triggered by H2S, while the influence of other small molecules is very weak, demonstrating the high detecting selectivity of this probe. Zhang et al also designed a sulfide-functionalized BODIPY-based fluorescent probe for selectively detecting endogenous H2S by confining sulfide-functionalized BODIPY within the interior of porous silica matrix. The other influencing molecules with size larger than the aperture of the porous silica are unable to react with sulfide-functionalized BODIPY. Therefore, this common fluorescence molecule can only react with the small H2S molecule with a substantial red shift in absorption and emission, giving high chemical selectivity and sensitivity.

Given that NIR fluorescent probes have high resolution with deep-tissue penetration, Xu et al developed an H2S-activated NIR-II nanoprobe (NIR-II@Si) for visualizing colorectal cancers (Figure 10A). NIR-II@Si is composed of a covalently cross-linked silica shell with two organic chromophores in its cavity, in which a boron-dipyrromethene (ZX-NIR) dye serves as an H2S-responsive chromophore to generate NIR-II emission, and an H2S-inert aza-BODIPY (aza-BOD) dye with strong emission at 700 nm serves as internal reference. Upon reaction with H2S, ZX-NIR was transformed to NIRII-HS accompanied by maximum emission shifting from 600 to 900 nm, while aza-BOD keeps maximum emission at 700 nm with similar intensity, forming ratiometric fluorescence with high signal-to-background ratios (Figure 10B and C). This H2S-responsive ratiometric fluorescence nanoprobe with excellent targeting capability exhibits excellent performance for selectively identifying the H2S-rich colon cancer cells. Moreover, the merits of NIR-II imaging at depth and spatial resolution enable this H2S-responsive probe to accurately identify colorectal tumors in animal models (Figure 10D).

Because of the high spatial resolution and deep tissue imaging penetration of photoacoustic imaging, enormous interest has recently been devoted to designing a smart photoacoustic nanoprobe for H2S detection. Shi et al developed an H2S-activated photoacoustic imaging nanoprobe Si@BODPA for in vivo H2S detection. Si@BODPA was fabricated using biocompatible silica as a core shell to encapsulate semi-cyanine-BODPA into its interior. In the presence of H2S, a nucleophilic substitution reaction between H2S and BODPA caused BODPA to convert into
BOD-HS, which displayed strong NIR absorption at 780 nm for photoacoustic imaging. Furthermore, Si@BODPA has excellent biocompatibility since the surface is modified by PEG. In the mode of HCT116 tumor-bearing mice, this Si@BODPA can provide real-time photoacoustic imaging of the endogenous H$_2$S generated in the HCT116 tumor, demonstrating the high activating effect and great application potential of this smart nanoprobe.

H$_2$S-responsive theranostic agents

H$_2$S is also an overproduced molecule in some cancer cells, such as colon cancer. Currently, the main diagnosis and therapy methods for colon cancer are colonoscopy diagnosis and surgical treatment, but there still remain some serious problems, such as missed diagnosis, misdiagnosis, recurrence, and metastasis. Using endogenous H$_2$S to activate the diagnosis and therapy functions of smart theranostic agents has been considered an effectively strategy to reduce the rate of misdiagnosis and improve the treatment efficacy of colon cancer. To date, several nanomaterials, including a Cu-based metal–organic framework and CuO, have been explored for designing H$_2$S-responsive theranostic agents.

Ma et al prepared a colon cancer antitumor agent based on H$_2$S-responsive photodynamic diagnosis (Figure 11A). They synthesized a copper-zinc mixed metal organic skeleton nanoparticle (NP-1), constructed of zinc metalated porphyrin (ZnPc) as ligand and Cu$^{2+}$ ions as building blocks. In NP-1, ZnPc served as photosensitizer, while Cu$^{2+}$ served as fluorescence quencher. Before activation, the fluorescence of ZnPc was quenched by Cu$^{2+}$ ions, resulting in a low yield of singlet oxygen. Upon encountering H$_2$S, the Cu$^{2+}$ ions would react with H$_2$S, followed by recovering the original fluorescence and singlet oxygen generation functions of NP-1 (Figure 11B and C). Cell and mouse tumor model treatment experiments demonstrated that NP-1 has excellent photodynamic efficiency upon triggering by endogenous H$_2$S (Figure 11D).

An et al designed a simultaneous turn-on photoacoustic imaging and photothermal therapy agent based on in situ reaction of cuprous oxide (Cu$_2$O) with endogenous H$_2$S at colon tumor sites (Figure 11E). The original agent of Cu$_2$O exhibited no obvious absorption in the NIR region before reaction with H$_2$S, giving a weak photoacoustic signal and photothermal effect at the normal tissue (Figure 11F and G). When Cu$_2$O entered the tumor site, the endogenous H$_2$S would trigger sulfidation of Cu$_2$O to form copper sulfide (Cu$_9$S$_8$), accompanied by strong absorption in the NIR region. This activated NIR absorption can be used for photoacoustic imaging and photothermal therapy of colon cancer tumor with high diagnosis sensitivity and minimal damage (Figure 11H).
Summary and outlook

In summary, this article presents recent advances in the design and fabrication of pH, GSH, H₂O₂, and H₂S-responsive nanomedicine agents, and their application in tumor diagnosis and treatment. Because the diagnosis and treatment functions of smart nanomedicine were designed to be silenced before activation, while turned “on” upon triggering by the TME, they exhibited higher theranostic sensitive and selectivity with lower harmful side effects, as compared with traditional nanomedicine agents. These merits make them highly promising for improving tumor diagnosis and therapy. In fact, in addition to pH, H₂O₂, GSH, and H₂S, there are many other TME-stimulating elements (eg, hypoxia, immune, enzyme, and protein) and exogenous elements (eg, light, magnetism, and ultrasound) that can be utilized to design smart nanomedicine agents. Furthermore, these elements can be merged together to explore multiresponsive nanomedicine agents. In this case, it is possible to activate the synergistic theranostic functions (eg, control the release of different drugs) at expected time points, further improving the tumor theranostic efficacies and mitigating the side effects. Besides, the permeable barriers for nanodrugs to effectively enter the tumor cells are also possible to overcome through multiresponsive steps. Despite these promising results, there are still many challenges to overcome for TME-responsive nanomedicine agents toward the clinical translation. Firstly, the safety issues of nanomedicine agents need to be thoroughly investigated. Secondly, the triggering efficiency of nanomedicine agents needs to be improved since the concentration of overproduced substances and the accumulation of nanoparticles in the tumor site are very limited. Finally, but not the least, the activated selectivity of nanomedicine agents needs to be further improved because most of the tumor-overexpressed substances also exist in the normal organs/tissues. Nevertheless, it is believed that with the continuous development of science and technology, these problems will be overcome, and these TME-responsive nanomedicine agents will facilitate the improvement of tumor diagnosis and therapy.

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