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Short review

Recent advances in Fenton and Fenton-like reaction mediated nanoparticle in cancer therapy

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ABSTRACT

Fenton and Fenton like reaction have been well clarified as efficient reactive oxygen species (ROS) sources in tumor, and have been widely developed into a cancer treatment method. Meanwhile, transition metal-based nanomaterials with Fenton or Fenton like reaction characteristics also have been well explored as therapeutic agents for the cancer therapy, mainly in chemo-dynamic and ferroptosis induced cancer therapy. Herein,to summarize recent advances in Fenton and Fenton like reaction mediated nanoparticles for cancer therapy, in this minireview, we first introduced the mechanisms of Fenton and Fenton like reaction and two therapeutic methods based on Fenton and Fenton like reaction, and then we introduced the well-designed nanoparticles with Fenton reaction or Fenton-like reaction characteristics for the cancer therapies. Finally its challenges and perspectives are discussed.

1. Introduction

Cancer has become the most fatal disease that seriously threaten human health and cause high mortality every year around the world [1]. Various therapeutic strategies have been put forward, for example, chemotherapy, radiotherapy and hormonal therapy have been applied and recognized in clinical cancer treatment [2–4]. Meanwhile, to allevite the possible side effects of the aforementioned treatment modalities and achieve better therapeutic effect, more and more novel cancer therapeutic methods are being studied. Moreover, some of the strategies study based on modulating the special metabolism of tumor and the tumor microenvironment (TME), *e.g.*, phototherapy [5], immunotherapy [6], as well as targeted therapy [7], chemodynamic therapy (CDT) [8], starvation therapy [9], and so on.

Among various treatment strategies, ROS plays a critical role in tumor growth and regression. ROS are general designation of oxygen-containing reactive species, mainly including superoxide anion, H_2O_2, ·OH, as well as lipid and protein peroxide [10]. The ROS in the physiological environment is mainly $O_2\bullet^-$, H_2O_2 [11] and are generated from single electron transferring of oxygen in mitochondrial electron transport chain. Compared with normal cell, ROS level is much higher in most tumor cells, and ROS was reported to play positive roles in carcinogenesis and tumor cell proliferation as key signaling molecules; however, the excessive ROS also can disrupt intracellular redox homeostasis, and cause cell death due to lipid and protein peroxidation and DNA damage [12].

Recently, Fenton reaction is well introduced in cancer therapy as lethal source of ROS, especially the ·OH. Fenton reaction was reported by Fenton in 1894, who found that Fe^{2+} catalyzed tartaric acid oxidation in H_2O_2 containing solution [13]. The rough reaction mechanism of Fenton reaction is shown in equations (1) and (2), which is put forward by Haber and Weiss in 1934 [14]. However, the detailed mechanism of Fenton and Fenton-like reaction is quite complex, and debate still existed, depending on nature of metal ion and substrate, as well as pH condition [15]. Fenton-like reaction is explored on some other transition metal ion like Cu^{2+}, Mn^{2+}, Co^{2+}, which also served as catalytic metal to produce ·OHs [16]. The main product of ·OH in Fenton reaction has attracted great

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Abbreviations

CDT chemodynamic therapy
H_2O_2 hydrogen peroxide
hydroxyl radical ·OH
$O2\bullet^-$ superoxide anion radical
DCFDA 2′,7′–dichlorofluorescin diacetate
2′,7′-dichlorofluorescein DCF
glutathione GSH
3,3′,5,5′-tetramethylbenzidine dihydrochloride hydrate TMB
glutathione peroxidase 4 GPX4
reactive oxygen species ROS
ferroptosis suppressor 1 FSP1
coenzyme Q_{10} CoQ_{10}
cyclohydrolase 1 GCH1
tetrahydrobiopterin BH4
Ca^{2+}-independent phospholipase $A_2\beta$ $iPLA_2\beta$
high-angle annular dark-field scanning TEM HAADF STEM
confocal laser scanning microscope CLSM
phosphate buffered saline PBS
polyvinyl pyrrolidone PVP
polyunsaturated fatty acid PUFA
tumor microenvironment TME
ferroportin 1 FPN 1
six-transmembrane epithelial antigen of prostate 3 STEAP3
divalent metal transporter 1 DMT-1
photothermal therapy PTT
photodynamic therapy PDT
reactive nitrogen species RNS
metal-organic frameworks MOF
sonodynamic therapy SDT
aminotransferase ALT
aspartate aminotransferase AST
red blood cell RBC
white blood cell WBC
hemoglobin HGB
mean cell hemoglobin MCH
mean cell hemoglobin concentration MCHC
Mean corpuscular volume MCV
hematocrit HCT

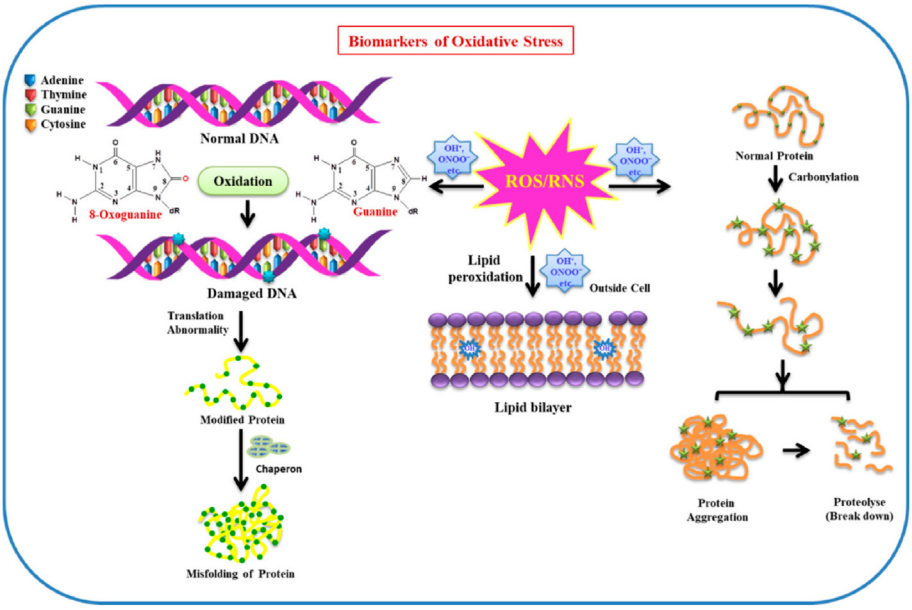


Fig. 1. Effect of ROS/RNS on biomolecules (DNA, protein, lipid, etc.) used as biomarkers of oxidative stress in cellular environment. Reprinted with permission from Ref. [16].

attention for its therapeutic potential in tumor cell death, since there is elevated H_2O_2 level in tumor cell, as indicated below in Eqs. (1) and (2):

$$Fe^{2+}+H_2O_2 \rightarrow Fe^{3+}+\cdot OH + OH^- \quad (1)$$

$$Fe^{3+}+ H_2O_2 \rightarrow Fe^{2+}+HOO\cdot+H^+ \quad (2)$$

Fenton and Fenton-like reaction transformed H_2O_2 into more toxic ·OHs. ·OHs, as active single electron molecule, have strong oxidizing ability to oxidize amino acid terminals in protein and polyunsaturated fatty acid chains in lipid, and to DNA damage, as shown in Fig. 1. However, it is highly active and reactive with half-life of 10^{-9} s [17], the short lifespan of ·OHs limits its diffusion and reaction range. Thus, it would be applicable to deliver Fenton reaction-based nanomaterials intracellularly into tumor cell for enhanced therapeutic effect and alleviative normal tissue damage.

CDT and ferroptosis induced therapy are developed as specific treatment ways of Fenton and Fenton-like reaction in cancer therapy, both CDT and ferroptosis therapy take advantage of ROS, especially ·OH produced by Fenton reaction. The objective of CDT and ferroptosis induced therapies are to promote Fenton reaction, and the strategies include delivering transition metal ion-based nanomaterials intracellularly or modulating iron metabolism in cancer cell and so on. CDT is applied as ·OH generated from Fenton and Fenton-like reaction. Various materials based on transition metal ion, especially iron ion, have been developed for CDT [18]. While ferroptosis is a kind of regulated cell death due to iron accumulation and following iron dependent lipid peroxidation [19]. Many genetic and metabolic modulation systems are involved in ferroptosis, like GPX4-GSH system, FSP1-CoQ_{10} system, GCH1-BH4 system, $Ipla_2\beta$ system and DHODH system [20]. Ferroptosis induced therapy aims to disrupt redox homeostasis and promote lipid

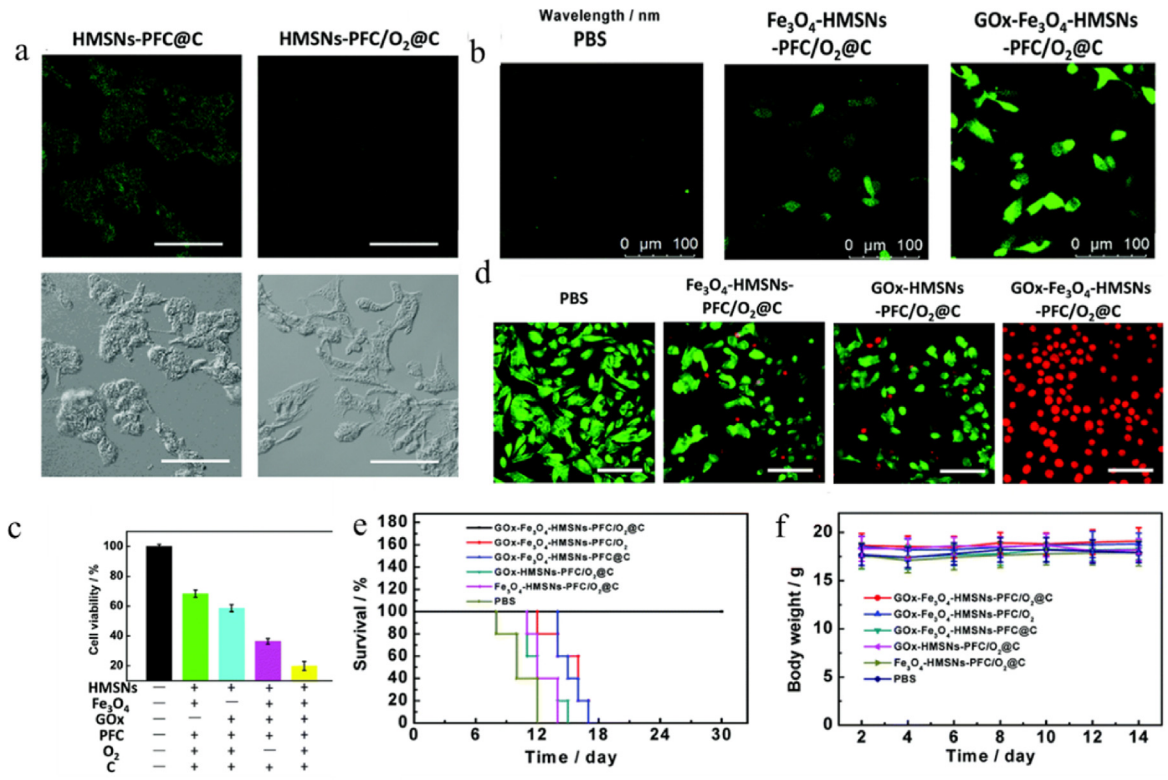


Fig. 2. a) Immunofluorescent staining images of HIF-1α in B16–F10 cells pre-treated with HMSNs-PFC@C or HMSNs-PFC/O_2@C in the hypoxic environment (scale bars are 100 μm). b) CLSM images of DCFH-DA stained B16–F10 cells treated with PBS, Fe_3O_4-HMSNs-PFC/O_2@C and Gox-Fe_3O_4-HMSNs-PFC/O_2@C. c) MTT assay of B16–F10 cells treated with different nanoreactors under anaerobic conditions. d) CLSM images of viable and dead cells distribution after treatment with PBS, Fe3O4-HMSNs-PFC/O_2@C, Gox-HMSNs-PFC/O_2@C, and Gox-Fe_3O_4-HMSNs-PFC/O_2@C under anaerobic conditions (scale bars are 100 μm). e) Survival rates of each group. f) Body weight of mice after various treatments. Reprinted with permission from Ref. [31].

peroxidation, especially PUFA. One of the approaches is modulating free ferrous ions metabolism in tumor cell [21,22]. Ferroptosis highly depends on bioavailable ferrous ion accumulation and the resulting Fenton reaction activity, and thus modulations on ferric ion transportation, storage and ferrous-ferric ion transformation are rational strategies for ferroptosis induction in cancer therapy [23].

In this mini-review, we introduce the specific applications of Fenton and Fenton-like reaction in nanomedicine field for cancer therapy, and we also focus on CDT and ferroptosis induced cancer therapy. Firstly, various transition metal ion-based nanoparticle, which can be used as Fenton reaction *in vitro* and *in vivo* are introduced here. Secondly, the ferric and ferrous ion delivery and modulation for Fenton reaction and ferroptosis induced therapy are also introduced. Finally, the challenges and future perspectives on Fenton and Fenton like reaction-based therapy are discussed.

2. Fenton reaction mediated CDT

Based on unique physiological TME, CDT is developed for cancer therapy. Compared with those in normal tissues, TME is mild acid environment (pH ~6.6) in extracellular fluid [24], and the H_2O_2 level and endogenous tumor cell both are significantly higher than normal tissues and cell [25], which constitutes the basic conditions for the Fenton reaction.

Various transition metal-based nanoparticle has been investigated for CDT, and most of them are iron based one. Other metals, like manganese ion based one, copper ion based one, are also investigated [8]. Many CDT enhancement strategies, such as improving endogenous H_2O_2 concentration, improving catalyst performance, optimizing reaction condition, are put forward [26]. In the following part, CDT related nanoparticles are introduced and classified as iron and non-iron based nanomaterials.

2.1. Iron-based nanoparticles

Iron-based nanomaterials are abundant, and many studies focus on iron oxide nanoparticles, iron sulfide nanoparticles, iron nanoclusters, ferrocene nanoparticles, as well as metal–polyphenol networks (MPN(Fe)) and metal–organic frameworks (MOF(Fe)) nanoparticles [27].

Fe_3O_4 nanoparticle is the most commonly materials in CDT, usually combined photothermal therapy [28–30]. However, there are two main problems in iron oxide-based nanoparticle application in CDT. One is the insufficient H_2O_2, and the other is insufficient Fe^{2+} content due to the poor conversion of Fe^{2+} and Fe^{3+} [27]. To solve these problems, modification on iron oxide nanoparticles has been explored.

To overcome the insufficient H_2O_2 for better CDT outcome, Huiwen et al. [31] prepared Gox-Fe_3O_4-HMSNs-PFC/O_2@C (C: B16–F10 cell membrane; HMSN: hollow mesoporous silica nanoparticles; PFC: perfluorohexane; Gox: glucose oxidase). Gox consumed glucose and O_2 were stored in PFC, producing H_2O_2 in higher amount, thus Fenton reaction enhanced and ·OH concentration increased *in vitro* and *in vivo* studies. The *in vitro* data showed that oxygen carrier of PFC relieved hypoxia since HIF-α expression reduced (Fig. 2a), and Gox-loaded nanoparticles induced higher ROS levels (Fig. 2b) and highest cell toxicity in B16–F10 cell (Fig. 2c and **d**). The *in vivo* data also supported the therapeutic effect and biosafety of designed nanoparticle, with survival period over 30 d and stable body weight of treated mice (Fig. 2e and **f**).

The bioavailable Fe^{2+} plays vital roles in Fenton reaction, but it willl be oxidized into Fe^{3+} after its catalyzing H_2O_2 into ·OH. However, then the catalytic ability of Fe^{3+} is much lower than Fe^{2+}, and Fe^{2+}/Fe^{3+} conversion is limiting step in Fenton reaction, thus impeding ROS production [32]. To overcome this issue, Ding Tao et al. [33] designed a kind of redox-mediator potentiated nanoreactor for Fe^{3+}/Fe^{2+} circulation to

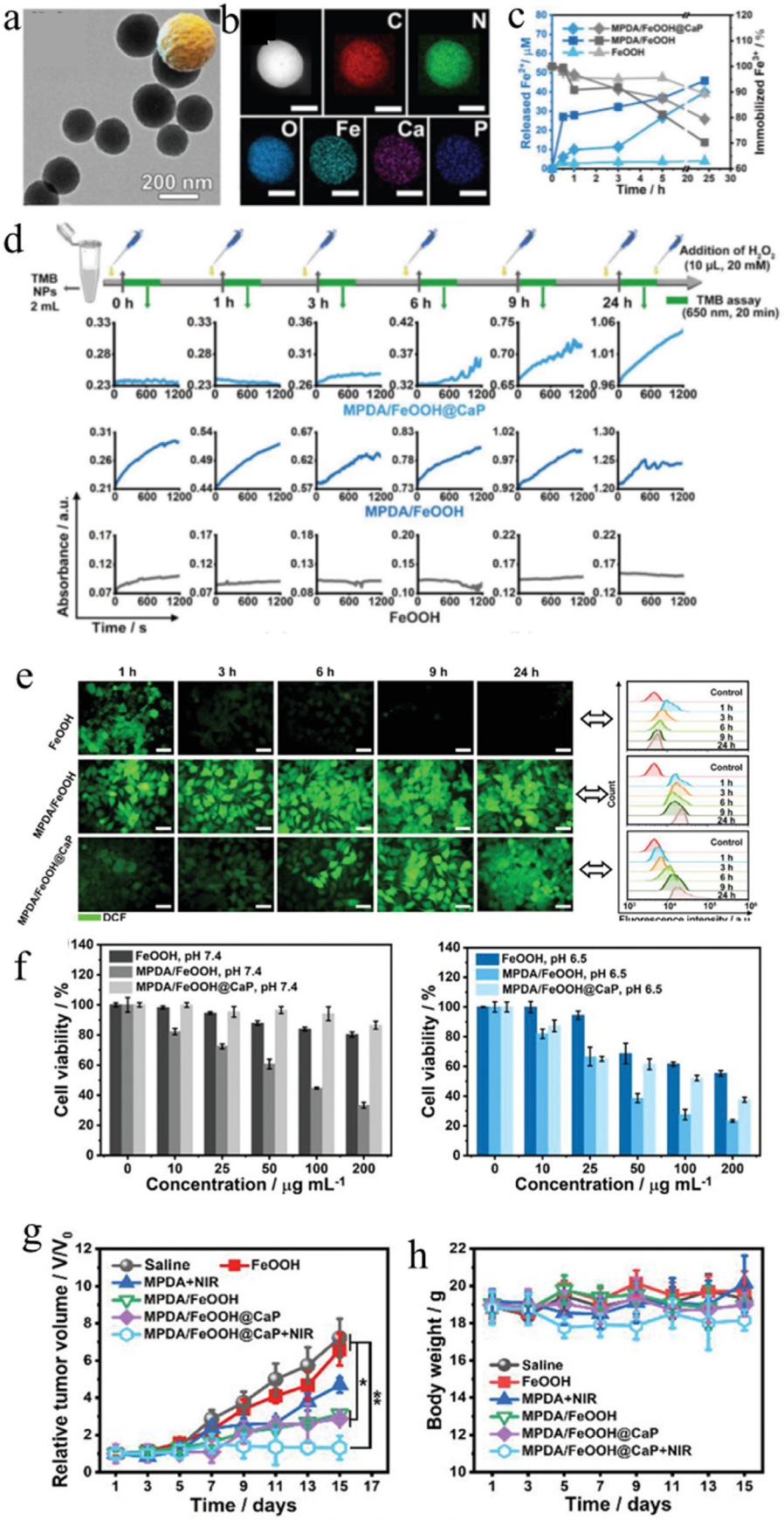
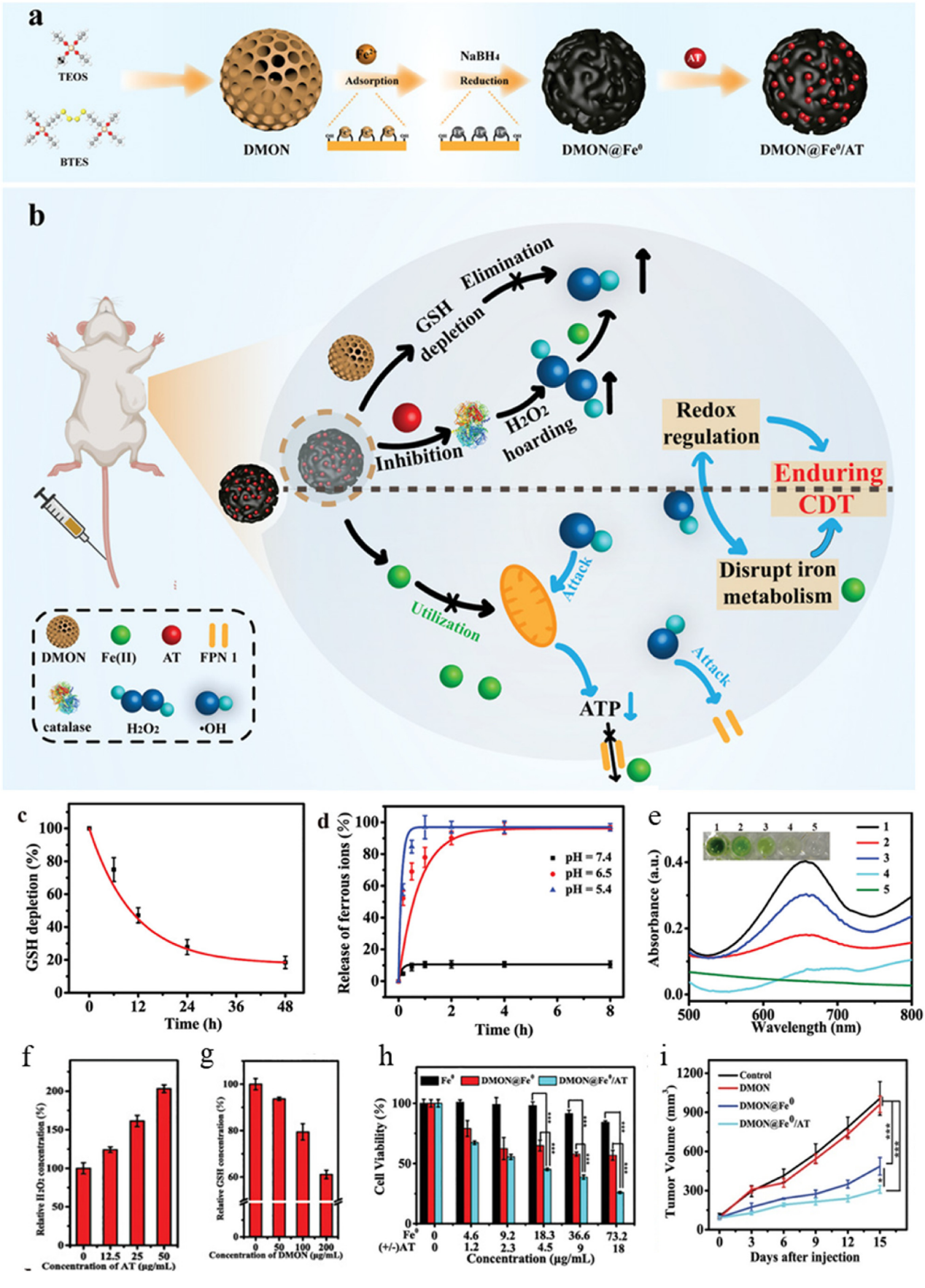


Fig. 3. a,b) TEM and corresponding HAADF STEM and element mapping images (scale bar represents 100 nm) of MPDA/FeOOH@CaP NPs. c) Time-dependent absorbance variations of TMB at 650 nm in the Fenton-like catalysis system upon the continuous addition of H_2O_2 (10 μL, 20 × 10^{-3} M) at predetermined time intervals (0, 1, 3, 6, 9, 24 h). The absorbance was continuously recorded for 20 min after each addition of H_2O_2, and the concentration of the probe TMB was 1 × 10^{-3} M. d) Transformation of Fe species in MPDA/FeOOH@CaP, MPDA/FeOOH, and FeOOH suspensions. e) CLSM images (scale bar: 50 μm) and corresponding flow cytometry analysis of the long-lasting intracellular ROS generation by monitoring the fluorescence signals of DCF at different time intervals. f) Cytotoxicity profiles of nanoparticles (MPDA/FeOOH, FeOOH, and MPDA/FeOOH@CaP) toward MCF-7 cells under different conditions (pH 7.4 or pH 6.5). g) Relative tumor volume and body weight of tumor-bearing nude mice during the treatment. Reprinted with permission from Ref. [33].



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sustain long-lasting ROS generation, named as MPDA/FeOOH@CaP (MPDA: mesoporous polydopamine). MPDA is used as redox mediator to reduce Fe^{3+} to Fe^{2+}. The size of nanoparticle was around 200 nm (Fig. 3a), and FeOOH and CaP coating was confirmed by STEM (Fig. 3b). When continually added H_2O_2 into FeOOH and MPDA/FeOOH, the ·OH generated from MPDA/FeOOH was constant and accumulated characterized by TMB (Fig. 3d), moreover, the Fe^{2+} released from MPDA/-FeOOH was significantly higher than FeOOH (Fig. 3c), which was corresponding with nanoreactor hypothesis. The cellular experiment proved long term ROS production ability though DCFDA probe up to 24 h (Fig. 3e), along with increased MCF-7 cell toxicity (Fig. 3f), and the *in vivo* result in experiments showed great tumor regression (Fig. 3g–h). The biosafety property of the NPs was good. When injected 10 mg/kg every 2d, MPDA/FeOOH@CaP showed negligible cell damage and inflammatory infiltration in liver and kidney though H&E staining, and no significant upregulation of AST and ALT level after 15 d treatment.

Besides iron oxide nanoparticles, iron-based nanoparticles for CDT are emerging, focusing on improving Fenton reaction efficiency in tumor intracellular environment. For example, the Liu *et al.* [34] reported DMON@Fe^0/AT (Fig. 4a) (DMON: S–S bond-rich dendritic mesoporous organic silica nanoparticles; AT: 3-amino-1,2,4-triazole), this kind of nanoparticle modulated redox homeostasis and intracellular iron metabolism. As designed, in mildly acid TME, DMON depleted GSH by redox reaction with S–S bonds, while Fe^0 was oxidized and Fe^{2+} released accompanied with release of catalase inhibitor of AT, causing H_2O_2 elevation and Fenton reaction activity (Fig. 4b). According to the scheme, GSH was depleted when incubated with DMON (Fig. 4c), and ferrous ion released out in burst at pH 6.5 and pH 5.5 along with ·OH generation (Fig. 4d–e). Cellular experiments also showed reduced GSH and elevated H_2O_2 (Fig. 4f–g), the expression of ferroportin 1 (FPN 1), which is the only known iron exporter, was reduced due to ATP inhibition, thus causing enhanced 4T1 cell toxicity (Fig. 4h). The ROS level in breast cancer mice models corresponded with cellular experiments, and tumor is greatly regressed (Fig. 4i), indicating the synergetic CDT enhancement. Besides, the biosafety of DMON@Fe^0/AT was good with low toxicity. After 3d and 30d injection of DMON@Fe^0/AT at 100 mg/kg, the blood biochemical indexes and hematology parameters, including ALT, AST, MCHC, LYM, HCT, RBC, WBC, MCH. MCV and HGB, had no significant difference with saline group.

Recently, MOF and macromolecules nanoparticles are also explored in CDT. The application of MOF in CDT has been introduced and elucidated by Yuyu Zhong *et al.* [35]. MOF is a kind of network materials composed of metal ions or their clusters (alkaline, metals, transition metals and lanthanides) with organic ligands (carboxylates, phosphorate ad polyamines) [36]. Compared with inorganic nanoparticle, MOF materials have better biodegradability and biocompatibility, and is easier to functionalize it based on properties of organic ligands, besides, the shape of MOF is quite flexible and can be designed with responsive degradation property, like pH responsiveness [35,37].

2.2. Non-iron based nanomaterials

Some transition metal-based nanoparticles, especially Mn [38–41] and Cu-based [42–45], are also explored in CDT based on Fenton-like reaction. Compared with Fe^{3+}, Cu^{2+} and Mn^{2+} exhibited more active Fenton like reaction in wide pH range, from pH 5.5 to 9. The rate of oxidizing species production on Cu^{2+} is about 100 folds higher than Fe^{3+} at pH 5.5 at 25 °C [46], so many Cu^{2+} and Mn^{2+}-based nanomaterials are explored and many of them are functionalized with GSH depletion and H_2O_2 self-production for CDT enhancement.

Lin *et al.* [47] firstly reported the MnO_2 delivery for GSH depletion and Mn^{2+} mediated Fenton-like reaction, using MS@MnO_2 (MS: mesoporous silica nanoparticles), which has been well cited and followed. Ou et al. [48] improved the penetration capability of hollow MnO_2 nanoparticle though oxygen driven nanoparticles moving (Fig. 5a). One side of hollow MnO_2 nanoparticles were doped with gold (Au) nanoparticles, as shown in Fig. 5b and **c**, the diffusion coefficient of Au@H–MnO_2 increased correspondingly with H_2O_2 concentration (Fig. 5d). In 2D-cell model, ROS level and cell toxicity in Au@H–MnO_2 treated B16 cell (melanoma cancer cells) was much higher than other groups (Fig. 5e and **f**), while the increased nanoparticle penetration ability and cell toxicity was confirmed in 3D-cell model (Fig. 5g and **h**). A novel approach of enhancing CDT effect though NPs penetration was developed.

Cu-based nanomaterials is explored in CDT, represented by copper peroxide nanoparticle [49–52]. The Cu_2O nanoparticle was reported by Lin *et al.* [53] as first example of a Fenton-type metal peroxide nanomaterial. The PVP coated Cu_2O nanoparticles, named as CP nanodots, had average size of 16.3 nm Cu_2O was aggregated into nanodots in 0.02 M NaOH solution (Fig. 6a–b), disassociated into Cu^{2+} and H_2O_2 in pH 5.5 intracellularly (Fig. 6c), the free Cu^{2+} played Fenton reaction and generated hydroxy radical in solution (Fig. 6d and **e**). Cellular experiments also confirmed the scheme though elevated ROS level and cell toxicity on U87MG cell line, as well as •OH-initiated lipid peroxidation. In U87MG tumor bearing mice, the tumor size was regressed at 10 mg/kg CDP nanodots dosage, and tumor cell has higher level of apoptosis compared with control group. The H_2O_2 self-supplied Cu_2O nanodots attracted great attention in CDT.

Recently, Ti^{3+} and Co^{2+} have been studied for CDT with great biosafety property, and Ti^{3+} and Co^{2+} based nanomaterials were designed as multi-functional therapeutic platform [54–56]. Fox example, D-MOF(Ti) (defect-rich Ti-based MOF) was fabricated by Shuang Liang *et al.* for SDT and CDT synergetic combination, Ti^{3+} nodes demonstrated Fenton-like activity in H_2O_2 solution though MB degradation, and in 4T1 cell though high ROS level. Furthermore, D-MOF(Ti) had great biosafety, since no significant toxicological effect though blood parameters within 30d at dosage of 15 mg/kg [54].

3. Ferroptosis induced cancer therapy

The mechanism of ferroptosis induced therapy is redox homeostasis imbalance and lipid peroxidation. There are two main approaches to disrupt redox homeostasis, enhancing ROS generation and destroying antioxidant system [19]. ROS level can be elevated though Fe^{2+}-mediated Fenton reaction. Free ferric and ferrous ion accumulation plays key role in Fenton reaction and ROS generation, the iron metabolism in ferroptosis is explained in Fig. 7. Fe^{3+} binds to transferrin (TF) in blood circulation and taken up by transferrin receptors (TFR-1), Fe^{3+} is encapsulated in endosome and reduced into Fe^{2+} after STEAP3 metalloreductases, Fe^{2+} was transported into labile iron pool in cytoplasm though DMT-1; Excessive labile iron was either exported extracellularly though ferroportin 1,or stored in ferritin heteropolymer [57,58]. The dedicated relationship between ferroptosis promotion and iron mechanism modulation is still unclear, but any changes in iron accumulation, including transportation, storage and valence state conversion have impact on ferroptosis sensitivity

Fig. 4. a) Schematic representation of the synthesis of DMON@Fe0/AT. b) *In vivo* application of DMON@Fe^0/AT and the mechanism of enduring CDT by mutually promoting iron metabolism and redox homeostasis regulation. c) Depletion rate of GSH after incubation of DMON with 10×10^{-3} M GSH for 12, 24, and 48 h. d) Ferrous ion release curves in different pH values PBS (pH = 7.4, 6.5, and 5.4) at different time points (10 min, 30 min, 1 h, 2 h, 4 h, and 8 h). e) Catalytic oxidation of TMB by DMON@Fe^0 under different conditions—1) DMON@Fe^0 in pH = 5.4 PBS $+100 \times 10^{-6}$ M H_2O_2; 2) DMON@Fe^0 in pH = 6.5 PBS $+100 \times 10^{-6}$ M H_2O_2; 3) DMON@Fe^0 in pH = 7.4 PBS $+100 \times 10^{-6}$ M H_2O_2; 4) 100×10^{-6} M H_2O_2; and 5) PBS). f) Intercellular concentration of GSH after treatment with various concentrations of DMON for 24 h. g) Intercellular concentration of H_2O_2 after treatment with various concentrations of AT for 24 h. h) Relative 4T1 cells viabilities after treated with different groups of nanoparticles for 24 h. i) Relative tumor volume change curves during 15 days treatment (at a DMON dosage of 100 mg kg−1 or an Fe0 dosage of 18.3 mg/kg). Reprinted with permission from Ref. [34].

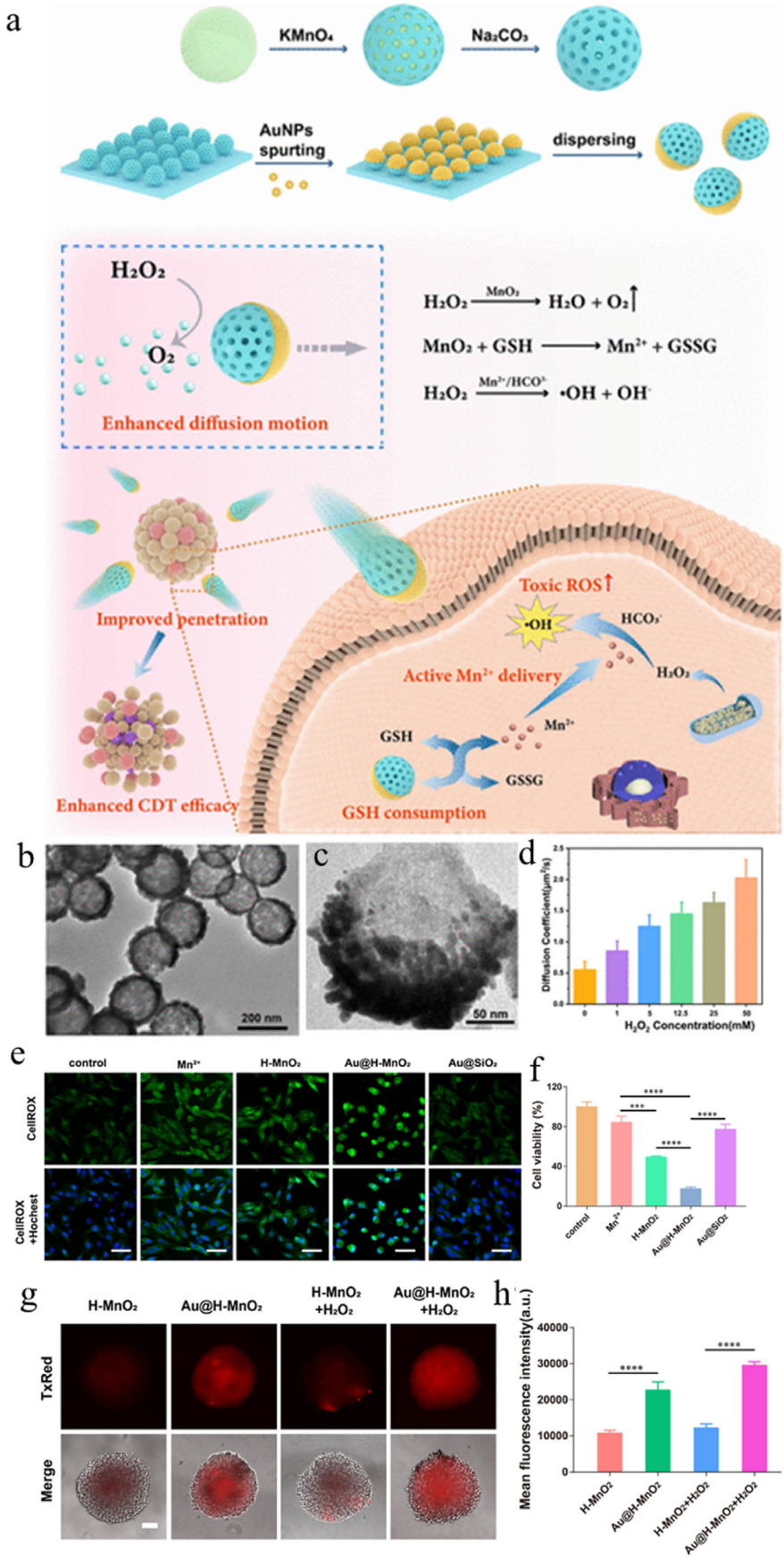

Fig. 5. a) Fabrication of Au@H–MnO_2 nanomotors and their application for active Fenton-like Mn^{2+} delivery and enhanced CDT. b,c) TEM image of H–MnO_2 nanoparticles and Au@H–MnO_2 nanomotor. d) Diffusion coefficients of Au@H–MnO_2 nanomotors. The motion of nanomotors was analyzed with ImageJ for 10 s (n = 26). E) Inverted fluorescence microscopy images of ROS in B16 cells probed by CellROX. Scale bars, 50 μm. f) Cell viability of B16 cells after incubation with different treatments. g) Penetration capability of Au@H–MnO_2 nanomotors. h) Mean fluorescence intensity of B16 tumor spheroids after incubating with Au@H–MnO2 nanomotors for 6 h. Reprinted with permission from Ref. [48].

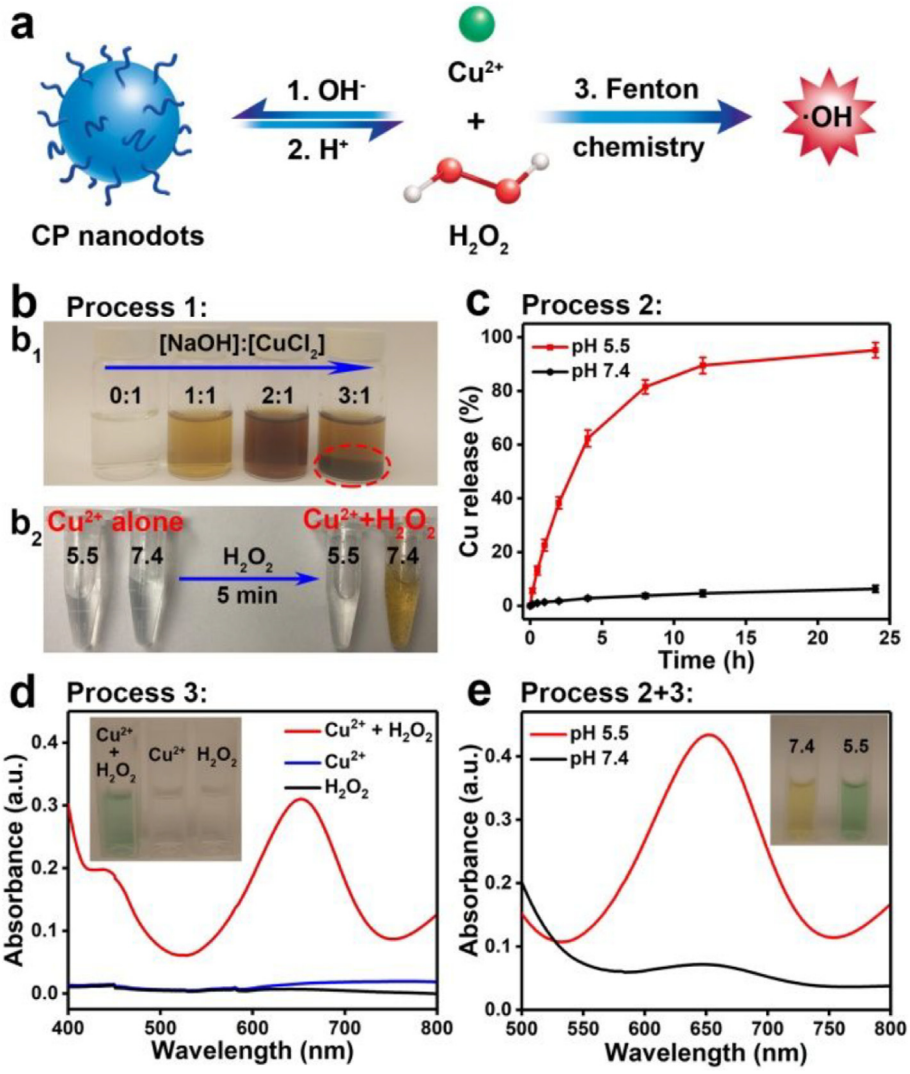

Fig. 6. (a) Schematic showing the formation and dissociation of CP nanodots for activatable •OH production. (b1) Photograph of CP materials obtained in the presence of PVP at different molar ratios of NaOH to $CuCl_2$. Unexpected precipitation (red circle) was observed during the synthetic process when the ratio was too high (3:1). (b2) Photograph of $CuCl_2$ solutions with different pH values before and after the addition of H_2O_2. Note that the CP formed at pH 7.4 was aggregated due to the absence of PVP stabilizer. (c) Cumulative Cu release from CP nanodots in different pH conditions, showing their acid-induced dissociation. (d) UV–Vis spectra and photographs (inset) of TMB aqueous solution treated with H_2O_2, Cu^{2+}, or Cu^{2+} plus H_2O_2 for 30 min. Note that the weak absorption between 600 and 800 nm at Cu^{2+}-treated group is from the $CuCl_2$. (e) Colorimetric detection of •OH generated by CP nanodots at different pH values based on TMB assay. Reprinted with permission from Ref. [53].

[57]. The iron delivery and iron mechanism regulation are rational strategies for inducing ferroptosis in cancer therapy.

3.1. Delivery of iron-based nanomaterials

Iron-based nanoparticles can be taken up though endocytosis pathway and be struck in lysosome at pH 5.0 environment, then Fe^{2+} is released from nanoparticle in acid condition, mediating Fenton reaction intracellularly and promoting lipid peroxidation and ferroptosis [59]. Recently, Zhou *et al.* [60] prepared Fe_3O_4/Gd_2O_3 hybrid nanoparticles (FGNPs) loaded with Sorafenib (SFN) and coated with mPEG-PPS-NH2 (PPS: poly(propylene sulfide)), named as SFN-FGNP@PPS-mPEG, for cyclo-acceleration of ROS generation. At the pH 5.0 lysosome acid environment, Fe_3O_4 was degraded and Fe^{2+} was released sustainably, while SFN released 60% after 1 d in 100 μM H_2O_2 condition, the released SFN inhibited Xc^- system, thus reducing cysteine uptake and GSH generation. Finally, Fe^{2+} mediated Fenton reaction and SFN mediated GSH reduction produced excessive ·OH, consequently oxidized PPS and disassembled the nanoparticle for accelerating Fe^{2+} and drug release. The 4T1 cellular experiments indicated 500-folds higher ROS level than control group, as well as half level of GSH and enhanced lipid peroxides level. The tumor size was regressed and survival rate of 4T1 bearing mice was over 40 d for SFN-FGNP@PPS-mPEG group.

The iron can also be coordinated in different polymers like tannic acid (TA) [61–63], gallic acid (GA) [64–66], and polydopamine (PDA) [67–69], and this kind of coordination is pH sensitive, iron can be released in pH 5.5 tumor endosomal environment and be reduced into Fe^{2+} though TA, GA and PDA [62]. Besides, iron can also be loaded in MOF [70] and zeolitic imidazolate framework (ZIF) [71] for ferroptosis based cancer therapy. Recently, Zeng *et al.* [72] reported the coordination of ferroptosis and PTT in 4T1 breast cancer therapy. The PTT effect was activated in TME and enhanced Fenton reaction kinetics, the overproduced ROS inhibited formation of heat shocking protein (HSP), thus relieving tumor cell self-protection effect after PTT. Cro-Fe@BSA nanoparticles was designed by Zeng *et al.* (Cro: croconaine) (Fig. 8). For *in vitro* experiments, Cro was functionalized as iron chelator with pH responsive release profile, about 60% iron was released out at pH 6.5 and 5.5 buffer in 2 d, the iron disassociation from Cro enhanced PTT effect since temperature increased from 47.2 °C at pH 7.4–55.8 °C at pH 5.5 buffer. Meanwhile, the enhanced PTT effect was accompanied with 10% more ·OH production in solution, cellular experiment confirmed the design and HSP expression level reduced by half after nanoparticles treatment. Under these conditions the tumor disappeared after 21 d treatment, showing excellent therapeutic effect of Cro-Fe@BSA.

3.2. Delivery of iron metabolism modulator

Unlike directly delivering iron ion into tumor cell for pro-ferroptosis, modulation on iron metabolism also gain a lot of attention. Modulations focus on iron exportation, importation, storage and Fe^{3+}/Fe^{2+}

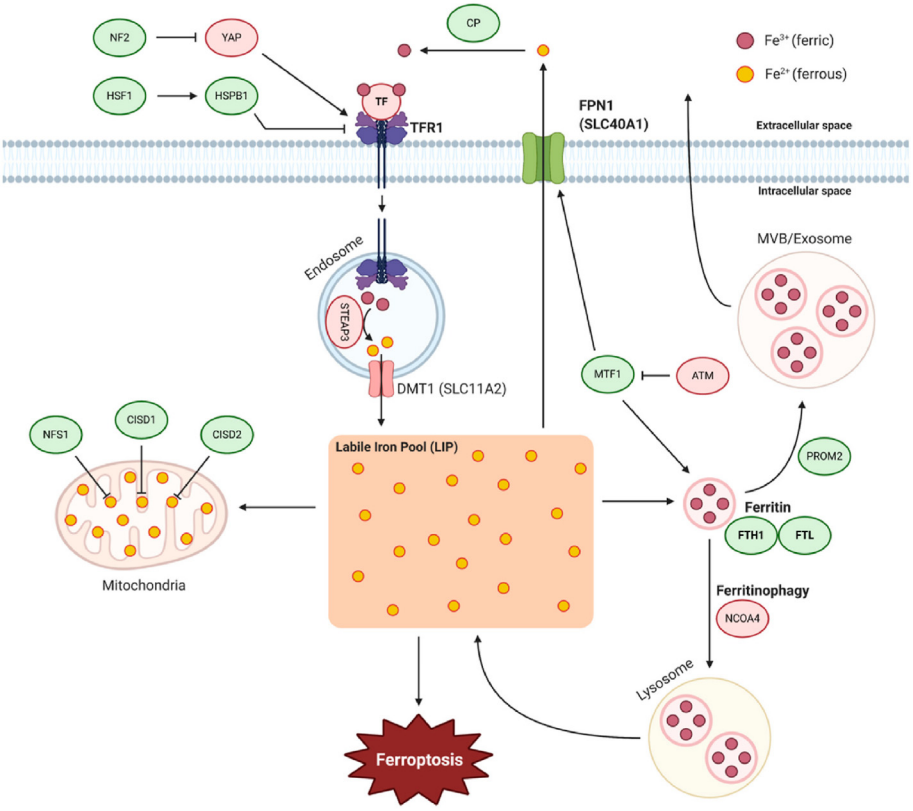

Fig. 7. Iron metabolism regulates ferroptosis. Ferric iron (Fe^{3+}, red circle) bound to TF can form a complex with TFR1 to be endocytosed into cells. In the endosome, ferric iron is reduced to ferrous iron (Fe^{2+}, yellow circle) by STEAP3 and transported into the cytoplasm by DMT1 or SLC11A2. Ferrous iron is stored in ferritin heteropolymers to protect cells and tissues from iron-mediated damage. Ferritin can undergo ferritinophagy, an autophagic degradation process, or exported out of the cell as MVB/exosomes. In the mitochondria, iron-sulfur clusters can be used by iron-sulfur proteins in various processes. Dysregulation in any of the above processes can lead to an increase in the labile iron pool and contribute to ferroptosis. Ferroptosis inhibiting and inducing factors are indicated in green and red, respectively. (Abbreviations: ATM, ATM serine/threonine kinase; CISD1/2, CDGSH iron-sulfur domain-containing protein 1/2; CP, ceruloplasmin; DMT1, divalent metal transporter 1; FPN1, ferroportin; FTH1, ferritin heavy chain 1; FTL, ferritin light chain; HSF1, heat shock factor 1; HSPB1, heat shock protein beta-1; MTF1, metal-regulatory transcription factor 1; MVB, multivesicular bodies; NCOA4, nuclear receptor coactivator 4; NF2, neurofibromin 2; NFS1, NFS1 cysteine desulfurase; YAP, yes-associated protein). Reprinted with permission from Ref. [57].

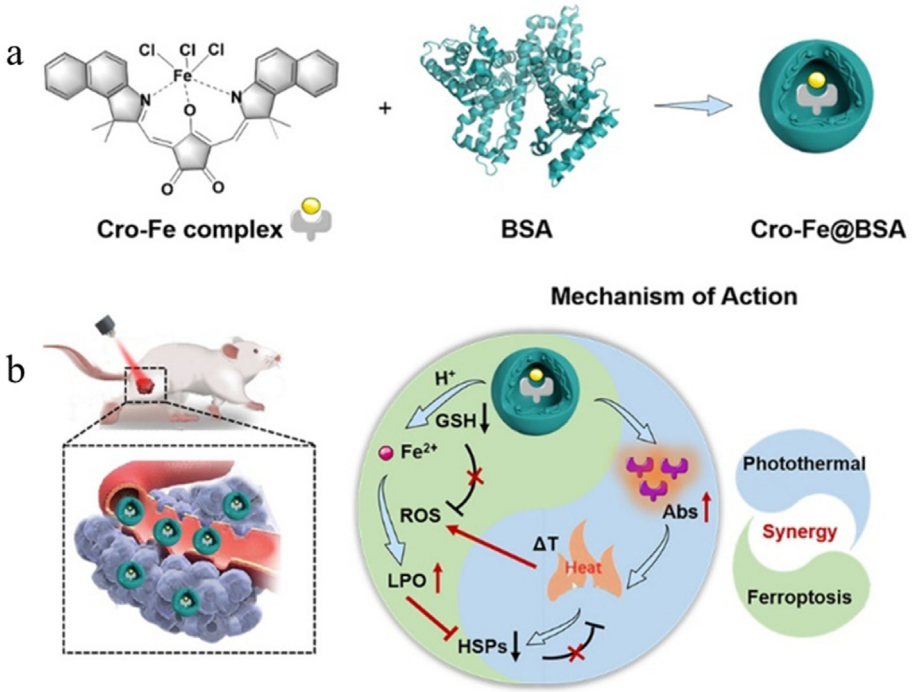

Fig. 8. a) Fabrication of Cro-Fe@BSA nanoparticles by the encapsulation of iron(III)-coordinated croconaine molecules with bovin serum albumin. b) Mechanism of the mutually beneficial combination of ferroptosis and the photothermal effect for cancer therapy. Reprinted with permission from Ref. [72].

conversion [73], concerning about transferrin, transferring receptor, and ferroportin 1. Recently, a kind of ferritin-hijacking nanoparticle (Ce6-PEG-HKN_{15}) was fabricated by Zhu *et al.* [74]. Ferritin targeting peptide of HKN_{15} was conjugated on Ce6, the typical photosensitizer. The nanoparticle specially accumulated around ferritin, and the ferroptosis was promoted when photodynamic effect destroyed ferritin and released stored iron for tumor cell ferroptosis (Fig. 9). The enhanced uptake and co-localization of ferritin and ferritin-hijacking nanoparticle after 4 h and

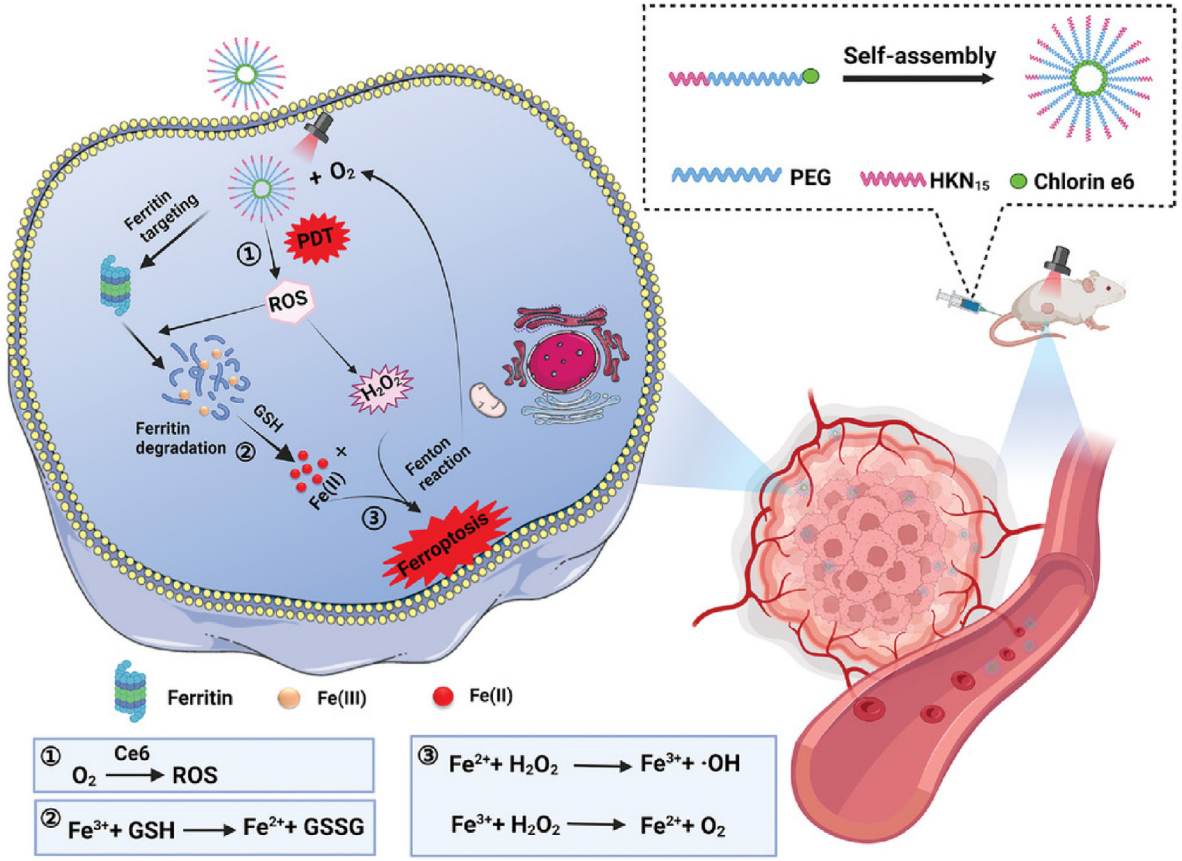

Fig. 9. Fabrication procedures and antitumor mechanisms of ferritin-targeting nanoparticles (Ce6-PEG-HKN15 NPs) for the synergistic PDT and ferroptosis therapy. Reprinted with permission from Ref. [74].

8 h incubation were confirmed in 4T1 cell, and 4T1 cell viability reduced from 100% to 20% after 660 nm laser treatment on nanoparticles, the mechanism behind ferroptosis was evaluated though GSH level, intracellular iron level, ·OH generation and mitochondrial morphology in 4T1 cell, which was corresponded with ferroptosis characteristics [75], the GSH level in 4T1 cell reduced to half and LPO level increased to 5-fold in Ce6-PEG-HKN_{15} group compared with PBS group, shrunken mitochondria and reduced cristae showed that 4T1 cell were regressed though ferroptosis. In 4T1 bearing mice model, the tumor was significantly impeded without tumor size increase, the survival period was over 40 d. Further modulation on iron metabolism and balance waits to be explored on ferroptosis induced cancer therapy.

4. Conclusions, challenges, and future perspectives

Advanced progresses have been achieved in the Fenton reaction-based cancer therapy and various studies in this field are growing quickly; however, it is still too early to apply this technology to the clinical treatment of cancer because it is still in its infancy [76–78] and several critical challenges or issues need to overcome or solved [79–81].

First, the biocompatibility and biodegradation of the agents based on Fenton-reaction need to be investigated further and must be ensured. Most of the reported therapeutic agents are inorganic elements-based materials, *e.g.*, Fe, Au, or Mn. Considering their high stability [79], it is difficult to control the biodegradation rate and improve the efficiency of body clearance.

Second, the targeting efficiency of the therapeutic agent based on Fenton-reaction must be greatly improved for better treatment outcomes. With optimized modification on the agents surface (*e.g.*, the iRGD peptide modification or cells membrane coating) can enhance the accumulation of the agents in the tumor lesion, but also help increase the blood circulation time and reduce the unnecessary uptake and removal by the immune system, such as the clearance by the mononuclear phagocyte system, which are all important for the passive-targeting process or active-targeting. Moreover, considering the pH in the lysosomes is low [77], decreasing the off-targeting by the normal cells can help reduce the side-effects of the therapeutic agents.

Third, the real-time monitoring of the Fenton-reaction based therapeutic agents should be introduced. Introducing the diagnosis functions into the agents allows for a better assessment of the agents biodistribution *in vivo*, which is critical for the treatment evaluation.

Forth, the combination between the Fenton-reaction and other cancer therapies (*e.g.*, the PDT or gene therapy) should be explored more. The radicals (like H_2O_2 and ·OH) in the tumor are very critical to the success of the treatment, it is highly recommended to effectively increase and utilize the radicals by integrating other therapeutic methods with Fenton-reaction based CDT, especially considering the heterogeneity of various types of tumors.

Finally, the mechanism of the cell death caused by Fenton-reaction based therapy needs to be investigated more, especially at the molecular level, which is very important for the future modification and design of the Fenton-reaction based therapeutic agents.

Overall, although there is a long way to go for the clinical application of the Fenton reaction materials, it is worth noting that if the above-mentioned concerns and obstacles can be effectively solved, it will be of great significance for its earlier entry into clinical trials.

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