Ferrite Nanoparticles-Based Reactive Oxygen Species-Mediated Cancer Therapy

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Ferrite nanoparticles have been widely used in the biomedical field (such as magnetic targeting, magnetic resonance imaging, magnetic hyperthermia, etc.) due to their appealing magnetic properties. In tumor acidic microenvironment, ferrite nanoparticles show intrinsic peroxidase-like activities, which can catalyze the Fenton reaction of hydrogen peroxide ($H_2O_2$) to produce highly toxic hydroxyl free radicals ($\bullet$OH), causing the death of tumor cell. Recent progresses in this field have shown that the enzymatic activity of ferrite can be improved via converting external field energy such as alternating magnetic field and near-infrared laser into nanoscale heat to produce more $\bullet$OH, enhancing the killing effect on tumor cells. On the other hand, combined with other nanomaterials or drugs for cascade reactions, the production of reactive oxygen species (ROS) can also be increased to obtain more efficient cancer therapy. In this review, we will discuss the current status and progress of the application of ferrite nanoparticles in ROS-mediated cancer therapy and try to provide new ideas for this area.

Keywords: ferrite nanoparticles, reactive oxygen species, cancer therapy, fenton reaction, external field, cascade reaction

INTRODUCTION

Cancer is one of the principal causes of morbidity and mortality in every country of the world. According to global cancer statistics of the World Health Organization, there were 18.1 million new cancer cases and 9.6 million cancer deaths in 2018, with the number of new cases rising 42.5% compared to that in 2008 (12.7 million) (Bray et al., 2018). In order to prevent the uncontrollable growth of tumor cells, the most conventional cancer therapeutic approaches used in clinical practice now are still surgery, chemotherapy, radiotherapy, and combination of them (Vahrmeijer et al., 2013; Barton et al., 2014; Pritchard et al., 2015; Sullivan et al., 2015; Sharma et al., 2016). However, surgery is often ineffective for advanced and metastasized cancers. Chemotherapy and radiotherapy suffer from severe side effects on account of the toxicity to normal cells and tissues. Based on the research of cancer-related biology and the development of biomedical engineering, a variety of alternative treatment strategies have been extensively studied to obtain more efficient cancer therapy, such as magnetic hyperthermia, photothermal therapy, photodynamic therapy, immunotherapy, and gene therapy (Dolmans et al., 2003; Yang et al., 2010; Kumar and Mohammad, 2011; Pardoll, 2012; Topalian et al., 2012; High and Roncarolo, 2019; Liu et al., 2019b). Most of these treatment strategies need to rely on the regulation of reactive oxygen species (ROS) to mediate tumor cell death. ROS are categorized as a class of incomplete reduction products of oxygen, mainly including superoxide anion ($O_2^-$), hydrogen peroxide ($H_2O_2$), hydroxyl radical ($\bullet$OH),...
and singlet oxygen (\(^{1}\text{O}_2\)) (Kumari et al., 2018). Superoxide anion can be generated as a byproduct of the electron transport chain in mitochondria or through activation of nicotinamide adenine dinucleotide phosphate oxidase (NOX) and exogenous stimulation (Murphy, 2009). Superoxide dismutase can reduce superoxide to hydrogen peroxide, which can be further converted into non-oxidizing water by cytosolic antioxidant systems under the catalysis of catalase, peroxiredoxins, and glutathione peroxidase (Winston and Giulio, 1991). The balance between the production and neutralization of reactive oxygen species in normal cells is beneficial to maintaining a proper ROS concentration to regulate intracellular signaling and homeostasis (Forman et al., 2010). Reactive oxygen species at high levels can damage proteins, lipids, and DNA, resulting in mutations and carcinogenesis in normal cells (Trachootham et al., 2009). Compared with normal cells, most tumor cells metabolize in distinct pathways leading to excessive ROS production (Schumacker, 2006). Cancer cells also have a higher level of antioxidant enzymes to enable them to survive in the presence of intrinsic oxidative stress without apoptosis (Birben et al., 2012). Increasing generation, regulating the types of reactive oxygen species, and inhibiting cellular glutathione peroxidase can break the balance between the production and elimination of ROS in tumor cell and tune the function of intracellular ROS from tumor promoting toward apoptotic signaling, inducing the apoptosis and death of tumor cell for cancer therapeutics (Liou and Storz, 2010). In order to enhance the effect of ROS-mediated tumor-specific therapeutic, various drugs and nanomaterials such as doxorubicin, cisplatin, Fe\(_3\)O\(_4\), gold, silver, polyoxomolybdate (POM), and molybdenum carbide have been studied for targeted delivery to tumor tissues and endocytosis by tumor cells to selectively increase the production of highly toxic ROS in tumor cells (Yanagie et al., 2006; He et al., 2012, 2016b; Maji et al., 2015; Kankala et al., 2017; Feng et al., 2019; Liu et al., 2019a; Dong et al., 2020; Maiti et al., 2020).

Among these nanomaterials, ferrite nanoparticles are widely studied due to unique magnetic properties and relatively high safety to human body, especially iron oxide nanoparticles, which have been approved by the US Food and Drug Administration for clinical applications, such as iron supplement, magnetic resonance contrast agent, and drug carrier (Liu et al., 2019c). Ferrite nanomaterials are composed of main ferric oxide and one or more oxides of other metals (such as manganese, copper, nickel, cobalt, or zinc). In tumor acidic microenvironment, ferrite nanoparticles exhibit peroxidase-like activity, which can catalyze the Fenton reaction of H\(_2\)O\(_2\) to produce highly toxic \(\cdot\text{OH}\), inducing the death of tumor cell (Chen et al., 2012). The peroxidase activity depends on the intrinsic properties of ferrite nanoparticles (chemical composition, crystalline phase, and particle size) and ROS-related bio-microenvironmental factors (physiological pH and buffers, biogenic reducing agents, and other organic substances). For further reading these factors in detail, an excellent review has been published by Yin and colleagues (Wu et al., 2014). In this review, we summarized the advances in the application of ferrite nanoparticles in ROS-mediated cancer therapy, and constructive perspectives were also provided.

**FERRITE-BASED ROS-MEDIATED CANCER THERAPY**

In 2007, Yan et al. first discovered that Fe\(_3\)O\(_4\) nanoparticles possess intrinsic peroxidase-like activity, which can catalyze the disproportionation of H\(_2\)O\(_2\) to produce highly toxic \(\cdot\text{OH}\) (Gao et al., 2007). Subsequently, researchers conducted extensive investigation on ferrite nanomaterials as nanoenzyme to mediate the generation of ROS for tumor treatment (Mai and Hilt, 2017). The specific mechanisms of the sufficient and highly toxic ROS production under the catalysis of ferrite nanoparticles in the existing publications can be roughly summarized as the following (shown in Scheme 1): (1) the intrinsic Fenton reaction catalytic activity of ferrite nanoparticles, (2) external field energy enhanced Fenton reaction, and (3) the cascade reactions to generate sufficient ROS.

**Intrinsic Fenton Reaction of Ferrite**

The intrinsic Fenton reaction catalytic activity is the most important mechanism of ferrite nanoparticles for ROS-mediated tumor therapy. Ferrite nanoparticles can specifically accumulate at the tumor site via enhanced permeability and retention effect and magnetic targeting and simultaneously release ferrous and ferric ions in tumor acidic environment to participate in the Fenton reaction with H\(_2\)O\(_2\) and generate \(\cdot\text{OH}\) (Wang et al., 2018). The Fenton and Fenton-like reactions can be shown as the following equations: 

\[
\text{Fe}^{2+} + \text{H}_2\text{O}_2 \rightarrow \text{Fe}^{3+} + \text{HO}^- + \text{H}^+ \quad (1) \\
\text{Fe}^{3+} + \text{H}_2\text{O}_2 \rightarrow \text{Fe}^{2+} + \text{HO}_2^- + \text{H}^+ \quad (2)
\]

(Bokare and Choi, 2016a,b; Maji et al., 2015; Kankala et al., 2017; Feng et al., 2019).

**SCHEME 1** | Schematic illustration of the ferrite nanoparticles-based ROS-mediated cancer therapy. Increasing generation of highly toxic ROS under the catalysis of ferrite nanoparticles can break the balance between the production and elimination of ROS based on these mechanisms: (1) intrinsic Fenton reaction catalytic activity of ferrite nanoparticles, (2) external field enhanced Fenton reaction, and (3) cascade reactions increased ROS.
The intrinsic catalytic activity of ferrite nanoparticles can be flexibly designed and controlled by adjusting the particles composition, size, morphology, etc.

Wang et al. pioneered the study of magnetic nanoparticles for tumor treatment (Zhang et al., 2013). They synthesized 6 and 13 nm magnetite nanoparticles (MNPs) through a one-pot method, which possessed enzyme-mimicking activity to produce ROS efficiently for cancer theranostics. The smaller size MNPs had higher enzyme-mimicking activity, and an ~99% tumor inhibition ratio was obtained by combining with intratumoral injection of exogenous hydrogen peroxide after treatment for 17 days. The size dependence of the catalytic activity of ferrite nanoparticles was further studied by Liu and colleagues. They investigated the cytotoxic effects of small Fe$_3$O$_4$ nanoparticles with different diameters (6, 9, and 14 nm) on human hepatoma cell lines, SK-HeP-1 and Hep3B (Xie et al., 2016). The 9 nm Fe$_3$O$_4$ nanoparticles mediated mitochondria-dependent intracellular ROS generation to induce cellular mitochondrial dysfunction and necrosis, while the 14 nm Fe$_3$O$_4$ nanoparticles led to plasma membrane damage. Luo et al. obtained similar results that a suitable size (15.1 nm) of superparamagnetic iron oxide nanoparticles (SPIONs) enhanced the uptake amount into MCF7 cells, leading to the formation of more ROS (Zhang et al., 2020c). Promoted ROS was produced in mitochondria by small size (7.3 nm) SPIONs, while more ROS was yield in plasma to destroy cytomembrane by larger size (15.1, 30.0 nm) SPIONs. As can be seen from the above description, the size may affect the distribution of the nanoparticles. It would be more efficient if the ferrite nanoparticles can be delivered to the desired area. Zhu et al. developed a pH-responsive iron oxides-loaded mesoporous silica nanosystem (FeO$_x$-MSNs), which could deliver FeO$_x$ to lysosomes and release Fe$^{2+}$/Fe$^{3+}$ in acidic environment to catalyze the decomposition of H$_2$O$_2$ to generate considerable ROS to damage breast carcinoma cells efficiently (Figure 1) (Fu et al., 2015).

The morphology has a significant impact on the properties of nanomaterials. Li et al. fabricated Fe$_3$O$_4$ nanoparticles with nanocluster, nanoflower, and nanodiamond structures by tuning the pH of the hydrothermal reaction (Figure 2) (Fu et al., 2017). The structure has a great influence on peroxidase-like activity, following the order of nanocluster > nanoflower > nanodiamond. However, nanodiamonds had the highest cellular endocytosis (43.2, 20.8, and 18.8% of the added nanoparticles for nanodiamonds, nanoclusters, and nanoflowers, respectively). The cell viability data indicated that the cancer cell killing activity of the Fe$_3$O$_4$ nanoparticles was induced by the generated intracellular ROS through the Fenton reaction with H$_2$O$_2$, which was codetermined by the cell endocytosis of the nanoparticles and their enzyme-like activity.

Non-ferrous metal species such as copper, zinc, and iridium are widely used to regulate the performance of ferrite nanoparticles. Alshamsan et al. prepared copper ferrite nanoparticles, which could induce evident oxidative stress by ROS generation and glutathione depletion, triggering the death of human breast cancer MCF-7 cells (Ahamed et al., 2016). Liao et al. also incorporated copper into ferrite nanoparticles to regulate the H$_2$O$_2$ catalytic ability (Kuo et al., 2020). They changed the loading amount of iron precursor concentration to control the Fe/Cu ratio of the CuFe NPs. The Combination of Fe and Cu in the oxide form could enhance the conversion of H$_2$O$_2$ to ROS, and the optimal Fe/Cu ratio was 2. Chuang et al. synthesized SnFe$_2$O$_4$ nanocrystals with sonication treatment, which could be delivered through inhalation for lung cancer therapy (Figure 3) (Lee et al., 2017). The lattice ferric ions can convert endogenous H$_2$O$_2$ into highly toxicity $\bullet$OH to effectively eradicate cancer cells through heterogeneous Fenton reaction. Wang et al. treated the cancer cells with iridium and Fe$^{2+}$ ions to biosynthesize the biocompatible iridium oxide and iron oxide nanoclusters under the redox microenvironment (Shaikh et al., 2020). Their results demonstrated that U87 and HepG2 cells incubated with Ir–Fe significantly increased the ROS generation compared to Ir ions alone, triggering the apoptosis to inhibit tumor growth. Siddiqui et al. compared the cytotoxic activity of copper oxide (CuO), iron oxide ($\gamma$Fe$_2$O$_3$), and zinc, iron, and copper oxide (CuZnFe$_2$O$_4$) in human breast cancer (MCF-7) cells (Siddiqui et al., 2020). The increase in ROS level could be important mechanism of metal oxide nanoparticles-induced cytotoxicity in cancer cells. The above-mentioned results fully indicated that single and multimetal oxide nanoparticles exhibited differential cytotoxic responses in cancer cells, and the ROS production could be regulated by the chemical composition of nanomaterials.

Surface modification also plays an important role in the preparation, stability, and activity of ferrite nanoparticles. Tiku synthesized phyllanthus emblica-coated iron oxide nanoparticles (IONPAs) using a green approach (Thoidingjam and Tiku, 2019). The phyllanthus emblica could act as stabilizing agents by binding to the surfaces of the formed IONPs, so that IONPA was smaller in size with better dispensability, leading to higher uptake in A549 lung cancer cells to produce more ROS to induce higher DNA damage and apoptosis. Small molecule coatings may significantly change the surface properties of the nanoparticles, which is needed to be considered in designing the nanoplatforms for cancer therapy. Hilt et al. observed that small molecule (citric acid, sodium phosphate, aminosilane, or dopamine) coatings could decrease surface reactivity of IONPs and inhibit ROS generation (Mai and Hilt, 2019). Conversely, Liu et al. reported that carboxy-functional Fe$_3$O$_4$ nanoparticles (Fe$_3$O$_4$@DMSA) with negative zeta potential had higher uptake efficiency, which promoted intracellular iron-retention-induced ROS production but inhibited the fusion of lysosomes and autophagosomes to enhance tumoricidal autophagy for cancer therapy (Figure 4) (Xie et al., 2020). Ge et al. developed a novel ellipsoidal composite nanoplate using a magnetic Fe$_2$O$_3$/Fe nanorod core enwrapped by a catalase-imprinted fibrous SiO$_2$/polydopamine shell (Fe$_3$O$_4$/Fe@F-SiO$_2$/PDA) (Chen et al., 2017a). The catalase-imprinted shell can selectively inhibit the activity of catalase to elevate H$_2$O$_2$ level, which could be converted into $\bullet$OH under the catalysis of Fe ions released by Fe$_3$O$_4$/Fe core, triggering apoptosis to effectively kill MCF-7, 293T, and Hela tumor cells combined with the near-infrared light photothermal effect of the polydopamine layer. Targeting and responsive molecules assembled on the surface of nanoparticles can improve delivery efficiency and selectivity. Horak et al.
prepared magnetic and temperature-sensitive solid lipid particles (mag. SLPs) using oleic acid-coated iron oxide, 1-tetradecanol, and poly(ethylene oxide)-block-poly(E-caprolactone), which could melt down in the tumorous tissue to produce more ROS than the non-magnetic SLPs and neat iron oxides, inducing apoptosis of Jurkat leukemic cells (Swietek et al., 2020). Sawant et al. developed novel pH responsive and mitochondria targeted poly-l-lysine-coated Fe$_3$O$_4$@FePt core shell nanoparticles (Mito-PANPs) (Pandey et al., 2020). Mitochondria directing triphenylphosphonium ion mediated the delivery of nanoparticles to mitochondria, enhancing ROS generation to provide multimodal therapy for glioblastomas. The gradient core–shell structure is widely used to modify the surface of functional nanomaterials. Hou et al. developed a pH-sensitive nanoreactor based on core–shell-structured iron carbide nanoparticles with amorphous Fe$_3$O$_4$ shells (Fe$_5$C$_2$@Fe$_3$O$_4$). The amorphous Fe$_3$O$_4$ shells were less stable against dissolution and able to release ferrous ions in acidic environments to generate •OH through the Fenton reaction of H$_2$O$_2$ and Fe$_3$O$_4$, effectively inhibiting the proliferation of tumor cells (Yu et al., 2019).

The effect of ROS-mediated tumor therapy can be significantly improved by combining ferrite nanoparticles with chemotherapeutic drugs, chemical or biological agents, etc. Bahadur et al. developed PEGylated mesoporous iron platinum–iron oxide composite nanoassemblies with high loading capacity of doxorubicin, which exhibited a higher efficiency of ROS generation compared to Fe$_3$O$_4$ and Pt under the synergistic catalytic effect of FePt and Fe$_3$O$_4$, resulting in efficient chemo- and thermal therapy for Hela cancer cells (Sahu et al., 2015). Yeh et al. presented an H$_2$O$_2$-loaded ultrasound contrast agent H$_2$O$_2$/Fe$_3$O$_4$-poly(D,L-lactide-co-glycolic acid (PLGA) polymersome, which could yield sufficient •OH through the Fenton reaction of encapsulated H$_2$O$_2$ and Fe$_3$O$_4$, completely removing the malignant tumors in a non-thermal process (Li et al., 2016). Watanabe et al. investigated the combined effects of Fe$_3$O$_4$ nanoparticles with chemotherapeutic agents (rapamycin or carboplatin) on prostate cancer cells in vitro (Kojima et al., 2018). Synergistic effect of Fe$_3$O$_4$ NPs was observed in DU145 cells with carboplatin and in PC-3 cells with rapamycin, increasing intracellular ROS levels to decrease cancer cell viability significantly. Hou et al. designed a PLGA-polymer matrix coated with Fe/FeO core–shell nanocrystals and coloaded with chemotherapy drug and photothermal agent (DOX-ICG@Fe/FeO-PPP-FA nanocapsules), which could in situ overproduce ROS by reacting with endogenous H$_2$O$_2$ in tumors, overcoming the tumor hypoxia-related resistance of chemotherapy and photodynamic therapy (Figure 5) (Wang et al., 2019c). Liu et al. developed a facile synergistic nanoplatorm (NanoTRAIL) using iron oxide cluster and tumor necrosis factor-related apoptosis-inducing ligand (TRAIL/Apo2L), which could release iron oxide NPs to generate ROS to provoke JNK-autophagy-dependent DR5...
upregulation, leading to enhancing TRAIL/Apo2L-induced apoptosis in colorectal cancer (Shi et al., 2020). Thenmozhi prepared PVP-coated iron oxide nanoparticles loaded with *syzygium aromaticum* extract, which could induce oxidative stress via ROS formation, enhancing MCF-7 breast cancer apoptosis (Thenmozhi, 2020). This interesting study of the application of biomass *syzygium aromaticum* extract can provide a useful reference for the application researches of traditional Chinese medicine.

The applicability of ROS-mediated treatment to different types of cancers has been extensively verified. Ahamed et al. prepared spherical iron oxide nanoparticles with a smooth surface and an average diameter of 23 nm, which could induce the reactive oxygen species generation in HepG2 and A549 cancer cells, upregulating tumor suppressor gene p53 and caspase-3 and caspase-9 apoptotic genes to trigger cancer cells apoptosis (Ahamed et al., 2013). In subsequent research, they found that the MCF-7 cells were slightly more sensitive to nickel ferrite nanoparticles than liver HepG2 cells induced by reactive oxygen species (Ahamed et al., 2015). Gokduman synthesized magnetite iron oxide nanoparticles with a diameter of ~20 nm, which could increase intracellular ROS, enhancing the anticancer activity of cisplatin by increasing the apoptosis of the cisplatin-resistant ovarian cancer cells (OVCAR-3 and SKOV-3) (Gokduman, 2019). Rajesh et al. developed a hybrid magnetic microsphere system (Fe$_3$O$_4$@LEC-CUR-PLGA-MMS) using iron oxide nanoparticle (Fe$_3$O$_4$ NP), lecithin (LEC), curcumin (CUR), PLGA, and polyethylene glycol (PEG) (Ayyanaar et al., 2020). The Fe$_3$O$_4$ could catalyze the generation of ROS in an H$_2$O$_2$ environment to release the CUR, showing greater cytotoxicity against A549 and HeLa S3 cells. Salehzadeh et al. synthesized Fe$_3$O$_4$@CPTMOS/TP NPs, which had an effect on induction of apoptosis and inhibition of the growth of gastric AGS cancer cells by increasing ROS production in the treated cells (Habibzadeh et al., 2020). The IC$_{50}$ value in AGS cells was estimated to be 95.65 µg/ml. Ramalingam et al. prepared...
hematite $\alpha$-Fe$_2$O$_3$ by wet chemical method, which showed dose-dependent anticancer activity against human metastatic ovarian cancer (OC) by inducing ROS generation, damaging the mitochondrial membrane, and triggering the apoptosis of OC PA-1 cells (Ramalingam et al., 2020). Pourahmad et al. investigated the effect of SPIONs on the oral tongue squamous cell carcinoma (OTSCC) (Jahanbani et al., 2020). SPIONs were able to increase the level of ROS formation in cancerous mitochondria to selectively initiate ROS-mediated apoptosis of SCC cells. As can be seen from the above descriptions, ROS-mediated therapies based on ferrite nanoparticles have broad applicability to a wide range of cancers.

The study of mechanisms and pathways for ROS-mediated cancer therapy based on ferrite nanoparticles has also attracted the attention of researchers. Liu et al. investigated the molecular mechanism of SPIONs induced cancer-cell-specific cytotoxicity through DNA microarray and bioinformatics analyses (He et al., 2016a). SPIONs can interfere with the mitochondrial electron transport chain to induce the formation of ROS, triggering cytotoxicity to the cancer cells. Han et al. reported that ultrasmall 9 nm Fe$_3$O$_4$ NPs could effectively internalize into cells and locate in the nucleus and induce ROS production and oxidative damage by disturbing the expression of antioxidant-related genes, suggesting a potential antitumor application (Ye et al., 2020). Ma et al. demonstrated polyethyleneimine-coated Fe$_3$O$_4$ magnetic nanoparticles (PEI-MNPs), which could contribute to ROS overproduction by the Fenton reaction, resulting in autophagy induction via mTOR-Akt-p70S6K and ATG7 signaling pathways to kill cancer cells (Figure 6) (Man et al., 2020). Further research on the mechanism will be beneficial to the development of more effective ferrite nanoparticle-based therapeutic agents.
External Field Enhanced Fenton Reaction

Only relying on the intrinsic Fenton reaction catalytic activity of ferrite nanomaterials often requires a high concentration to generate enough ROS to kill tumor cells, which may increase the burden of iron removal based on the kidney and liver and cause adverse damage to the body (Ranji-Burachaloo et al., 2018). External electromagnetic waves such as X-ray, near-infrared light and alternating magnetic field can be absorbed by the ferrite-based nanoplatfor to improve the production of reactive oxygen species (Laurent et al., 2011; Pilar Vinardell and Mitjans, 2015; Xiong et al., 2019). Ultrasound, a typical high-frequency mechanical wave, can also be used as an external energy source. Gorgizadeh et al. synthesized a nickel ferrite/carbon nanocomposite (NiFe₂O₄/C) as sonosensitizer (Gorgizadeh et al., 2019). Radiation of ultrasound into NiFe₂O₄/C effectively induced cavitation formation and ROS production, resulting in remarkable efficacious recovery in mouse melanoma cancer model by intratumorally injection at dosage of \( \sim 100 \, \text{mg kg}^{-1} \).
Kryschi et al. first studied the citrate-coated superparamagnetic iron oxide nanoparticles as X-ray radiosensitizer (Klein et al., 2012). The increased catalytically active iron oxide nanoparticle surfaces can enhance the ROS generation for about 240% under the X-ray exposure. In subsequent research, they synthesized 9–20 nm \((\gamma Fe_2O_3)_{1-x}(Fe_3O_4)_x\) surface stabilized with citrate or malate anions, which can drastically enhance the ROS concentration of more than 300% via the Fenton reaction in 1 Gy X-ray-irradiated tumor cells (Klein et al., 2014). Hadjipanayis et al. showed that cetuximab-conjugated iron oxide nanoparticles (cetuximab-IONPs) could sensitize ionizing radiation therapy by increasing ROS formation and DNA double strands breaks (Bouras et al., 2015). Hilt et al. developed a cell-penetrating peptide functionalized iron oxide nanoparticles (TAT-Fe_3O_4) to increase the efficacy of radiation therapy (Hauser et al., 2016b). Radiation promoted the production of the superoxide anion in mitochondria, which was further converted to hydrogen peroxide by superoxide dismutase, and the generated \(H_2O_2\) could be catalyzed to the highly reactive hydroxyl radical by the Fenton reaction with iron oxide nanoparticles for the enhancement of radiation therapy. Kryschi et al. synthesized functionalized superparamagnetic magnetite (Fe_3O_4) and Co-ferrite (CoFe_2O_4) nanoparticles with self-assembled monolayer coatings, which have long-term stability and could be activated through X-ray exposure with a single dosage of 1 Gy to induce ablation of the surface coverage and release either \(Fe^{2+}\) or \(Co^{2+}\) ions, enhancing the production of the highly hydroxyl radical via the Fenton reaction to kill the cancerous MCF-7 cells efficiently (Figure 7) (Klein et al., 2018).

Light waves are also widely used as external field energy sources. Near-infrared light irradiation can be efficiently converted into heat to enhance ROS generation. Miao et al. synthesized Zn^{2+}-doped magnetic nanoparticles via hydrothermal route, which revealed excellent photothermal effect to generate localized heat and increase the dissolution of magnetic nanoparticles in the acid medium to enhance ROS generation upon a near-infrared (NIR) light irradiation, inducing...
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FIGURE 6 | (A) Schematic illustration for roles of ROS on PEI-MNPs elicited responses in cancer cells. (B,C) PEI-MNPs induced overproduction of ROS, triggering the activation of NF-κB and TGF-β pathways. (D) Western blotting experiments of the cancer cells treated with PEI-MNPs. *P < 0.05; **P < 0.01; ***P < 0.005 vs controls. Reproduced, with permission, from Man et al. (2020). Copyright 2020, Royal Society of Chemistry.

cancer treatment (Qi et al., 2016). Chen et al. confirmed that the bacterial magnetic nanoparticles could induce increased level of intracellular ROS along with heat under near-infrared light irradiation to trigger an efficient tumor cell kill (Chen et al., 2016). Dong et al. fabricated a nanoplatform based on iron oxide nanoparticles, indocyanine green, and hyaluronic acid (IONPs-ICG-HA) (Wang et al., 2019a). The iron oxide could convert intracellular H₂O₂ to generate fatal reactive oxygen species through Fenton reaction, which could be boosted by increased temperature of photothermal effect of ICG, enhancing synergistic phototherapy in cancer treatment. Li et al. developed a tumor-targeting iron sponge γGDYO-Fe₃O₄-CREKA (TTIS) nanocomposite, which could accelerate the release of iron ions to enhance the efficiency of the Fenton reaction and generate
more ROS by the heat produced in the process of photothermal therapy (Min et al., 2020). You et al. designed a more stable and high-ROS-yielding Pt/Fe3O4@SP-PLGA lipo-polymersom, which could significantly increase the generation of •OH for ROS-mediated cancer therapy through the reaction between succinic peroxide (SP) and iron oxide under NIR irradiation (You et al., 2019). Photosensitizers can be activated by laser irradiation to improve the electron–hole pairs separation efficacy and redox potentials, leading to strong ability in generating ROS. Ji et al. prepared 2D ultrathin Z-scheme highly oxidized ilmenite nanosheets (FeTiO3@Fe2O3) with much strong oxidation and reduction potentials in the valence band (VB) of Fe2O3 and the conduction band (CB) of FeTiO3, which could enhance the generation of O2− from O2 on the CB of FeTiO3 and •OH
from H$_2$O$_2$ on the VB of Fe$_3$O$_4$ for antitumor therapy under irradiation of 650 nm laser (Figure 8) (Ou et al., 2020).

Ferrite nanoparticles have unique magnetic heating transfer efficiency to generate heat, enhancing the effect of ROS-mediated cancer therapy (Johannsen et al., 2010; Silva et al., 2011). The alternating magnetic field is the most commonly used due to its large penetration. Hilt et al. showed that peptide-conjugated magnetic nanoparticles (TAT-IONP) could increase cellular ROS generation in both A549 and H358 cell lines upon exposure to an alternating magnetic field, resulting in an increase in apoptosis via the Caspase 3/7 pathways (Hauser et al., 2016a). Orel et al. designed magnetic nanodots composed of doxorubicin-loaded Fe$_3$O$_4$ nanoparticles, which could release more free iron to promote the formation of highly reactive oxygen species combined with electromagnetic fields, achieving remote modulation of redox state of Walker-256 carcinosarcoma tumor.
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FIGURE 9 | (A) Schematic illustration for FVIOs-GO-mediated MTD by combination of a heating effect and ROS-related immunologic effect. (B) Quantification of ROS generation of 4T1 breast cancer cells. (C) Quantification of M1 macrophages for treatments. (D) Tumor volume vs. days after treatments. *$0.01 < P < 0.05$; **$0.001 < P < 0.01$; ***$P < 0.001$. Reproduced, with permission, from Liu et al. (2020). Copyright 2020, American Chemical Society.

for cancer nanotherapy (Orel et al., 2018). Lin et al. synthesized magnetic hydroxyapatite nanoparticles by coprecipitation with the addition of Fe$^{3+}$ (mHAP), which could increase intracellular ROS concentration to cause DNA damage of HepG2 cells with possible MKK3/MKK6 and ATF-2 of p38 MAPK inhibition under exposure to alternating magnetic field (Yang et al., 2018). Zhang et al. designed a magnetic hydrogel nanozyme utilizing PEGylated Fe$_3$O$_4$ nanoparticles and a-cyclodextrin, which could enhance tumor oxidative stress level by generating more ROS through promoted peroxidase-like enzymatic activity of Fe$_3$O$_4$ nanozyme at 42 hyperthermia induced by a non-invasive external alternating current magnetic field (Wu et al., 2019). Fan et al. demonstrated a biocompatible elaborate ferrimagnetic vortex-domain iron oxide nanoring and graphene oxide hybrid nanoparticle (FVIOs-GO-CREKA), which had high thermal conversion efficiency to significantly amplify the generation of ROS under an alternating magnetic field, promoting macrophage polarization to proinflammatory M1 phenotypes and elevating tumor-infiltrating T lymphocytes to provoke a strong immune response at a physiological tolerable temperature below 40 in a hypoxic tumor microenvironment (Figure 9) (Liu et al., 2020). Hilger et al. reported that the magnetic heating treatment could induce more production of ROS and alter messenger RNA (mRNA) expression of Ki-67, TOP2A, and TPX2, resulting in reducing tumor volumes superior to that of extrinsic heating (hot air) significantly (Ludwig et al., 2017). The effect of treatment under static magnetic field has also attracted the interest of researchers. Pazik et al. investigated the viability of canine mastocytoma tumor cells cultured with cobalt–manganese ferrite nanoparticles (Co$_{0.2}$Mn$_{0.8}$Fe$_2$O$_4$) under 0.5 T static magnetic field (Marycz et al., 2017). The nanoparticles and magnetic field increase the temperature of tumor cells and the formation of reactive oxygen species, inducing apoptotic response.

Multifield coupling can often produce better synergistic therapeutic effects. Hassan et al. designed nanohybrid using nanoflower-like iron oxide and spiky copper sulfide shell (IONF@CuS), which could efficiently convert light and magnetic stimulation into heat and form concurrent reactive oxygen species upon laser irradiation for a tri-therapeutic strategy merging magnetic hyperthermia and photothermal and photodynamic therapy (Curcio et al., 2019). Fan et al. designed biocompatible Fe$_3$O$_4$-Pd Janus nanoparticles, which could enhance ROS generation due to the interface synergistic effect in producing hydroxyl radicals by Fe$_3$O$_4$ nanoparticle-based Fenton reaction and Pd nanosheet-based catalytic properties under external alternating magnetic field plus laser irradiation, exhibiting a high tumor-inhibition efficacy [100% tumor inhibition rate at a dose of 6 mg kg$^{-1}$ under alternating magnetic
field (AMF) (300 kHz; 300 Oe) and laser (808 nm; 0.5 W cm\(^{-2}\)) toward 4T1 orthotopic breast tumor (Figure 10) (Ma et al., 2019). Sharma et al. developed manganese doped-iron oxide nanoclusters, which could trigger heat-induced enhancement of the Fenton reaction for the generation of \(\bullet \text{OH}\) under the dual application of magnetic hyperthermia and photothermal stimulation, resulting in a remarkable anticancer effect mediated by ROS-dependent apoptosis via the mitochondrial pathway (Gupta and Sharma, 2020).

**Cascade Reactions Increased ROS**

The rapid growth of the tumor tissues and the incomplete blood vessels lead to a hypoxia environment within solid tumors (Knowles and Harris, 2001). The concentration of intratumoral \(\text{H}_2\text{O}_2\) is generally considered to be as low as 50–100 \(\mu\text{M}\), which is not high enough to generate an effective amount of hydroxyl radicals for a satisfactory cancer therapy (Chen et al., 2017b). Intratumoral injection of hydrogen peroxide is an effective method to increase the ROS-mediated tumor therapeutic effect (Zhang et al., 2013). However, this method has poor controllability and safety, causing damage to the surrounding healthy tissues. The cascade reactions have shown a good prospect in overcoming the tumor hypoxia and increasing the ROS production.

The most commonly used strategy is to generate more intratumoral hydrogen peroxide *in situ* through cascade reactions for the subsequent Fenton reaction. The \(\beta\)-*lapachone* was used earlier in such cascade reactions, which could undergo redox cycles to generate high \(\text{H}_2\text{O}_2\) levels inside cancer cells. Gao et al. developed pH-responsive superparamagnetic iron oxide nanoparticles (SPION micelles), which could selectively release iron ions in tumor acidic environment to react with \(\text{H}_2\text{O}_2\) generated from \(\beta\)-*lapachone* to produce 10-fold highly active hydroxyl radicals, displaying a synergistic efficacy for cancer treatment with ROS-generating anticancer drug (Huang et al., 2013). In another similar study, Chen et al. constructed a nanomedicine by encapsulating \(\beta\)-*lapachone* (La) and IONPs into the hydrophobic core of nanostructure formed by polydrug and polymer, which could be internalized by tumor cells and disintegrated in acidic environment to release La and iron ions (Wang et al., 2019b). The released La generated massive \(\text{H}_2\text{O}_2\) through the catalysis of the nicotinamide adenine dinucleotide (phosphate) [NAD(P)H]: quinone oxidoreductase 1 (NQO1), which would further be converted to highly toxic \(\bullet \text{OH}\) by Fenton reaction with iron ions, resulting in improved antitumor activity. Ascorbic acid, a known antioxidant, can also be used to produce endogenous \(\text{H}_2\text{O}_2\). Wang et al. synthesized \(\text{Fe}_3\text{O}_4@C\) nanoparticles modified with folic acid (\(\text{Fe}_3\text{O}_4@C\)-FA), which could create hydroxyl radicals from \(\text{H}_2\text{O}_2\) yielded by the exogenous ascorbic acid, inducing the selective killing of cancer cells owing to ROS accumulation in human prostate cancer PC-3 cells (An et al., 2019).
In a similar study, as low as 0.1 mM exogenous vitamin C was catalyzed by iron oxide nanoparticle to generate H$_2$O$_2$ followed by ROS production in the form of hydroxyl/superoxide radicals, inducing effective tumor cell death (Pal and Jana, 2020). Cisplatin is also commonly used as cascade reaction trigger agent. Lin et al. constructed self-sacrificing iron oxide nanoparticles with cisplatin (IV) prodrug (FePt-NP2), which could release cisplatin and Fe$^{2+}$/Fe$^{3+}$ (Ma et al., 2017). The released cisplatin could activate nicotinamide adenine dinucleotide phosphate (NADPH) oxidase to trigger oxygen to generate superoxide radical, which could be further dismutated by superoxide dismutase to form downstream H$_2$O$_2$. The generated H$_2$O$_2$ would be catalyzed by Fe$^{2+}$/Fe$^{3+}$ to the toxic hydroxyl radicals, causing ROS-mediated oxidative damages to lipids, proteins, and DNA and inducing tumor cell apoptosis. This strategy was also adopted by Chen et al. to design cisplatin-loaded Fe$_3$O$_4$/Gd$_2$O$_3$ hybrid nanoparticles with conjugation of lactoferrin and RGD dimer (FeGd-HN@Pt@LF/RGD2), which could release cisplatin, Fe$^{2+}$, and Fe$^{3+}$ after endocytosis in the endosomes, leading to high inhibition efficacy on orthotopic brain tumors (Shen et al., 2018). Ni et al. synthesized FA/Pt$^+$-si-GPX4@IONPs for gene treatment of glioblastoma (Zhang et al., 2020b). The cascade reactions triggered by Pt laid the foundation for efficient ROS production to induce a combination of ferroptosis and apoptosis. Another cascade reaction strategy developed by Shi et al. reported a sequential catalytic nanomedicine using natural glucose oxidase and synthetic ultrasmall Fe$_3$O$_4$ nanoparticles

**FIGURE 11** | Schematic illustration for (A) preparation of polymersome nanoreactors and (B) cascade reactions in the nanoreactors. (C) Chemical structure of PEG-b-P(CPTKMA-co-PEMA). (D) Cascade reactions equations occurring in the nanoreactors. Reproduced, with permission, from Ke et al. (2019). Copyright 2019, American Chemical Society.
to integrate into the large mesopores of dendritic mesoporous silica nanoparticles (GFD NCs) (Huo et al., 2017). The glucose oxidase (GOD) released from nanocatalysts could deplete the glucose to produce considerable amounts of $H_2O_2$, which could be converted into highly toxic hydroxyl radical through Fenton-like reaction catalyzed by $Fe_3O_4$ nanoparticles to trigger the apoptosis and death of tumor cells. This strategy was further studied by Ge et al.. They engineered ultrasmall iron oxide nanoparticles (USIONs) and GOD-coloaded PEG-b-P(CPTKMA-co-PEMA) polymersomes nanoreactors (Fe/G@R-NRs), which could occur cascade reactions including glucose consumption to generate $H_2O_2$ by GOD, production of $\cdot OH$ through Fenton reaction between $H_2O_2$ and iron ion released by USIONs, and $\cdot OH$-triggered rapid release of polyprodrug for orchestrated cooperative cancer therapy including starving therapy, chemodynamic therapy, and chemotherapy (Figure 11) (Ke et al., 2019). Xu et al. developed glucose oxidase and polydopamine-functionalized iron oxide nanoparticles (Fe$_3$O$_4$@PDA/GOx NPs), in which the enzymatic activity of GOx was stably retained due to the excellent biocompatibility of polydopamine (Zhang et al., 2019). For cancer cells incubated with the 200 nm NPs, the $\cdot OH$ accumulation within the cells was about 2-fold higher than that with 20 nm NPs treatment, efficiently inducing the apoptosis of cancer cells. Peroxide can be employed as potent $H_2O_2$ supplier to sustain the ferrite nanoparticles-mediated Fenton reaction. Shi et al. constructed 2D multifunctional therapeutic nanoreactors by conjugating iron oxide nanoparticles and calcium peroxide onto niobium carbide (Nb$_2$C-IO-CaO$_2$) (Gao et al., 2019). The CaO$_2$ could react with $H_2O$ to produce $H_2O_2$ in the acidic tumor microenvironment, which was subsequently disproportionated into highly toxic $\cdot OH$ by the IO nanoparticles for inducing tumor cell death. With laser irradiation, graphene oxide can produce more reactive graphene radicals to enhance the ROS formation. Huang et al. developed a near-infrared absorbing nanoagent using graphene oxide loaded with iron hydroxide/oxide (GO-FeO$_x$H) via one-step electrooxidation (He et al., 2017). The electron transfer from GO to the $Fe^{3+}$ of FeO$_x$H could promote

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**FIGURE 12** (A) Schematic diagram of ISP-NMs and application for cancer treatment. (B) Fluorescent intensity of cancer cells after treatment. (C) Tumor volume changes during 14 days. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$ drugs treated groups versus one of control; #$P < 0.05$, ##$P < 0.01$, ###$P < 0.001$ other drugs treated groups versus the group of ISP-NMs+M. Reproduced, with permission, from Zhang et al. (2020a). Copyright 2020, Elsevier.
FIGURE 13  (A) Schematic illustration of ferumoxytol-altered polarization of tumor-associated macrophages to release ROS, inducing cell death. (B) Signs of proinflammatory macrophage activation. (C) Quantitative measures of hydroxyl radical. (D) Coculture leads to increased caspase-3 expression of cancer cells. (E) Serial bioluminescence imaging after intravenous injection of ferumoxytol at a dose of 10 mg Fe kg$^{-1}$. Reproduced, with permission, from Tarangelo and Dixon (2016) and Zanganeh et al. (2016). Copyright 2016, Macmillan Publishers Limited.
## TABLE 1 | Summary of current ferrite nanoparticles used for ROS-mediated cancer therapy.

| ROS production | Ferrite-based nanoplatform | Brief description | References |
|----------------|---------------------------|------------------|------------|
| Intrinsic fenton reaction | Fe$_3$O$_4$ (6, 13 nm) | Smaller size, higher enzyme activity | Zhang et al., 2013 |
| | Fe$_3$O$_4$ (6, 9, and 14 nm) | Small size NPs destroy mitochondria, while larger size destroy cytomembrane | Xie et al., 2016 |
| | SPIONs (7.3, 15.1, 30.0 nm) | pH responsive, delivered to acidic lysosomes | Zhang et al., 2020c |
| | Fe$_3$O$_4$ nanocluster, nanoflower, and nanodiamond | Fe$_3$O$_4$ nanodiamonds induce the highest cell killing effect | Fu et al., 2017 |
| | CuFe$_2$O$_4$ | Non-ferrous metal species regulate the ROS production | Ahamed et al., 2016 |
| | MB-CuFe NPs | Coating reduces nanoparticle size | Kuo et al., 2020 |
| | SnFe$_3$O$_4$ | DMSA-coating promotes uptake efficiency | Chen et al., 2017a |
| | Iridium oxide and iron oxide | Catalase-imprinted shell inhibits catalase activity to elevate H$_2$O$_2$ level | Swietek et al., 2020 |
| | CuO, γFe$_2$O$_3$, CuZnFe$_2$O$_4$ | Targeting molecules, responsive molecules, improved delivery efficiency and selectivity | Pandey et al., 2020 |
| | IONPA | Gradient core-shell structure, differential release | Yu et al., 2019 |
| | UC-IONP, CA-IONP, SP-IONP, AS-IONP, DA-IONP | Combining ferrite nanoparticle and chemotherapeutic drugs, chemical and biological agents, etc. improves ROS-mediated tumor therapy. | Sahu et al., 2015 |
| | Fe$_2$O$_3$@DMSA, Fe$_2$O$_3$@APTS | Broad applicability to a wide range of cancers: HepG2, A549, MCF-7, OVCAR-3, SKOV-3, HeLa S3, AGS, metastatic OC, OTSCC, etc. | Ahamed et al., 2013 |
| | Fe$_3$O$_4$@LEC-CUR-PLGA-MMS | Broad applicability to a wide range of cancers: HepG2, A549, MCF-7, OVCAR-3, SKOV-3, HeLa S3, AGS, metastatic OC, OTSCC, etc. | Ayyanaar et al., 2020 |
| | Fe$_3$O$_4$@CPTMOS/TP NPs | Broad applicability to a wide range of cancers: HepG2, A549, MCF-7, OVCAR-3, SKOV-3, HeLa S3, AGS, metastatic OC, OTSCC, etc. | Habibzadeh et al., 2020 |
| | α-Fe$_2$O$_3$ | Mechanisms: mitochondrial electron transport chain, antioxidant-related genes, mTOR-Akt-p70S6K and ATG7, etc. | He et al., 2016a |
| | SPIONs | | |
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| ROS production | Ferrite-based nanoplatform | Brief Description | References |
|----------------|---------------------------|-------------------|------------|
| PA-SAM functionalized Fe₂O₃ and CoFe₂O₄ MNPs | Improved catalytic activity under NIR photothermal energy | Klein et al., 2018 |
| Zn²⁺-doped magnetic nanoparticles | | Qi et al., 2016 |
| Bacterial magnetic nanoparticles | | Chen et al., 2016 |
| IONPs-ICG-HA | Nanoplatform depolymerizes under NIR Photothermal energy | Min et al., 2020 |
| γGdY0-Fe₃O₄-CREKA (TTIS) | 650 nm laser irradiation formed photoexcited electron-hole | You et al., 2019 |
| Pt/Fe₂O₃@SP-PLGA | Improved catalytic activity under AMF magnetic heat | Hauser et al., 2016a |
| FeTiO₃@Fe₂O₃ | | |
| TAT-IONP | | |
| Doxorubicin-loaded Fe₂O₃ nanoparticles | Magnetic heating superior to extrinsic hot air heating | Ludwig et al., 2017 |
| mHAP | | |
| Magnetic hydrogel nanozyme (MHyZ) | | |
| PVIOs-GO-CREKA | | |
| Iron oxide magnetic nanoparticles | | |
| Co₀.2Mn₀.8Fe₂O₄ | 0.5 T static magnetic field | Marycz et al., 2017 |
| IONF@CuS | Synergistic effect of multi-field coupling (AMF and laser irradiation) | Curcio et al., 2019 |
| Fe₂O₄-Pd | | |
| Manganese doped-iron oxide nanoclusters (MNCs) | | |
| Cascades increased ROS | | |
| SPION micelles | β-lapachone increases H₂O₂ | Huang et al., 2013 |
| LaCIONPs | | |
| Fe₃O₄@C-FA | Ascorbic acid increases H₂O₂ | An et al., 2013, Pal and Jana, 2020 |
| Vitamin C-conjugated Fe₃O₄ | | |
| FePt-NP2 | Cisplatin activates NADPH oxidase to generate H₂O₂ | Ma et al., 2017 |
| FeGd-HN@Pt@LF/RGD2 | Glucose oxidase consumes glucose to generate H₂O₂ | Shen et al., 2018, Zhang et al., 2020b |
| FA/Pt+si-GPX4@IONPs | | |
| GFD NCs | | |
| Fe/G@R-NRs | | |
| Fe₂O₃@PDA/GOx NPs | CaO₂ as H₂O₂ supplier | Gao et al., 2019 |
| Nb₂C-IQ-CaO₂ | Graphene oxide produces ROS under laser irradiation. | He et al., 2017 |
| GO-FeO₂-H | | |
| MFMSNs-Ce6 | Ferrite nanoparticles catalyze decomposition of H₂O₂ to O₂ to overcome tumor hypoxia, improving ROS-mediated cancer therapy. | Km et al., 2017 |
| UCMnFe-PS-PEG | | |
| MnFe₂O₄@MOF-PEG | | |
| Copper ferrite nanospheres (CFNs) | | |
| HP-HIONs | | |
| ISP-NMs | | |
| Ferumoxytol nanoparticles | Ferumoxytol acted on tumor-associated macrophages to adapt an antitumor “M1” phenotype, enhancing macrophage ROS production. | Zanganeh et al., 2016 |
| Fe₃O₄-Au JNPs self-assembled vesicles | poly(lipid hydroperoxide) reacts with released Fe²⁺ to generate ROS | Song et al., 2019 |
the reaction with O$_2$ to generate superoxide anion radicals under NIR light irradiation, which would be converted into H$_2$O$_2$ through disproportionation reaction. The generated H$_2$O$_2$ then underwent a reaction with Fe$^{2+}$ of Fe$_2$O$_4$H to produce amplified hydroxyl radicals, triggering near-infrared activated ROS-mediated photodynamic therapy.

Ferrite nanoparticles are also used to catalyze the production of molecular oxygen to overcome tumor hypoxia, improving the ROS-mediated tumor therapeutic effect. Hyeon et al. designed manganese ferrite nanoparticle anchored mesoporous silica nanoparticles loaded with molecule chlorin e6 (MFMSNs-Ce6) (Kim et al., 2017). The manganese ferrite could catalyze decomposition of H$_2$O$_2$ to evolve O$_2$, which could be further converted to singlet oxygen by photosensitizer Ce6, improving photodynamic therapeutic outcomes for hypoxic tumor. Some similar studies were carried out by other researchers. Lin et al. prepared photosensitizer-loaded and PEG-modified MnFe$_2$O$_4$-decorated large-pore mesoporous silica-coated β-NaYF$_4$:20%Yb,2%Er@β-NaYF$_4$ upconversion nanoparticles (UCMnFe-PS-PEG) as NIR light-mediated and O$_2$ self-sufficient photodynamic therapy (PDT) agents (Ding et al., 2019). The sub-10 nm MnFe$_2$O$_4$ nanoparticles not only provided magnetic guidance to the tumor but also worked as a Fenton catalyst to generate O$_2$ in situ to overcome tumor hypoxia. The tumor growth was greatly inhibited, and some of the tumors even disappeared after 16 days of treatment. A biocompatible nanoplateform [MnFe$_2$O$_4$@metal-organic framework (MOF)] developed by Zhang et al. using a coating of porphyrin-based MOF as the photosensitizer and manganese ferrite nanoparticle (MnFe$_2$O$_4$) as the enzyme can not only catalyze H$_2$O$_2$ to produce O$_2$ to overcome the tumor hypoxia but also consume glutathione, achieving better therapeutic efficacy (Yin et al., 2019). The tumor growth was considerably suppressed after mice were treated with MnFe$_2$O$_4$@MOF-PEG (i.v. injection of 200 µl, 6.25 mg kg$^{-1}$ TCPP) and laser irradiation (0.8 W cm$^{-2}$, 8 min, 24 h post-i.v. injection). Zhang et al. showed “all in one” theranostic agents copper ferrite nanospheres (CFNs), in which the coupling between Fe$^{2+}$/Fe$^{3+}$ and Cu$^+$/Cu$_2^+$ redox pairs could produce more •OH and O$_2$ through Fenton reactions under 650-nm laser illumination (Liu et al., 2018). The produced O$_2$ could be further converted into O$_2^-$ by photogenerated electron/hole pair for synergistic tumor ablation of photoenhanced chemodynamic therapy/photodynamic therapy/photothermal therapy. Lin et al. synthesized a novel nanoplateform composed of hollow iron oxide nanoparticles and hematoporphyrin sonosensitizers (HP-HIONs) (Zhang et al., 2020d). The HIONs possessed nanzyme activity for catalyzing decomposition of hydrogen peroxide to produce O$_2$, which could be further converted to ROS by sonodynamic therapy for efficient cancer cell apoptosis. Wei et al. synthesized iron oxide nanoparticles-loaded stomatocytes@ZnPc nanomotors (ISP-NMs), in which IONPs catalyzed decomposition of endogenous H$_2$O$_2$ to generate O$_2$ as propelling force to expand the distribution of ZnPc (Zhang et al., 2020a). The generated O$_2$ was supplied to produce more ROS (1$^1$O$_2$), enhancing PDT performance (Figure 12).

Some other strategies have also been developed to increase ROS generation. Daldrup-Link et al. coincubated adenocarcinoma with iron oxide nanoparticle compound ferumoxytrol and macrophages (Zanganah et al., 2016). Ferumoxytrol nanoparticles increased presence of proinflammatory M1 macrophages in the tumor to enhance the production of hydrogen peroxide and hydroxyl radical for macrophage-modulating cancer immunotherapies (Figure 13). Chen et al. constructed double-layered vesicles with Fe$_2$O$_4$ face-to-face localized in the inner side and Au extended to the outer side by self-assembly of iron oxide-gold Janus nanoparticles (Fe$_3$O$_4$-Au JNPs) using hydrophilic poly(ethylene glycol)-grafted Au and poly(lipid hydroperoxide)-co-poly(4-vinyl pyrene)-coated Fe$_3$O$_4$. In the acidic tumor environment, the vesicles disassembled into single JNPs, allowing Fe$_3$O$_4$ to react with H$^+$ to release Fe$^{2+}$. The released Fe$^{2+}$ further reacted with poly(lipid hydroperoxide) to generate reactive oxygen species (1$^1$O$_2$) and increase intracellular oxidative stress for better inhibition of tumor growth (Song et al., 2019).

CONCLUSION AND FUTURE OUTLOOK

In the past nearly 10 years, ROS-mediated cancer therapy using ferrite nanoparticles has been rapidly developed, and researchers have published a large number of related publications (summarized in Table 1). This review was carried on the classification and summarization of the application of ferrite nanoparticles in ROS-mediated cancer therapy. Based on the analysis of the current literature, it can be seen that various modification strategies for the ROS-mediated cancer therapies based on ferrite nanoparticles are producing more and more successful results, especially in combination with drugs, biological and chemical agents, and/or co-exposure of other energy fields such as X-rays, lasers, and alternating magnetic fields, becoming potential effective tumor therapy strategies. However, to date, only iron oxide nanoparticles have been approved for the magnetic response diagnosis and the magnetic hyperthermia tumor therapy (Park et al., 2017; Shi et al., 2017). Few clinical trials have been reported for any tumor therapy based on ferrite nanoparticle-induced ROS (Liang et al., 2020). The ferrite nanoparticle-induced ROS can kill the cancer cell and also can trigger the toxic effect on the normal tissues and vasculature. Therefore, in order to solve this dilemma, on the one hand, the high-performance ferrite nanoparticles should be developed to produce much more ROS so that the dosage of the particles can be reduced. On the other hand, the smart (stimulus-responsive) ferrite nanoparticles should be designed to produce more controllable ROS in tumor tissue and little to no ROS outside tumor tissue.

Having achieved the excellent performance of ROS-mediated cancer therapy based on ferrite nanoparticles on small animal model, there are still many important challenges before clinical application. First, further studies on the development of strategies for controllable synthesis of ferrite nanoparticles in large scale are needed to satisfy the requirement for clinical
translation and commercialization. Second, the biosafety should be fully investigated on large animals, as most of the current ferrite nanoparticles biosafety evaluation in vivo is based on small animals, and the biosafety of the nanoparticles remains largely unexplored in large animals and even in human models. It is appealing to combine efforts from the researchers in the fields of oncology, biochemistry, nanotechnology, medicine, and materials to shed light on the future of ROS-mediated cancer therapy based on ferrite nanoparticles.

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AUTHOR CONTRIBUTIONS

SY, SZ, and MZ wrote the manuscript. SY and HZ revised the manuscript. HF provided useful suggestions. All authors contributed to the article and approved the submitted version.

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