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Review

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Some synergetic therapy strategies for overcoming hypoxia for photodynamic therapy of cancer

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Abstract

As an emerging strategy in antitumor therapy, photodynamic therapy (PDT) has garnered significant attention in recent years for the treatment of various malignant tumors. This is due to its low side effects, superior spatial selectivity, and maximum preservation of normal tissue function. However, the hypoxic nature of tumors, continuous oxygen consumption, and microvascular damage associated with PDT treatment have impeded its development. Therefore, the focus of antitumor therapy has shifted towards enhancing the efficacy of PDT by addressing tumor hypoxia. The objective of this review is to assess and summarize the recent advancements in tumor treatment using synergistic therapy strategies (PDT+X, where X represents photothermal therapy, chemodynamic therapy, chemotherapy, immunotherapy, Photoacoustic therapy, *etc*.) that overcome hypoxia. Additionally, this review aims to outline the advantages and disadvantages of various collaborative methods for improving tumor hypoxia, while also discussing the challenges that lie ahead for future research.

Keywords: Nanomaterials, photosensitizer, photodynamic therapy, deep tumor hypoxia

INTRODUCTION

Cancer causes millions of deaths every year and thus strongly impacts our society[1-4]. The recent years have witnessed the emergence of diverse tumor treatment modalities with different efficacies and limitations, as exemplified by surgery, radiotherapy, chemotherapy, endocrine therapy, immunotherapy, and molecular targeted therapy[1,5]. Photodynamic therapy (PDT) has become a promising method of cancer treatment, offering the benefits of minimal invasiveness, high effectiveness, high selectivity, and low toxicity[6-8]. PDT has a track record of application to colon[9], lung[10,11], prostate[12], head and neck[13-15], brain[16], skin[17], pancreas[18], and breast[19] cancers.

The general mechanism of PDT involves three primary elements, namely light with a specific wavelength, a photosensitizer (PS), and molecular oxygen[20-23]. Presently, most PDT processes occur only when oxygen is present[24-26]. Nonetheless, PDT can also occur in hypoxic environments even without oxygen[27]. Upon irradiation with specific-wavelength light, PSs generate reactive oxygen species (ROS), which may contribute to cell death (e.g., apoptosis, necrosis, autophagy, ferroptosis, pyroptosis, necroptosis, parthanatos, and mitotic catastrophe), microvascular system destruction, and immune responses, via two (type-I and type-II) routes. Initially, the PS ground state (PS_0) absorbs light to afford an unstable and short-lived excited singlet state (^1PS) that can easily return to PS_0 by releasing light energy (fluorescence) or thermal energy (nonradiative decay). Alternatively, ^1PS can experience intersystem crossing to afford a more stable and longer-lived triplet state (^3PS) that can return to PS_0 by releasing light energy (fluorescence/phosphorescence) or thermal energy. Most importantly, ^3PS can react with various substances through type-I and type-II routes to generate ROS. In the type-I route, ^3PS engages in electron transfer with the surrounding cellular substrates to form free radicals capable of generating ROS ($O_2^{\bullet-}$, $^{\bullet}OH$, and H_2O_2). In the type-II route, ^3PS transfers energy to $^3O_2$ and converts it into the highly reactive $^1O_2$. The toxic ROS generated from ^3PS exert antitumor effects by promoting various biological processes, mainly tumor cell killing, tumor vessel damage, and tumor immune reactions [Figure 1][5]. Although type-I and type-II routes can occur simultaneously, the latter route is believed to be dominant for clinically proven PSs[28].

Solid tumors are intrinsically prone to rapid proliferation, which inevitably results in hypoxic tumor microenvironments (TMEs)[29]. In solid tumors, O_2 concentration varies by location, and the deeper the solid tumor site, the lower the oxygen concentration[29]. We know that, in the absence of oxygen, type II-PDT can no longer function to produce ROS for tumor destruction. Additionally, as tumors progress rapidly, continuous oxygen consumption increases tumor hypoxia; therefore, PDT is significantly less effective against tumors[25]. Tumor hypoxia is usually classified as chronic or acute. The more prevalent chronic hypoxia is caused by the increase in the distance of O_2 diffusion from tumor vessels during tumor growth[30]. Hypoxia could dramatically decrease the efficacy of PDT, influence the genomic and proteomic changes of tumor cells, and result in tumor progression, tumor invasion, and metastasis[31-33]. Moreover, hypoxia upregulates the expression of hypoxia-inducible factor 1 (HIF-1), which induces autophagy to protect tumor cells and thus results in resistance to PDT[34].

So far, much effort has been directed at overcoming the hypoxia-associated limitations of PDT, as outlined in several reviews that mainly focus on methods of increasing O_2 levels (e.g., via the generation of O_2 in tumor sites and direct O_2 delivery into tumors) or reducing O_2 consumption[3,29,35]. Photodynamic therapy (PDT) is subject to severe limitations such as limited tissue penetration depth[36], hyperoxygen dependence[37,38] and phototoxicity[39,40]. In order to overcome the limitation of PDT, many strategies have been proposed, such as the emergence of non-photo-induced photosensitizers, which can effectively overcome the limitation of penetration depth and phototoxicity. PDT combined with anoxic therapy can increase the oxygen content of tumor microenvironment effectively, thus enhancing the effect of PDT. In

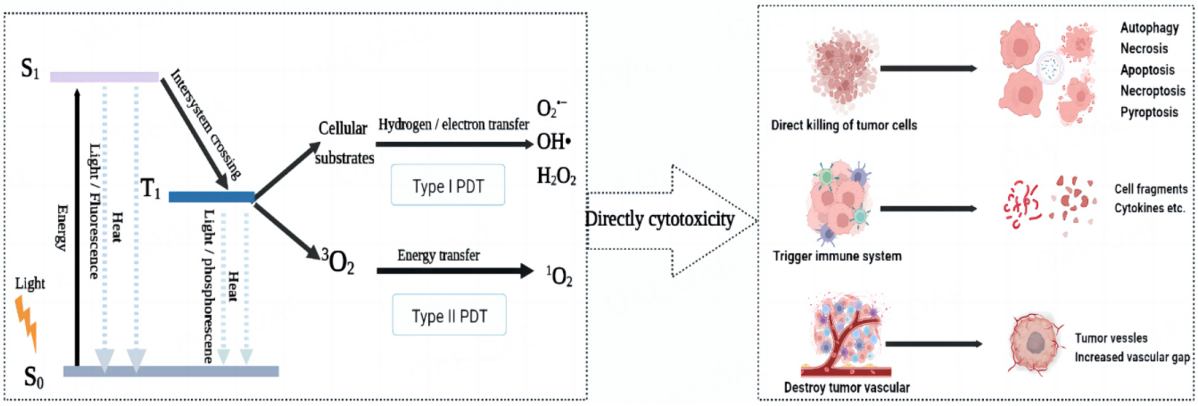

Figure 1. Schematic illustration of the photochemical reactions for type I and type II PDT and related antitumor effects.

this review, we concentrate on some strategies that have synergy between different therapies to overcome hypoxia. Next, we use examples to illustrate how these strategies work, and in the last, we discuss the challenges and future prospects associated with these strategies.

SYNERGETIC THERAPY STRATEGIES

Combination of PDT with photothermal therapy

As a non-oxygen-dependent cancer treatment, photothermal therapy (PTT) has been developed to improve antitumor effects via the use of photothermal agents to convert optical energy into thermal energy and thus cause irreversible cell damage[25,41-43]. An increase in local temperature (mild heating) was shown to increase the tumor blood flow and O_2 content[44-46]. Therefore, PTT is a favorable method of overcoming tumor hypoxia and enhancing the efficacy of PDT. PTT treatment is known to cause the upregulation of the heat shock protein (HSP), which protects tumor cells[47]. Given that PDT-generated ROS were reported to downregulate HSP[48], PDT can improve the efficacy of PTT. So far, various materials have been designed for synergetic PPT-PDT treatment, including magnetic melanin[49,50], CuS[51,52], Prussian blue nanoparticles[53-57], poly(dopamine) (PDA)[58-60], gold nanospheres[61-63], graphene oxides[64-66], BP[67-69], and WS_2 nanosheets[70].

Song *et al.* created a PTT-PDT self-synergetic nanoplatform (RGD-BPNS@SMFN) based on temperature-dependent CAT-like (Catalase is an enzyme that catalyzes the decomposition of hydrogen peroxide into oxygen and water) effects to eliminate tumor[71] [Figure 2A]. This kind of self-synergetic phenomenon was found due to the PTT-promoted inherent CAT-like activity which increased the O_2 concentration of TME and further enhanced PDT efficiency. Photothermal performance is shown in Figure 2B, BPNS@SMFN elevated the temperature under irradiation by 808 nm from 25 °C to 45 °C. Meanwhile, photodynamic performance is shown in Figure 2C, BPNS@SMFN generated ROS inferiorly to the bare BPNS without H_2O_2, but when added H_2O_2, ROS production dramatically elevated in BPNS@SMFN treated group. *In vitro* experiments, CCK-8 results showed that in unitary PDT or PTT treatment, BPNS, BPNS@SMFN and RGD-BPNS@SMFN all presented subtle differences in cytotoxicity. However, RGD-BPNS@SMFN exhibited a dramatic decline in cytotoxicity in the PDT-PTT or PTT-PDT treatments, indicating the mutual promotion in dual phototherapeutic mode. Moreover, studies also found that the therapeutic order made different cell viability; RGD-BPNS@SMFN in PTT-PDT order had a better performance which may result in the effect of temperature on PDT efficacy [Figure 2D]. *In vivo*, BPNS@SMFN with dual phototherapy treatment groups inhibited tumors more dramatically than unitary PDT or PTT [Figure 2E and F], indicating the synergetic promotion outcomes of phototherapies *in vivo*.

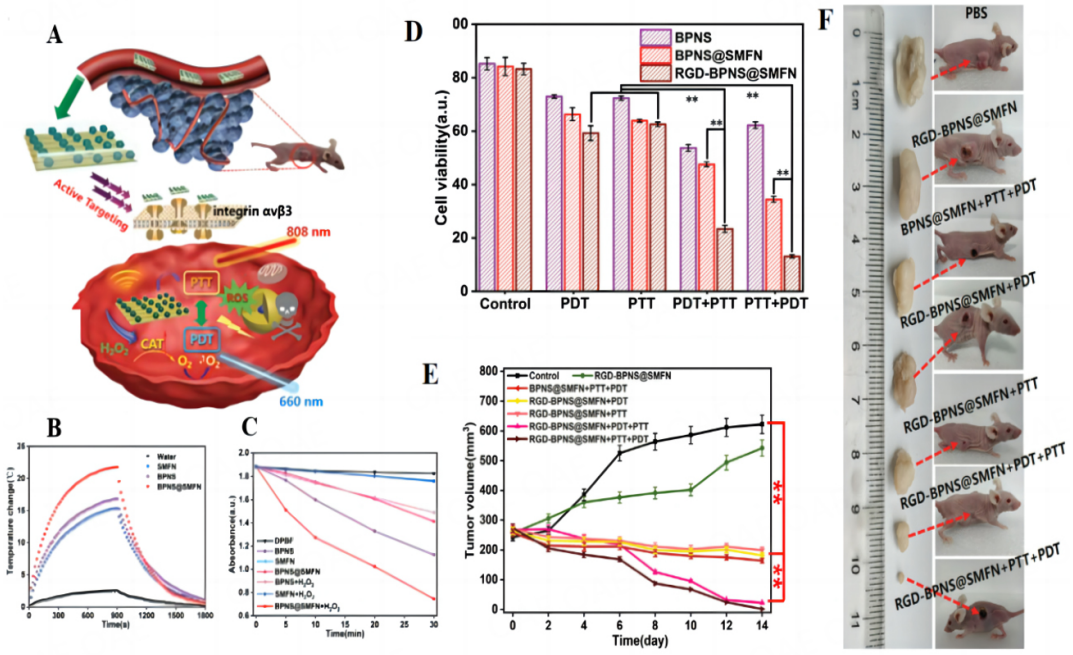

Figure 2. (A) The targeted self-synergetic phototherapy process of the nanoplatform as prepared based on the temperature-dependent CAT-like behavior; (B) photothermal curves of BPNS, SMFN and BPNS@SMFN dispersion under 808 nm laser irradiation; (C) Time-dependent absorbance values at 415 nm of the different samples after mixing with DPBF; (D) *In vitro* cell viabilities of HeLa cells after different treatments with nanomaterials as-synthesized; (E) oxygen generation curves of three materials (SMFN, BPNS, BPNS@SMFN) at different pH (pH 6.5 and 7.4) over time; (F) the oxygen generation curves of different materials under different treatment mixed with fixed H_2O_2 concentration (500×10^{-3} m) over time tumor volumes variation in different treatment groups with time. Reprinted from ref.[71] with permission. $^{**}P < 0.01$, Copyright 2022, Wiley-VCH.

Combination of PDT with hypoxia-activated therapy

Given the difficulty of increasing intratumoral oxygen levels and the limitations of monotherapies, several strategies have been developed to overcome the hypoxia limitation of PDT and have achieved marginal benefits. Hypoxia-activated prodrugs (HAPs), which act only under hypoxic conditions and are significantly cytotoxic to hypoxic cells but have little effect on normal cells, hold great promise for the enhancement of PDT efficiency[72].

Several studies combined PSs and HAPs into nanoparticles. He *et al.* chose banoxantrone (AQ4N), which can be enzymatically converted into toxic AQ4 under hypoxic conditions, as the HAP, and designed a covalent organic framework (COF)-based AQ4N-encapsulating nanoplatform (THPPTK-PEG NPs) composed of a PS (tetra(4-hydroxyphenyl)porphine (THPP)) and a $^1O_2$-cleavable thioketal (TK) linker[73]. After laser irradiation at 660 nm, THPPTK-PEG NPs generated large amounts of cytotoxic ROS with antitumor activity, as the PS consumed large amounts of O_2 and then aggravated the hypoxia within the tumor. Simultaneously, PDT-generated ROS cleaved the TK linker to disintegrate the COF and selectively release AQ4N into the tumor. Both *in vivo* and *In vitro* experiments showed that the highest cytotoxicity and tumor inhibition efficacy were observed for the THPPTK-PEG + laser group. Furthermore, HIF-1α staining revealed that THPPTK-PEG NPs and AQ4N@THPPTK-PEG NPs may aggravate tumor hypoxia after laser irradiation, resulting in hypoxia-activated cascade chemotherapy in tumors. Therefore, hypoxia-activated therapy and PDT have a synergistic effect on anticancer activity.

Combination of PDT with chemodynamic therapy

chemodynamic therapy (CDT), an oxidation therapy, has attracted much attention due to its ability to generate ROS via Fenton-type and Fenton-like reactions[74,75]. Specifically, CDT uses transition metal (e.g., Fe, Mn, Cu, Ni, and Co) catalysts to convert H_2O_2 into cytotoxic $^{\bullet}OH$ and thus inflict significant oxidative damage to tumor cells[76-83]. Unlike O_2, H_2O_2 is highly abundant in TMEs, and CDT is therefore not affected by hypoxia[84,85] and may be a promising strategy for enhancing PDT antitumor efficacy.

So far, Fe-based materials are the most suitable catalysts for therapeutic applications, generating $^{\bullet}OH$ radicals and thus inducing lipid peroxidation (LPO) in tumor cells[86]. Fenton-type reactions can be represented as follows[75]:

$$Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + {}^{\bullet}OH + OH^-,$$

$$Fe^{2+} + {}^{\bullet}OH \rightarrow Fe^{2+} + {}^{\bullet}OOH + H^+,$$

$$Fe^{3+} + {}^{\bullet}OOH \rightarrow Fe^{2+} + O_2 + H^+.$$

Unlike PDT, which induces apoptosis, Fe-based CDT treatment inflicts iron-dependent LPO-associated oxidative damage that induces regulated cell death, which can also be denoted as ferroptosis[86-89]. The combination of PDT and ferroptosis has been developed into a promising strategy. Ferroptosis-inducing agents can be generally classified as nanoparticle platforms (e.g., inorganic Fe-containing nanoparticles[90] and Fe-organic frameworks such as Fe-MOFs[91]) and protein-based nanocarriers (e.g., ferritin[92]). Several nanoparticles have shown a significant capability for enhancing antitumor efficacy but exhibited some drawbacks related to biocompatibility and tumor-targeting prospects[93].

Wang *et al.* designed a novel hypoxia-responsive nanoreactor BCFe@SRF for cancer synergistic therapy. They encapsulated the covalently crosslinked Ce6, bovine serum albumin (BSA) and ferritin, together with sorafenib (SRF) inside a protein [Figure 3A][94]. BSA-Ce6 is a prospecting protein-based PDT material. Ferritin acted as ferroptosis inducer, which converted H_2O_2 into •OH to amplify ROS concentration. SRF not only destroyed the oxidative defense system of tumor but also promoted ferroptosis for further enhancement. Azobenzene (Azo) was used as a cross-linker in the BCFe@SRF, which can be cleaved under hypoxic conditions. Thus, under hypoxic conditions, BCFe@SRF could be degraded to release Ce6 for photodynamic therapy and ferritin for chemodynamic therapy [Figure 3B]. After 670 nm light irradiation, BC-treated cells exhibited a 47.1% viability under hypoxia compared to 41.0% under normoxia, which indicates that hypoxia affects PDT efficiency. Meanwhile, BCFe@SRF treated cells had a 12.4% viability under hypoxia compared to 36.0% viability under normoxic conditions, owing to the degradation of Azo-crosslinked nanosystems which released more Ce6 to enhance therapeutic efficacy [Figure 3C]. Similarly, with the CCK-8 assay, the BCFe@SRF + laser + hypoxia group demonstrated the best ability to kill cancer cells in the live/dead staining assay [Figure 3D]. To verify the hypothetic mechanism of BCFe@SRF, Fer-1 was used as an inhibitor for ferroptosis in the vitro experiments. CCK-8 assay showed that the toxicity was obviously inhibited after adding Fer-1 [Figure 3E] through inhibited ROS generation [Figure 3F]. *In vivo* performance, compared to single PDT (BC + laser) treated group or ferroptosis group (BCFe@SRF), BCFe@SRF + laser group exhibited greater tumor inhibition and reduction [Figure 3G and H].

Zhou *et al.* suggested that the efficacy of ROS is limited by their short half-life and low diffusion radius and speculated that the direct targeting of vital ROS-sensitive organelles such as mitochondria could enhance efficacy[95]. To test this hypothesis, the authors developed a multifunctional nanoplatform targeting and

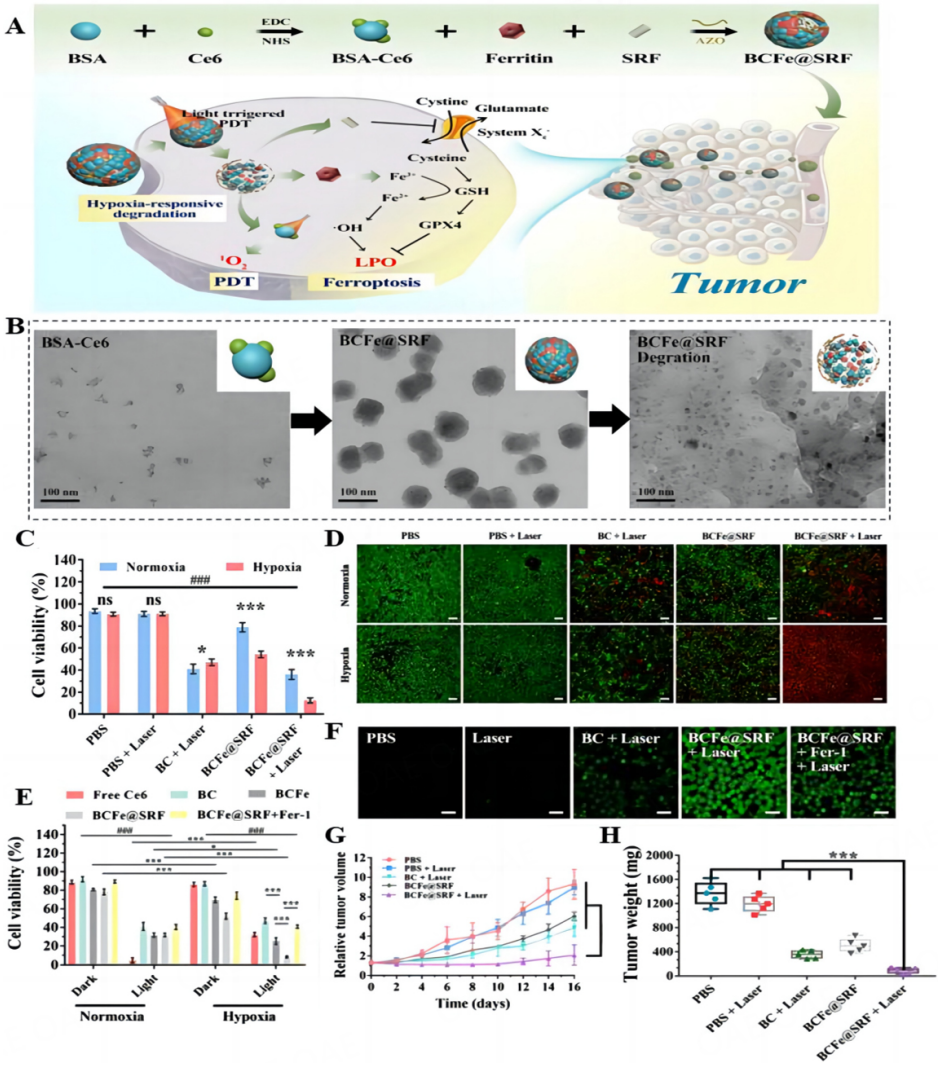

Figure 3. (A) Fabrication procedures and antitumor mechanisms of BCFe@SRF nanoreactor for the designed synergistic PDT and ferroptosis therapy; (B) TEM images of a BSA-Ce6, BCFe@SRF, and BCFe@SRF degradation product; (C) A CCK-8 cell viability assay of hepa 1-6 cells treated with BCFe@SRF (Ce6 concentration: 1 μM) mediated PDT (670 nm light, 50 $mW \cdot cm^{-2}$, 5 min) in normoxic or hypoxia condition; (D) Live/dead staining assay (green: live cells; red: dead cells); (C) CCK-8 cell viability assay; (E) CCK-8 cell viability assay; (F) Fluorescence microscopy images of hepa 1-6 cells treated with different formulations and ROS indicator DCFH-DA with or without laser irradiation in hypoxic condition; (G) Time-dependent tumor growth curves; (H) average weights of the excited tumors at the end of the indicated treatment. Reprinted from ref.[94] with permission. $^*P < 0.05$; $^{***}P < 0.001$; $^{\#\#\#}P < 0.001$. Copyright 2022, BMC.

damaging mitochondria through a combination of PDT and Fenton reactions (Fe_3O_4@Dex/TPP/PpIX/ss-MPEG)[96]. Fe_3O_4 decomposed and diffused into the cytoplasm to react with H_2O_2 and generate O_2 and $^{\bullet}OH$. Nondecomposed nanoparticles were localized in mitochondria and then directly generated ROS. Furthermore, the Fenton reaction-produced O_2 could also be utilized as a raw material for PDT and thus increase its efficiency. In this way, Fenton reactions combined with PDT can greatly enhance tumor treatment[83,82].

However, the related clinical translation is limited by the insufficient generation of $^{\bullet}OH$ and the low rate of Fe-based Fenton reactions[97]. Cu-based Fenton-like reactions have a greater CDT potential than Fe-based Fenton reactions because of the adaptability to weakly acidic TMEs, high rate of $^{\bullet}OH$ generation, and

greater rate of the former. The redox properties of Cu are strikingly similar to those of Fe, e.g., both Cu^{+} and Cu^{2+} easily react with H_2O_2[83,98-100]:

$$Cu^{2+} + H_2O_2 \rightarrow Cu^{+} + HO_2^{\bullet} + OH^{-},$$

$$Cu^{+} + H_2O_2 \rightarrow Cu^{2+} + {}^{\bullet}OH + OH\text{-}.$$

The Cu^{2+}/H_2O_2 Fenton-like system is applicable over a broader pH range than the Fe^{3+}/H_2O_2 system in view of the higher solubility[101]. In addition, Cu^{2+} complexes are more easily decomposed by $^{\bullet}OH$ than Fe^{3+} complexes, which precludes the deactivation of Fenton reactions[102]. Furthermore, Cu^{2+} can be reduced by GSH to increase the concentration of redox-active species (Cu^{+}) used to generate $^{\bullet}OH$ (Cu^{2+} + GSH → Cu^{+} + GSSG)[103]. Such characteristics highlight the favorable properties of the Cu^{2+}/H_2O_2 Fenton-like system for enhancing the efficacy of antitumor therapies.

In a study by Li *et al*., Cu^{2+}-mediated protein self-assembly (C-m-ABs) was developed by integrating copper with photosensitizer (ICG)[104]. Under light irradiation, C-m-Abs activates Photo-Fenton-like reaction to generate large ROS through the reduction of Cu^{2+} and ICG simultaneously [Figure 4A]. As shown in Figure 4B, ROS generation capacity was measured using 1,3-diphenylisobenzofuran, which is used as a ROS probe. Compared to the control group, DPBF suffered significant degradation after the addition of copper agents, and it should be noted that C-m-Abs + GSH treated group exhibited the fastest degradation rate of DFBF. *In vitro* cell-killing experiments showed that C-m-Abs exhibited excellent cytotoxicity [Figure 4C-E]; furthermore, C-m-Abs presented significantly higher cytotoxicity than free DOX with a PH of 5.0, suggesting that the lower PH, the more release of DOX from C-m-Abs. Figure 4D showed that compared to the free ICG, C-m-Abs (no DOX) induced more cytotoxicity under different irradiations. Moreover, C-m-Abs+ laser induced more cytotoxicity than DOX + ICG [Figure 4E]. *In vitro* experiments showed that C-m-Abs treated groups inhibited tumors more than control and DOX groups [Figure 4F and G].

In addition to ROS generation, Cu-based Fenton-like reactions may be accompanied by the oxidation of the diamagnetic Cu^{+} to the paramagnetic Cu^{2+} by H_2O_2, which may be used to develop *in situ*-generated MRI contrast agents for tumor imaging and diagnosis. Liu *et al.* reported a nanomaterial for multimodal imaging-guided synergetic therapy (CDT + PTT) acting as a highly efficient CDT agent, photothermal conversion agent (PTT), and self-generated MRI contrast agent[105]. Considering all these properties of Fenton and Fenton-like agents, we believe that future works will promote the development of photo- and chemodynamic therapies.

Combination of PDT with chemotherapy

Chemotherapeutics can improve the sensitivity of tumor cells to ROS, while ROS can enhance the uptake of chemotherapeutics by tumor cells; the combination of PDT with chemotherapy has become one of the most common cancer treatments[106,107]. Given that many PS components are chemotherapeutics, as mentioned above, this approach is not discussed separately herein.

Combination of PDT with immunotherapy

With the use of immune checkpoint inhibitors (ICI), cytokines that stimulate lymphocytes, and CAR-T cells, immunotherapy has transformed cancer treatment[108-115]. However, only 10%-30% of patients gain benefits from ICIs, possibly because of the "cold tumor" phenomenon, which refers to the lack of tumor-infiltrating T-cells and immunosuppressive TMEs[116,117]. Immunogenic cell death (ICD) is currently viewed as a promising strategy for activating the immune TME to enhance the efficacy of immunotherapy. ICD

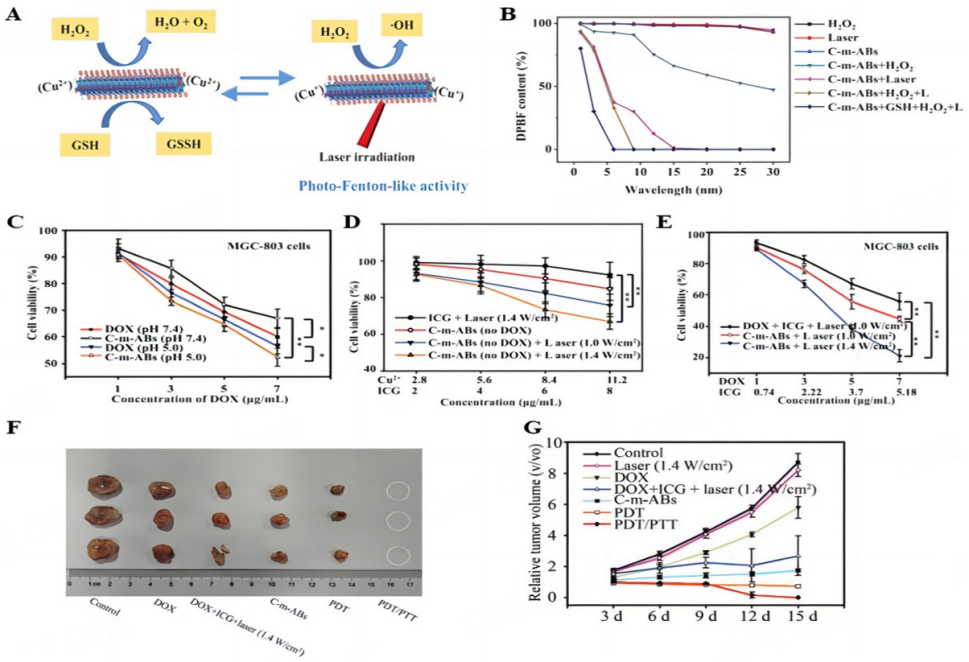

Figure 4. (A) C-m-ABs displays Photo-Fenton-like activity in the schematic illustration; (B) An 8-min reaction time was used to deplete DPBF after undergoing different treatments; (C) The viability of MGC-803 cells was analyzed using C-m-ABs containing different levels of DOX at pH 7.4 or 5.0 for 12 h; (D) Cell viability of MGC-803 cells treated with C-m-ABs (no DOX) and ICG under laser irradiation (1.0 W cm^{-2} or 1.4 W cm^{-2}); (E) To test MGC-803 cell viability, C-m-ABs and DOX + ICG were employed, respectively, under laser irradiation (1.0 W cm^{-2} or 1.4 W cm^{-2}); (F) Visual images of excised tumor at 15 day after treated with DOX, DOX + ICG + laser (1.4 W cm^{-2}), C-m-ABs, C-m-Abs + laser (1.0 W cm^{-2}) (PDT group), and C-m-ABs+laser (1.4 W cm^{-2}, PDT/PTT group); (G) Curves of relative tumor volume fluctuation over time. Reprinted from ref.[104] with permission. Copyright 2019, Wiley-VCH.

releases tumor-specific antigens and DAMPs to elicit antigen-specific immune reactions[118-120]. Pyroptosis, an ICD-causing PDT, holds great promise for augmenting tumor immunogenicity to overcome tumor immune suppression[121]. Therefore, the synergistic effects of PDT and immunotherapy have attracted much attention in view of the capability of this combination to convert immunosuppression into immunogenic TMEs and thus intensify the efficacy of both PDT and immunotherapy[122-124]. Wan *et al.* focused on RGX-104, an optimal liver-X nuclear hormone receptor (LXRβ) agonist to eliminate myeloid-derived suppressor cell (MDSC)-caused immunosuppressive activity[125]. The authors copackaged RGX-104 and a PS (Ce6) and designed a pH-responsive size-transformable nanoparticle delivery system (MRC NPs)[126]. RGX-104 reduced MDSCs to propel antitumor immunity, while Ce6 induced pyroptosis to increase tumor immunogenicity and generated ROS in tumor sites. Most recently, X-ray-induced PDT was combined with immunotherapy in cancer treatment with very good outcomes[124].

Combination of PDT with photoacoustic therapy

Photoacoustic therapy (PAT) is relatively different from other tumor therapies, as it inflicts mechanical damage to tumor cells using photoacoustic shockwaves without considering phototoxicity and resistance[127]. The oxygen-independent nature of PAT increases its chances of overcoming hypoxia during PDT[128]. Zhang *et al.* developed a new photoacoustic/dynamic therapeutic (PADT) agent based on a new PS (Gd(III)-phthalocyanine, GdPc)[129], showing that it can simultaneously generate acoustic cavitation for photophysical damage and $^1O_2$ for photochemical damage upon pulse-wave (PW) laser irradiation. *In vitro* experiments, after irradiation at 680 nm (0.3 W cm^{-2}), GdPcP-pretreated cells displayed direct mechanical damage and large $^1O_2$ contents. In other *In vitro* experiments, the activity of HepG2 cells in the PADT group significantly decreased (to 53.5% of the original) under hypoxic conditions, while that in the PDT group

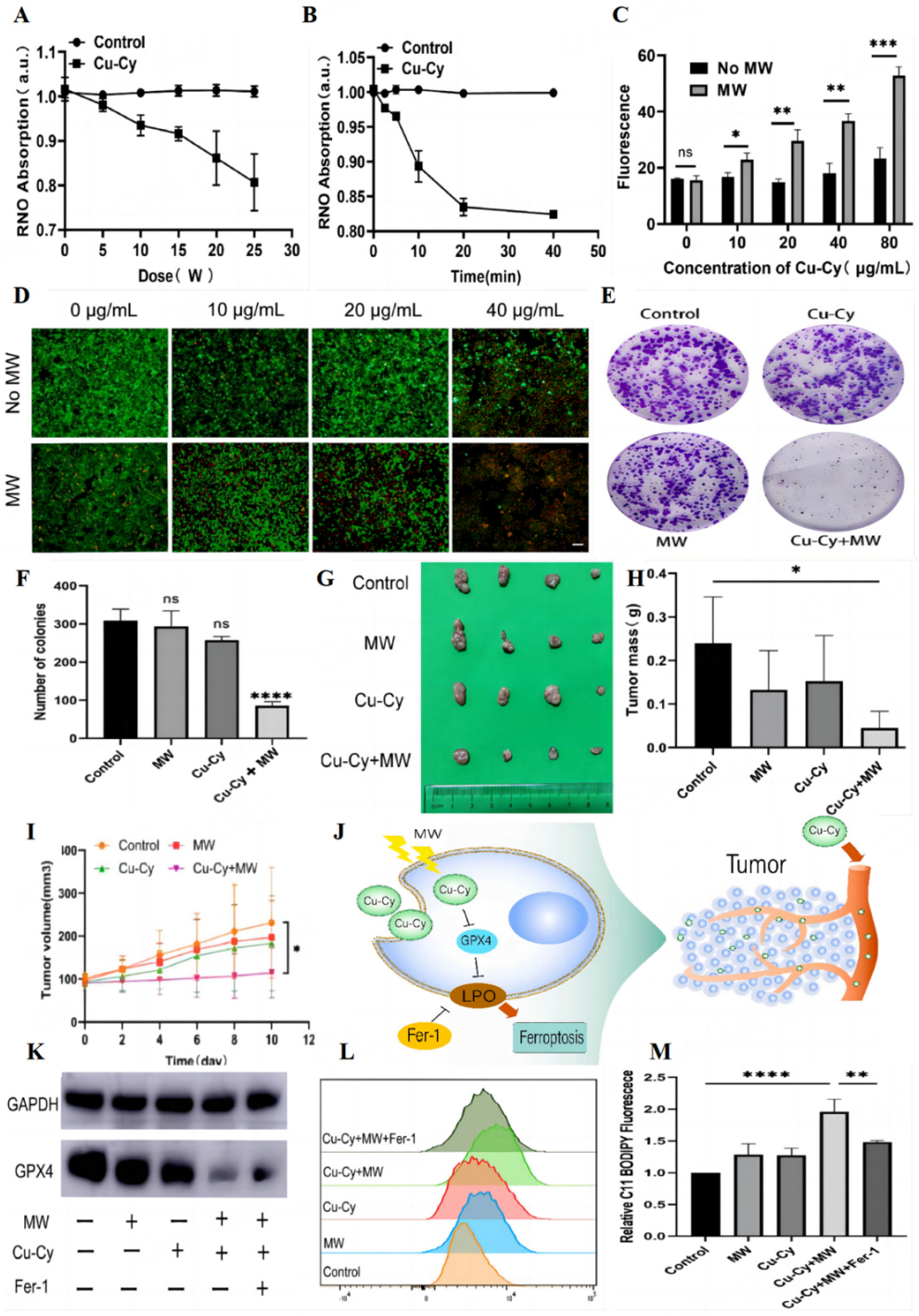

Figure 5. (A) ROS were detected by RNO-ID using Cu-Cy aqueous solution (0.2 mg/mL) irradiated with different MWs of different power for 5 min. (B) Cu-Cy aqueous solution (0.2 mg/mL) irradiated with MW at 20 W for different times was detected by the RNO-ID method. (C) A comparison of SOSG fluorescence intensity with different Cu-Cy concentrations after MW irradiation. (D) A live/dead staining image of HCT15 cells treated with Cu-Cy and MW irradiation (20 W, 3 min). (E) MW-induced colony formation in HCT15 cells. (F) A calculation was made to determine the average number of clones. (G) Experiment images showing each group's results using the xenograft model. (H) Tumor mass changes. (I) Tumor volume changes. (J) An illustration of how Cu-Cy-mediated dynamic microwave therapy (MWDT) induces ferroptosis in colorectal cancer cells. (K) Western blot assay of GPX4 expression. (L) FCM assay of cellular LPO with BODIPY-C11 probe detection. (M) FCM analysis of relative fluorescence intensity of HCT15 stained with the C11 BODIPY probe. Scale bar: 50 μm; *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$; ****$P < 0.0001$. Reprinted from ref.[131] with permission. Copyright 2022, Elsevier.

decreased only to 80.3%. Under *in vivo* hypoxic conditions, subcutaneous tumor models showed significantly stronger tumor inhibition in the PADT group compared to the PDT group after 18 days of different treatment regimens. This study suggested that the PW irradiation of GdPc resulted in mitochondrial damage and programmed cell death due to the strong acoustic effect and the high quantum yield of $^1O_2$.

PDT with microwave radiation

Microwaves can propagate through all types of tissues and stimulate photocatalysis in order to produce ROS oxygen-independently by plasmonic effects caused by microwave radiation[130]. PDT induced by microwaves is an excellent replacement for PDT based on type I[131]. The effect of MW is to dilate the blood vessels, increase blood flow velocity, and, in turn, increase oxygen content while activating photosensitizers in the body[132]. For instance, Copper-cystamine (Cu-Cy), a new type of photosensitizer researched and invented by Chen's team[133], can be activated by UV[134], microwave[100,135], ultrasound[136] and X-Ray[137-142] and generate large amounts of singlet oxygen for killing tumor cells[100]. As microwave radiation is utilized with Cu-Cy nanoparticles at the tumor site, this will create $^1O_2$[130]. This form of therapy may also be used with other chemicals such as Iodine or Chloride[143]. These methods may provide other options in decreasing tumor size depending on the location.

According to Zhou's study, through Cu-Cy nanoparticle-mediated microwave dynamic therapy, ferroptosis can be induced as a cancer treatment option[131]. They used RNO-ID and SOSG to verify that ROS could be produced after MW irradiation of Cu-Cy, and the results showed that singlet oxygen increased with the increase of MW irradiation time and Cu-Cy concentration [Figure 5A-C]. *In vitro* experiments, Human CRC cells HCT15 can be inhibited by Cu-Cy nanoparticles activated with MW. Cu-Cy at 40 μg/mL almost killed all cells after microwave activation [Figure 5D]. Significant inhibition of cell colony formation was observed in Figure 5E and F when MW-activated Cu-Cy nanoparticles were compared to other groups. *In vivo* experiments, compared to control group or MW group, Cu-Cy group, the Cu-Cy +MW group obviously inhibited the tumor mass and tumor growth [Figure 5G-I]. At the same time, by inducing ferroptotic death with microwave PDT using Cu-Cy nanoparticles, Zhou found that microwave PDT can effectively destroy colorectal cells [Figure 5J]. As seen in Figure 5K, Western blot assay showed that GPX4 in HCT15 treated with MWDT was underexpressed compared to other groups (Blank, MW alone or Cu-Cy alone group). However, when ferroptosis inhibitor Fer-1 was added, this change was reversed. Ferroptosis was generally considered to be characterized by lipid peroxidation (LPO) inside cells[144]. C11-BODIPY fluorescent probe measurements showed that when HCT15 cells were treated with Cu-Cy + MW, the LPO was higher than when cells were treated with MW alone or Cu-Cy alone [Figure 5L and M]. As a result, human CRC cells were shown to undergo ferroptosis via MW-activated Cu-Cy.

More sensitizers have been discovered in recent years, such as graphitic-phase carbon nitride (g-C_3N_4) quantum dots (QDs)[145], AIEgens (TPEPy-I and TPEPy-PF6)[146] and TiO_2[147] nanoparticles. Researchers found that it can activate and produce ROS under MW irradiation, killing tumor cells. MWPDT produces singlet oxygen and increases the oxygen content of the tumor microenvironment, providing a new therapeutic method for tumor treatment. X-ray has been widely used in clinical cancer theranostics, because of its strong penetration ability[148]. X-ray can activate photosensitizers and produce reactive ROS. Existing studies have found that radiokinetic therapy (RDT) is an oxygen-dependent dynamic therapy, so it is not elaborated in this article.

PDT with radiotherapy

Radiotherapy (RT) is an important mode of tumor therapy[149], which mainly uses radiation to damage the DNA of tumor cells to cause cell death, and can also produce ROS to cause cell apoptosis and enhance the

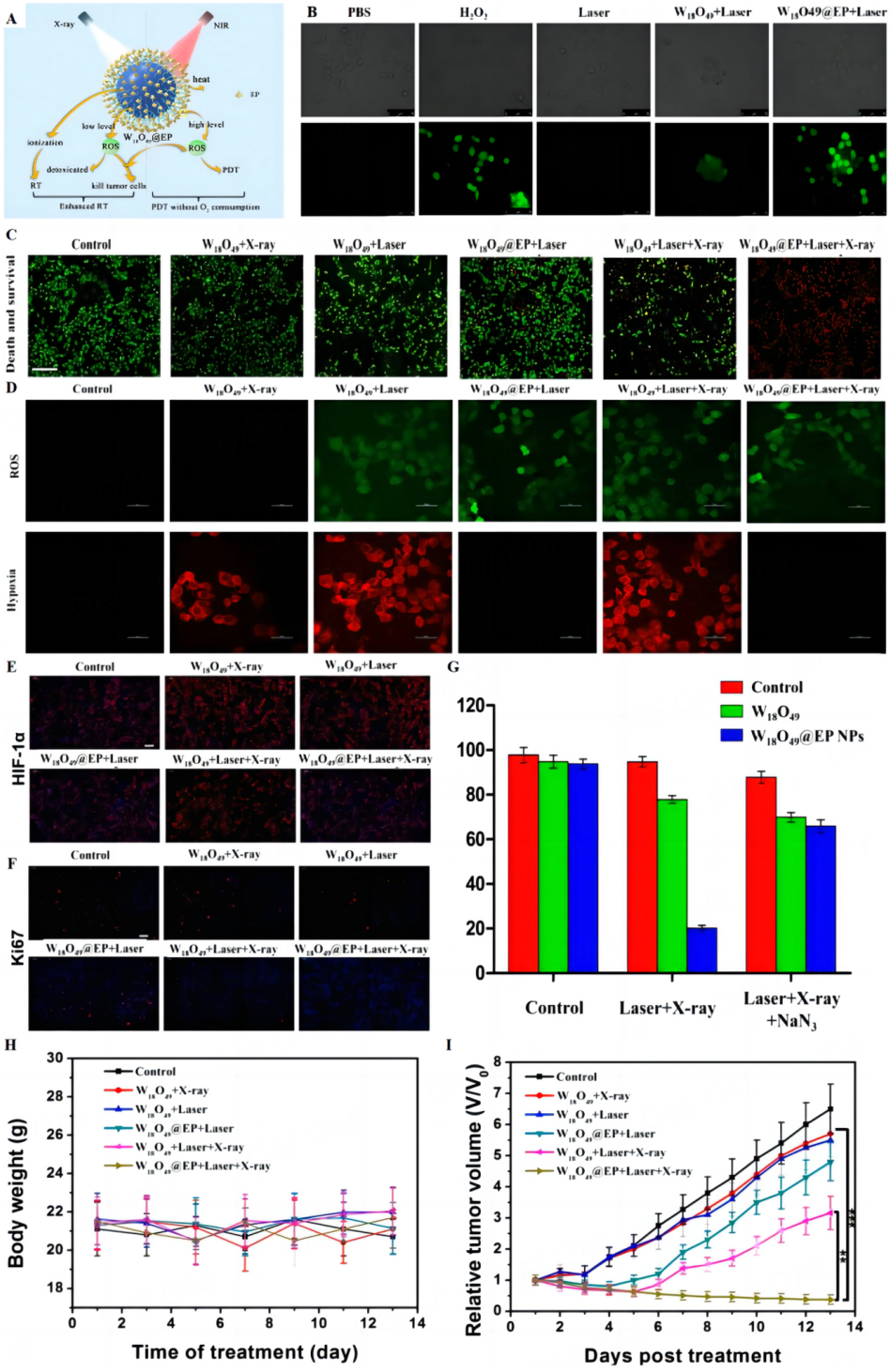

Figure 6. (A) The mechanism of $W_{18}O_{49}$@EP under NIR and X-ray. (B) The production of ROS within cells after various treatments. (C) A comparison of cell death following different treatments. Red: dead cells; green: living cells. (D) Hypoxia and intracellular ROS levels after different treatments. (E) Red fluorescence marks HIF-1 expression in cells after different treatments. (F) The expression of Ki67 in cells after different treatments is marked by red fluorescence. (G) Cell survival after different treatments. (H) Tumor-bearing mice's body weight after different treatments. (I) Volumes of tumors in mice treated differently. Reprinted from ref.[160] with permission. Copyright 2022, frontiers.

therapeutic effect of radiation therapy[150]. The effect of PDT on the killing of tumor cells is dependent on ROS[5]. In tumor microenvironments, ROS production is reduced by hypoxia, which was effectively overcome by RT produced ROS at the tumor site, thus enhancing the tumor therapeutic effect of PDT[137,151-159].

A novel $W_{18}O_{49}$ nanoparticle with photothermal effect and RT sensitization was synthesized by Wang *et al.*, which can produce ROS in the presence of X-ray[160]. The anthracene endoperoxide derivative compound (abbreviated as EP) can generate ROS when exposed to the NIR. The ROS generated above will strengthen the effect of ROS on inducing apoptosis. So, they covalently connect $W_{18}O_{49}$ and EP to become $W_{18}O_{49}$@EP to achieve the purpose of combining PDT and RT [Figure 6A]. They used fluorescent probe H2DCFDA to assess the ability to generate ROS and found that the combination of EP and $W_{18}O_{49}$ NPs resulted in a large amount of ROS being produced [Figure 6B]. Their *In vitro* experiments found that almost all cells died after RT and PDT ($W_{18}O_{49}$@EP + Laser + X-ray), significantly improving the killing effect of the tumor compared to the control group. At the same time, the anoxia state of tumor cells was observed after the anoxia induction factor was labeled. The results showed that the anoxia state of the $W_{18}O_{49}$@EP + Laser + X-ray group was significantly improved. Ki67 index results also showed that the $W_{18}O_{49}$@EP + Laser + X-ray group effectively inhibited cell proliferation. The ROS removal experiment proved that $W_{18}O_{49}$@EPNPs can produce ROS, thus improving the efficacy of RT combined with PDT [Figure 6C-G]. Compared with the group, the tumors in the $W_{18}O_{49}$@EP + Laser + X-ray group basically disappeared after 2 w treatment, achieving a good therapeutic effect [Figure 6H and I]. Their results demonstrate that $W_{18}O_{49}$@EP releases ROS under near-infrared light (NIR) to achieve effective PDT without inducing hypoxia.

Some other photosensitizers, such as AVPt@HP@MNPs[161]and AuNCs-ICG nanozymes[162], have been found to have the characteristics of catalase, catalyzing the decomposition of hydrogen peroxide into oxygen in tumors, effectively solving the problem of hypoxia in the tumor microenvironment, and significantly improving the efficacy of PDT combined with RT. At the same time, AuNCs-ICG nanozymes will gather in large numbers in the tumor area and absorb X-ray, thus increasing the radiation dose in the tumor area and improving the efficacy of radiotherapy.

Summary

PDT is an important treatment for cancer because it is efficient, selective, minimally invasive, and has low toxicity. It damages tumor cells, vessels, and immune responses by creating ROS using energy transfer to oxygen. However, solid tumors often lack oxygen, making them difficult to treat with PDT. We discovered two main ways to generate ROS with PDT: the type-I process and the type-II process. We also identified several synergistic therapy strategies, such as combining PDT with PTT, hypoxia-activated therapy, CDT, immunotherapy, PAT, chemotherapy, Microwave Radiation, and Radiotherapy. The advantages and disadvantages of these strategies are summarized in Table 1. However, deep PDT as a clinical tool is still being explored and evaluated. Computer-aided drug design and target drug delivery techniques are being used to develop more effective photosensitizers for PDT. Additionally, developing PDT materials that can induce multiple tumor cell death modalities simultaneously would improve treatment effectiveness and prevent resistance. Combining type-I PDT with other treatments using multifunctional nanomedicine may be an efficient way to achieve multi-mode collaborative therapy.

Table 1. The comparison of the strategies to relieve tumor hypoxia

Strategy	Advantages	Disadvantages
Synergetic therapy		
Combined PDT with photothermal therapy (PTT)	(1) In one sense, increasing local temperature (mild heating) increases tumor blood flow and O_2 content, but at the same time, ROS generated by PDT can downregulate heat shock protein (HSP) expression	(1) Light penetration of tissues is limited; (2) This strategy needs to provide compelling efficacy and safety benefits
Combined PDT with hypoxia-activated therapy	(1) Hypoxia-activated prodrugs (HAP), which act only under hypoxic conditions and have significant cytotoxicity in hypoxia cells but little effect on normal cells	(1) It is difficult for this strategy to retain and penetrate due to increased interstitial fluid pressure and a dense extracellular matrix
Combined PDT with chemodynamic therapy (CDT)	(1) CDT utilizes Fenton or Fenton-like reactions, with transition metals as catalysts, to convert H_2O_2 to •OH to destroy tumor cells. In contrast with the O_2, H_2O_2 is highly abundant in TME, so that CDT is not affected by hypoxia; (2) In addition to triggering by the endogenous chemical energy, CDT can modulate the hypoxia and immunosuppressive TME	(1) There are still some concerns about the biocompatibility, tumor-targeting capacity of current studies; (2) The therapeutic performance was still far from satisfactory
Combined PDT with immunotherapy	(1) The synergistic effects of PDT and immunotherapy attracted more attention due to their capability to convert immunosuppression into immunogenic TME to intensify both PDT and immunotherapy efficacy	(1) The biodegradability of inorganic nanomaterials and polymer-based nanomedicines is typically poor, severely limiting their clinical application (2) Combination cancer therapies need more advanced nanomedicines to boost effectiveness and safety
Combined PDT with photoacoustic therapy (PAT)	(1) Photoacoustic therapy (PAT) can cause the target tumor cells directly mechanical damage via the photoacoustic shockwave without considering the phototoxicity and resistance	(1) Some materials are toxic and have shallow penetration, which restrict their clinical application
PDT with Microwave Radiation	(1) Microwave Radiation can dilate the blood vessels, increase blood flow velocity, and, in turn, increase oxygen content while activating photosensitizers and producing ROS in the body (2) Microwave Radiation has a strong penetration depth compared to ultraviolet light, and can be used for the treatment of deep tumors	(1) Research on MDT and EDT is still in its infancy
PDT with Radiotherapy	(1) Radiotherapy (RT) is an important mode of tumor therapy, which mainly uses radiation to damage the DNA of tumor cells to cause cell death, and can also produce ROS to cause cell apoptosis and enhance the therapeutic effect of radiation therapy (2) The penetration force of Radiotherapy is stronger than ultraviolet light, microwave	(1) The disadvantages of radiotherapy, such as side effects

DECLARATIONS

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Authors' contributions

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Searched the information, materials and updates and wrote the drafts: Li Y (Ya Li)
Helped for editing, checking and formatting: Cai Y
Edited and formatted the figures: Li Y (Yiyang Li)
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Conceptualization, Instruction, Funding acquisition, and Writing, Visualization, Validation, Supervision: Kenar N, Lim HS, Chen X, Chen W

Availability of data and materials

Not applicable.

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Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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