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Hyperbaric Oxygen-Facilitated Cancer Treatment: A Minireview

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Hypoxia in malignant tumors is a major factor in inducing the failure of clinical cancer treatment. Although several strategies have been developed to relieve hypoxia, most are still in the preclinical research phase. Therefore, hyperbaric oxygen (HBO), an approved adjuvant therapy for alleviating hypoxia clinically, is an excellent choice for enhancing the efficacy of cancer treatment that is impeded by tumor hypoxia. In this minireview, recent advances in HBO-facilitated cancer treatment, including clinical applications and nanomedicine-mediated cancer therapy are introduced. At the end of this minireview, the potential challenges faced by HBO therapy before clinical use are discussed. It is hoped that this review will provide a reference for future clinical research on the application of HBO in cancer treatment.

1. Introduction

Cancer, also known as malignant tumor, has become a major public health problem worldwide,[1] and many therapeutic strategies, including radiotherapy and chemotherapy, have been developed to cure it. However, hypoxia in the tumor microenvironment (TME) is an inherent characteristic of almost all solid tumors and is a major barrier in cancer therapy. It is related to the structural and functional abnormalities of tumor microvasculature and the imbalance between O_2 supply and consumption, caused by the uncontrolled proliferation of tumor cells.[2–5] Hypoxia in the TME is closely associated with the progression, invasion, and metastasis of tumor[6] and induces the expression of hypoxia-inducible factor-1α (HIF-1α), which can lead to multidrug resistance, autophagy upregulation, and apoptosis inhibition in tumor cells. Thus, hypoxia significantly reduces the curative effect of many therapies such as radiotherapy, chemotherapy, and photodynamic therapy (PDT).[2,7–12] Therefore, conquering hypoxia in the TME is a promising strategy to enhance the efficacy of tumor treatment modalities. Strategies such as carrying oxygen into tumor tissues via oxygen carriers such as hemoglobin (Hb) and perfluorocarbon and generating oxygen in situ by decomposing endogenous H_2O_2 have been developed to relieve hypoxia in the TME.[13–16] However, most of the strategies mentioned above are only in preclinical studies and require more comprehensive investigations to realize practical clinical applications.

Hyperbaric oxygen (HBO) can help treat some diseases by allowing patients to inhale pure oxygen at more than one atmospheric pressure to alleviate tissue hypoxia and has been approved for the treatment of a variety of diseases such as necrotizing soft-tissue infections and carbon monoxide poisoning.[17,18] According to Henry's law, the amount of oxygen dissolved in the tissue and blood is proportional to the partial pressure of oxygen in contact with the tissue or blood.[18] In addition, because the additional oxygen provided by HBO is dissolved in plasma rather than in Hb, it can easily diffuse to places where red blood cells cannot reach, such as deep tumors, to relieve tissue hypoxia. Thus, HBO is simpler, more effective, and easier to employ in clinical cancer treatment than other strategies used to overcome hypoxia in tumors. In this minireview, we summarize the recent research advances in HBO-facilitated cancer treatment and discuss them in the order of different therapies: chemotherapy, chemodynamic therapy, phototherapy, and immunotherapy (**Figure 1**).

2. HBO-Facilitated Cancer Treatment

HBO has been approved for use as adjuvant therapy by the Food and Drug Administration (FDA) and the Undersea and Hyperbaric Medical Society. HBO has been utilized widely in clinical disease treatment, and the clinical therapeutic effect of HBO for cancer has been studied for decades. **Table 1** lists some clinical trials on HBO-facilitated cancer treatment. Most of these trials illustrated that patients with cancer may benefit from HBO treatment.[19–28] For example, Maier et al. conducted a clinical trial in 52 patients with advanced cancer of the upper gastrointestinal tract to evaluate the efficacy of the combination of PDT and HBO.[28] Their results showed that after combination therapy, the tumor size decreased significantly, and the mean survival time also remarkably increased, indicating that HBO

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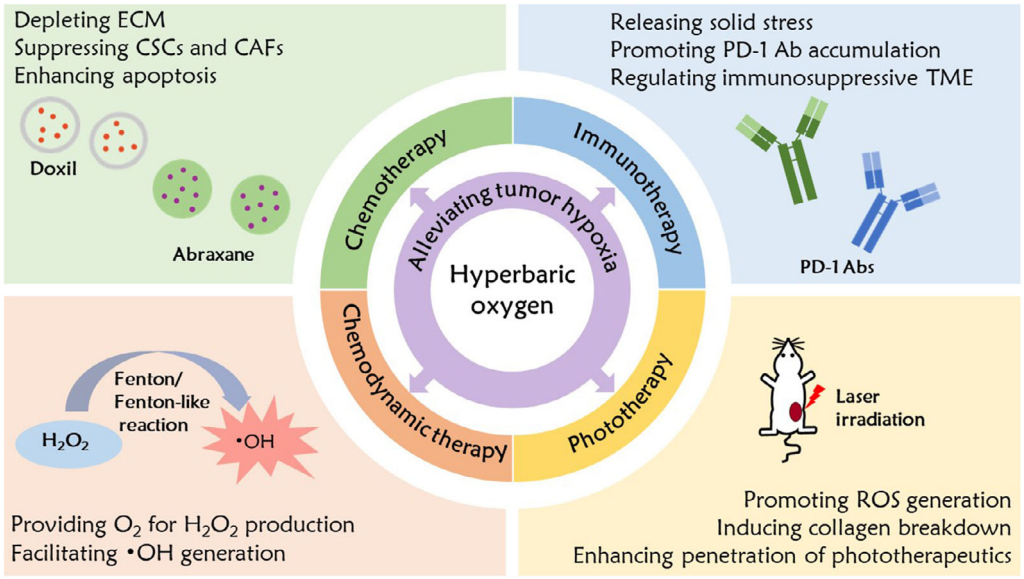

Figure 1. Schematic of the chief effects of HBO in different types of cancer treatment.

Table 1. Some clinical trials of HBO-facilitated cancer treatment and their effectiveness.

Therapy type	Cancer type	Effectiveness	References
Surgery	HCC	Effective but not significant	[19]
Radiotherapy	Esophageal carcinoma	Significantly effective	[20]
	Advanced squamous cell carcinoma of the head and neck	Effective	[21]
	Carcinoma of cervix	Not effective	[22]
Chemotherapy	Breast cancer	Significantly effective	[23]
	Advanced gastric cancer	Effective	[24]
PDT	Advanced malignant bronchial tumor	Effective	[25]
	Lung cancer	Effective	[26]
	Advanced esophageal carcinoma	Effective	[27]
	Advanced cancer of the upper gastrointestinal tract	Significantly effective	[28]

may enhance the efficacy of PDT in the clinic. Moreover, Zhang et al. conducted a clinical trial in 45 patients with advanced esophageal cancer to investigate the clinical efficacy of a combination of a I^{125} particle-integrated covered esophageal stent (hereinafter referred to as I^{125}) and HBO.[20] The study also revealed that the total effective rate in the I^{125} + HBO group was noticeably higher than that in the group without HBO. Furthermore, HBO has been used to enhance the efficacy of combination therapies in clinical trials. Yahara et al. investigated the therapeutic effect of HBO-mediated combined intensity-modulated radiotherapy (IMRT) and chemotherapy.[29] Their results showed that the combination of temozolomide (TMZ; for chemotherapy), HBO, and IMRT is a promising strategy that exhibited low toxicity and yielded a long overall survival duration in patients undergoing glioblastoma treatment. Meanwhile, Mehmet Salih Iyikesici combined metabolically supported chemotherapy, ketogenic diet, hyperthermia (HT), and HBO for stage IV non-small cell lung cancer (NSCLC) treatment.[30] The findings indicated that combination therapy may increase the treatment response rate and survival outcome in NSCLC treatment without eliciting notable side effects. Collectively, these clinical trials indicated that combining cancer treatment with HBO application is a promising strategy to boost the efficacy of the treatment and is worthy to be incorporated into new combination strategies.

2.1. HBO-Facilitated Chemotherapy

Chemotherapy remains one of the main cancer treatment strategies currently available. However, hypoxia-induced drug resistance is an essential factor that leads to chemotherapy failure.[31,32] Therefore, overcoming tumor hypoxia is an effective approach to improving chemotherapy outcomes. Among the various methods available to overcome tumor hypoxia, HBO is an excellent choice. HBO can potentiate the chemosensitization of cancer cells and significantly enhance the therapeutic effect of chemotherapy by overcoming tumor hypoxia.[33–37] For example, IR-780 is a near-infrared (NIR) fluorescent agent with a high

affinity for mitochondria. However, its antitumor effect is limited by the hypoxic TME. Shen et al. combined IR-780 with HBO to enhance bladder cancer treatment.[34] In the cited study, IR-780 showed a high antitumor effect when combined with HBO by facilitating the cellular uptake of IR-870 via increasing the plasma membrane potential and producing excessive reactive oxygen species (ROS) in the mitochondria to disrupt their electron transfer chain. Peng et al. combined HBO with sorafenib, a first-line medicine for hepatocellular carcinoma (HCC), to enhance the antitumor effect of sorafenib.[33] The combination of sorafenib and HBO showed more notable synergistic growth inhibition in hepatoma cells than did sorafenib alone, which was attributed to hypoxia alleviation in HCC and enhanced apoptosis caused by sorafenib and the ROS products of HBO treatment. The abovementioned examples highlight that HBO is a robust adjuvant therapy that enhances the efficacy of chemotherapy, implying its potential application in clinical cancer treatment. Additionally, HBO has been used to enhance the efficacy of treatments that combine chemotherapy and other therapeutic modalities. Ohguri et al. investigated the therapeutic efficacy of a combination of chemotherapy, mild HT, and HBO.[38] The group treated with HBO, mild HT, and carboplatin showed remarkably delayed tumor growth compared with that shown by the group treated with mild HT and carboplatin. This result indicated that the therapeutic effect of the combination of chemotherapy and HT can also be promoted by HBO. Xie et al. combined HBO and TMZ-loaded porous silicon nanoparticles (TMZ/PSi NPs) to treat gliomas.[39] Noticeable suppression of tumor growth (with an 84.2% tumor suppression rate) was observed with the use of HBO and TMZ/PSi NPs together. Besides, the proliferation rate of tumor cells in the "HBO + TMZ/PSi NPs" group was lower than that in the group with TMZ/PSi NPs treatment alone, illustrating that HBO could remarkably magnify the treatment effect of TMZ/PSi. Moreover, after HBO treatment, hypoxia was relieved, and the proportion of cells in the G2/M phase increased, induced by the combination of TMZ/PSi NPs and HBO. This implied that the arrest of glioma cells at the G2/M phase could be the mechanism governing the action of HBO-enhanced TMZ/PSi NPs. This study confirmed that the combination of nanomedicine and HBO is a promising method for amplifying its treatment effects.

However, HBO may also exacerbate the side effects of some conventional drugs, especially drugs exerting antitumor effects via the production of ROS, such as doxorubicin (DOX). Hence, the combination of HBO and conventional drugs is regarded as a contraindication.[40,41] Given that Doxil (a type of commercialized DOX-loaded liposome) can remarkably reduce the side effects of DOX, Wu et al. combined Doxil with HBO to promote its antitumor efficacy for the first time (**Figure 2**a).[42] HBO relieved tumor hypoxia and led to the

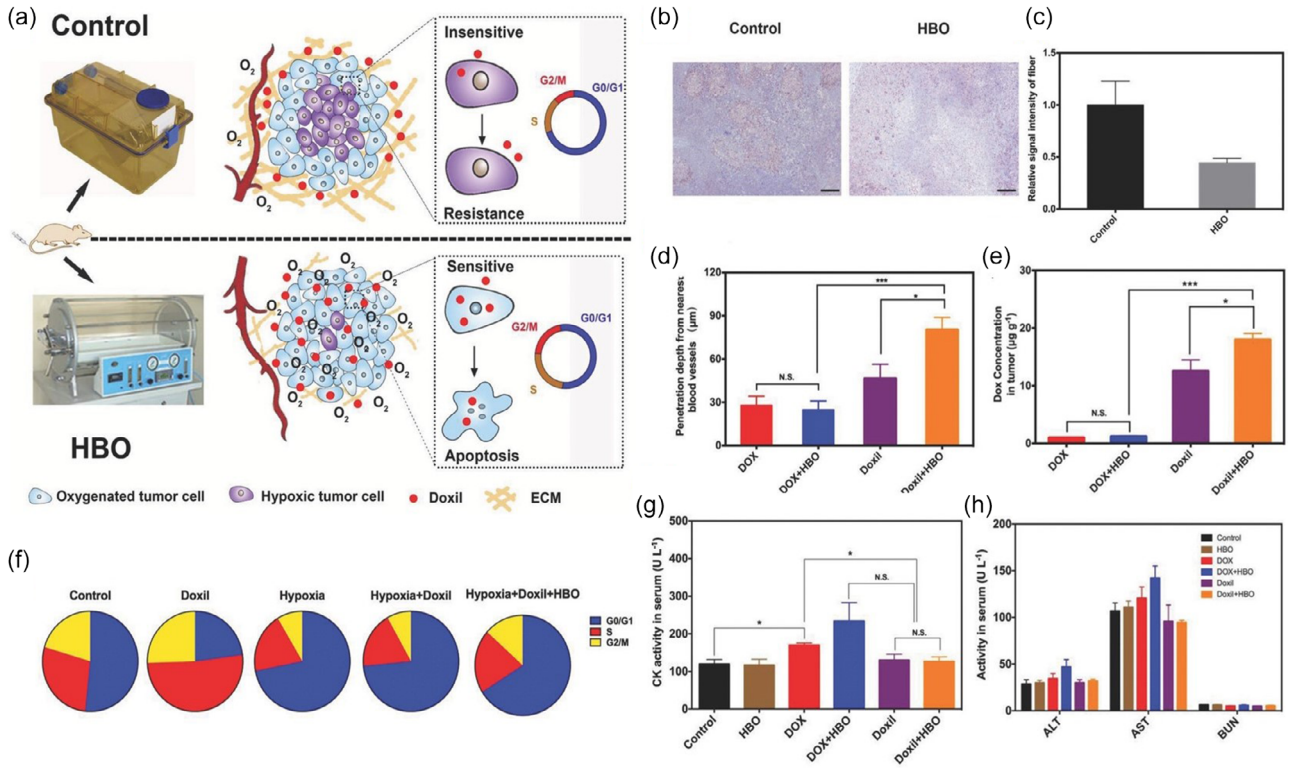

Figure 2. a) Schematic illustrating the mechanism of HBO-boosted Doxil efficacy. b) Masson's trichrome staining results of tumor tissues from the mice with or without HBO treatment. Scale bars: 50 μm. c) Semiquantitative analysis results of b). d) Penetration depths and e) DOX concentrations of various DOX-containing drugs in the tumors from the mice after various treatments. f) Proportions of BEL-7402 cells in different cell cycles as determined by flow cytometry. Before analysis, the cells were subjected to different treatments as indicated. g) Activities of CK and h) ALT, AST, and BUN in the serums of mice after various treatments. Abbreviations: ALT: alanine aminotransferase; AST: aspartate aminotransferase; BUN: blood urea nitrogen; CK: creatine phosphokinase; ECM: extracellular matrix. Reproduced with permission.[42] Copyright 2018, Wiley-VCH.

downregulation of HIF-1α. Considering that connective tissue growth factor (CTGF), which is a critical regulator of tumor collagen deposition, is mainly induced by HIF-1α,[43] the authors inferred that the collagen fiber deposition may be inhibited by HBO by interrupting the HIF-1α/CTGF/collagen I pathway and evaluated the influence of HBO on extracellular matrix (ECM). After HBO treatment, the fibril content in the tumor tissues was reduced by 44% compared to that in the group without HBO treatment (Figure 2b,c). Furthermore, CTGF and collagen I declined remarkably (by approximately 73% and 95%, respectively) after HBO treatment, indicating that HBO promoted the decrease of collagen fibril deposition in ECM by regulating the HIF-1α/CTGF/collagen I pathway. The combination of HBO and Doxil showed the highest tumoral Doxil content and the deepest tumor penetration in vivo, which was 1.73 and 2.87 times the penetration depth when using Doxil and DOX alone, respectively (Figure 2d,e), indicating that the tumoral accumulation of DOX was significantly enhanced by the combination of HBO and Doxil. Next, the sensitization mechanism by which HBO facilitates the antitumor effect of Doxil was explored. The rate of tumor cells that were stagnant in the G0/G1 phase after HBO treatment was lower than that without HBO treatment (Figure 2f), implying that the tumor cells became sensitive to Doxil, which caused DNA damage and arrested cells in the S phase, leading to cell apoptosis with the assistance of HBO. Thus, the antitumor efficacy of Doxil was noticeably amplified with the help of HBO, which was further confirmed in vivo by tumor inhibition experiments. Lastly, the side effects of combined HBO and Doxil treatment were studied. The activity of creatine phosphokinase (CK) in serum (an index of cardiomyocyte damage) was detected, and the results showed that the CK activity in the "HBO + Doxil" group was significantly lower than that in the "HBO + DOX" group, implying decreased cardiotoxicity of Doxil and HBO (Figure 2g). The activities of alanine aminotransferase (ALT, an index of liver function), aspartate aminotransferase (AST, an index of liver function), and blood urea nitrogen (BUN, an index of kidney function) in the sera of mice did not differ between the "Doxil + HBO" group and the control group (Figure 2h). In addition, tumor metastasis was not observed during the in vivo antitumor experiments. This work collectively indicated that HBO is an excellent strategy to enhance the antitumor efficacy of Doxil without causing side effects.

Moreover, Liu et al. employed Doxil and Abraxane (commercialized paclitaxel-loaded albumin) with HBO for efficient cancer therapy and cancer metastasis suppression via the alleviation of hypoxia and effective elimination of cancer stem-like cells (CSCs) (**Figure 3**a).[44] They discovered that in a CSC viability assay, the half-maximal inhibitory concentration (IC_{50}) of Doxil and Abraxane decreased remarkably with the help of HBO. Simultaneously, the hypoxia-mediated expansion of CSCs could be directly inhibited by HBO, suggesting that the combination of HBO and commercialized nanomedicines may be an efficient method to restrain CSCs. Additionally, collagen and fibronectin decreased prominently and the solid stress was reduced, as revealed in a previous study.[42] Given that the increase in solid stress caused by excessive ECM is a critical factor in the abnormal vasculature of tumors, HBO which can promote the degradation of ECM in tumor, may hold the capacity to normalize tumor blood vessels. To verify this assumption, the authors explored the structure and function of tumor blood vessels. The study revealed that with the assistance of HBO, the number of blood vessels, especially the small blood vessels, decreased, and the organization of blood vessels improved, illustrating that the structure of the vasculature was normalized (Figure 3b,c). Blood perfusion was also detected, and after HBO treatment, blood perfusion significantly increased depending on the treatment frequency, indicating the role of HBO in normalizing the function of the vasculature (Figure 3d,e). Subsequently, the delivery of commercialized nanomedicines was studied. As shown by previous studies, HBO treatment caused the degradation of excessive ECM and normalization of the vasculature to boost the accumulation and penetration of Doxil.[42] Furthermore, the authors revealed that the cell internalization of Doxil and Abraxane in 4T1 tumors was facilitated by HBO, which led to a higher late apoptosis ratio than that during the use of Doxil and Abraxane alone. These results suggested that combining commercialized nanomedicines (Doxil and Abraxane) with HBO is promising for annihilating CSCs because HBO can achieve enhanced penetration, accumulation, and cellular uptake of Doxil and Abraxane. Therefore, the influence of Doxil, Abraxane, and HBO on CSCs in an orthotopic tumor model was studied. After HBO treatment alone, the proportion of CSCs was reduced, and when combined with Doxi, approximately 97% of the CSCs were eliminated (Figure 3f,g), confirming that HBO directly inhibited CSCs and enhanced the efficacy of Doxil and Abraxane for CSC annihilation in tumor tissues. Finally, tumor metastasis was reduced by HBO treatment because CSCs are a major factor in tumor metastasis, and HBO can inhibit CSCs. This study further demonstrated that HBO can increase the cancer treatment efficacy of commercialized nanomedicines and clarified the possible mechanism of HBO-enhanced nanomedicine-based cancer treatment.

Inspired by the finding that the antitumor effect of Abraxane is enhanced by HBO,[44] Wang et al. combined HBO with a first-line drug dosage, Abraxane plus gemcitabine (GEM), to promote its therapeutic effect in pancreatic ductal carcinoma (PDAC) treatment (**Figure 4**).[45] They noticed that both the transcription and expression of cancer-associated fibroblast (CAF)-related markers, including fibroblast activation protein (FAP) and α-smooth muscle actin (α-SMA), were reduced remarkably by HBO application, indicating that CAFs might be affected significantly by HBO. Additionally, the expression of α-SMA was proportional to that of HIF-α, implying that HBO inhibited the formation of CAFs by alleviating hypoxia in PDAC tumors. Furthermore, the quantity of transforming growth factor-β1 (TGF-β1) generated by PDAC cells also decreased after HBO treatment, compared with that in a hypoxic condition, leading to the inhibition of fibroblast proliferation and α-SMA and FAP synthesis. Thus, HBO suppressed CAF formation by relieving hypoxia and eliminating the interactions between CAFs and cancer cells. Considering that one main function of CAFs is the synthesis of ECM components (such as fibronectin and collagen I), the authors studied whether HBO was effective in regulating the ECM in a PDAC tumor. They confirmed that the transcription and expression of ECM components, such as fibronectin and collagen I, decreased after HBO treatment, in line with previous findings.[42,44] Notably, the expression of collagen I was also proportional to that of α-SMA, illustrating that HBO decreased ECM

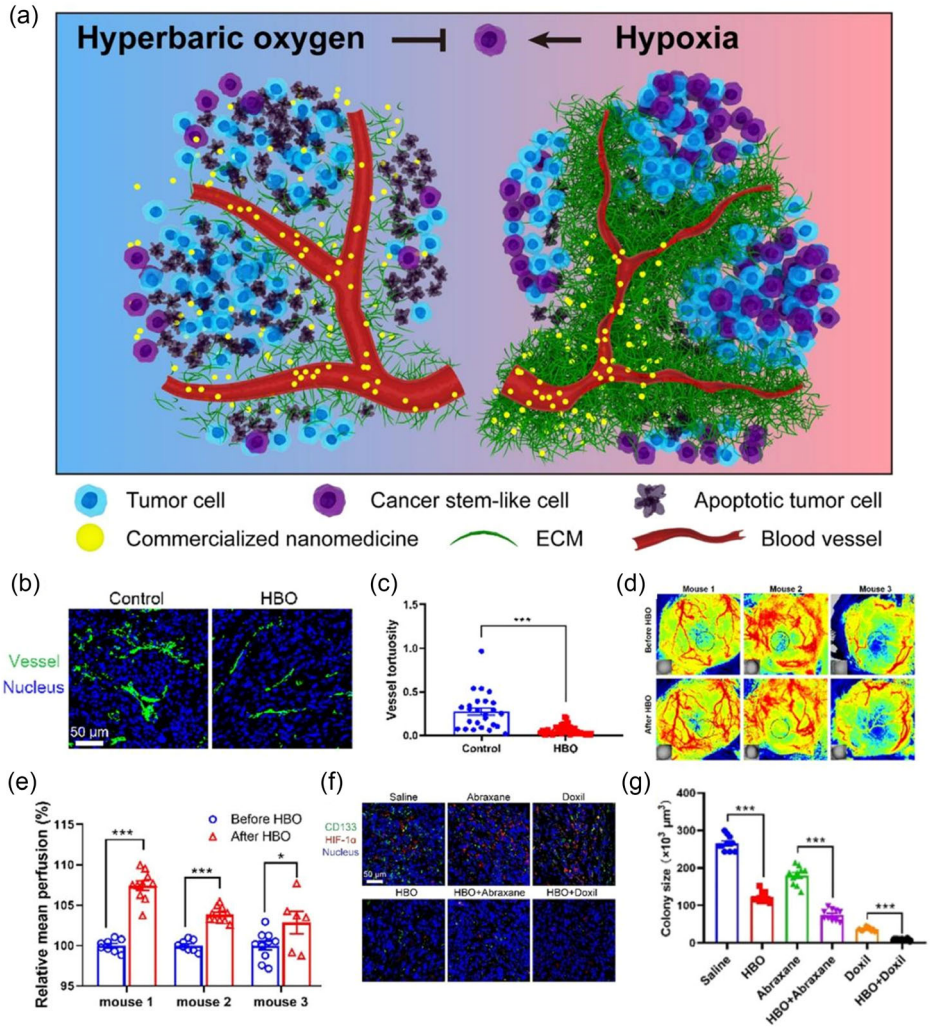

Figure 3. a) Schematic indicating the mechanism of HBO-facilitated enhancement of commercialized nanomedicine (Doxil and Abraxane) therapy in eliminating CSCs and suppressing tumor growth. b) Immunofluorescence staining results of the blood vessels in tumor with or without HBO treatment. c) Quantification results of the blood vessel tortuosity in tumor with or without HBO treatment. d) Blood perfusion images in tumor before and after HBO treatment. e) Relative mean blood perfusion in tumor. f) Immunofluorescence staining results of CSCs ($CD133^{+}$). g) Colony sizes of CSCs in the tumor spheroids, which were formed in fibrin gels. Reproduced with permission.[44] Copyright 2021, Elsevier.

via the inhibition of CAFs. Moreover, the depletion of ECM caused by HBO led to the regulation of PDAC tumor mechanics. The mean Young's modulus in the "HBO + GEM + Abraxane" group decreased remarkably compared with that in the "GEM + Abraxane" group. The structure and function of the tumor vasculature in PDAC were also regulated by HBO treatment, similar to that observed in the previous study.[44] Moreover, the accumulation, penetration, cytotoxicity, and apoptosis rate induced by the combination of GEM and Abraxane in PDAC were augmented significantly by HBO, which implied that HBO-mediated tumor ECM modification was beneficial for chemotherapy. Meanwhile, both CSCs and CAFs decreased in the groups treated with HBO, and a positive correlation was detected between CSCs and CAFs, suggesting that CAFs are also key factors for CSC growth. Collectively, using HBO with "GEM + Abraxane" boosted the antitumor efficacy and enhanced the metastasis inhibition effect of the therapy by suppressing CAFs, regulating tumor ECM, and modulating CAF-mediated CSC niche for eliminating CSCs. Finally, the combination of HBO and "GEM + Abraxane" showed only ignorable side effects, suggesting that this combination is a safe strategy for PDAC treatment. This study investigated the mechanism of HBO-facilitated nanomedicine therapy in detail, revealing that CAF suppression is also critical in PDAC treatment, and provided a new strategy for clinical PDAC treatment. These results[39,42,44,45] collectively demonstrated that combining nanodrugs with HBO is a promising and safe strategy to potentiate the therapeutic efficacy of nanomedicines that have been approved for clinical cancer treatment and are worthy of future clinical trials.

In general, HBO facilitates the therapeutic effects of chemotherapy by relieving tumor hypoxia. In nanomedicine-based

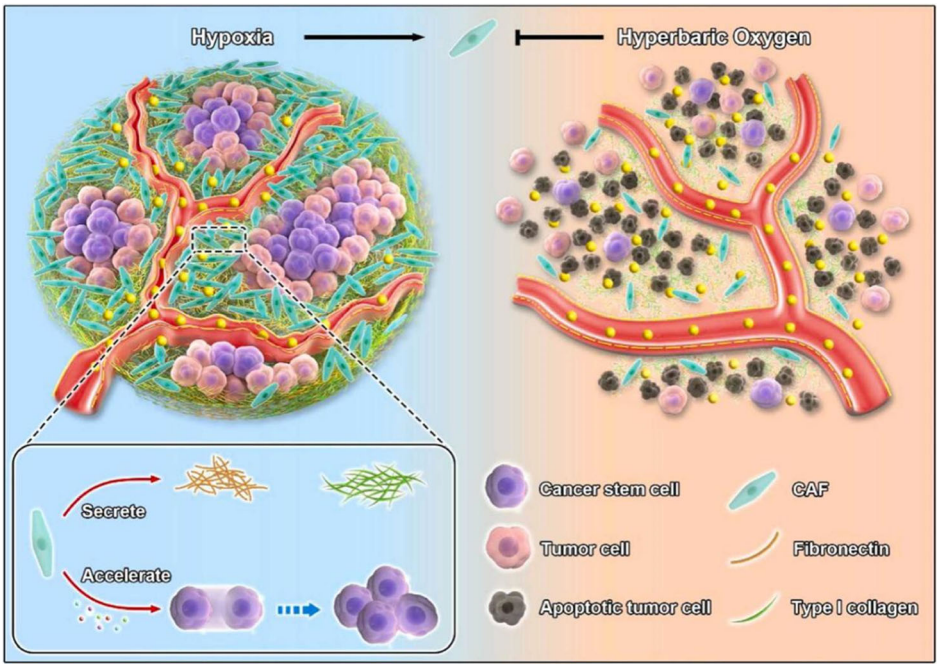

Figure 4. Schematic depicting the effects of HBO in potentiating the efficacy of Abraxane- and GEM-based therapy against PDAC. Reproduced with permission.[45] Copyright 2022, Elsevier.

chemotherapy, HBO can also enhance its efficacy via the inhibition of CAFs, depletion of excessive ECM, and direct or indirect suppression of CSCs (**Figure 5**). As an FDA-approved therapeutic agent for mitigating hypoxia, HBO is more advantageous in terms of its low cost, simple operation, ability to ensure direct and controllable oxygen supply, and noninvasiveness than other strategies that can relieve hypoxia in tumor tissues. The safety of the combination of HBO and some commercialized nanomedicines has also been confirmed by animal experiments. Thus, the combination of these two strategies (HBO and commercialized nanomedicines) is more likely to be applied in clinical cancer treatment than combining commercialized nanomedicines with other O_2-supply strategies (such as transporting oxygen to tumors via hemoglobin or decomposing endogenous H_2O_2). However, HBO has some side effects, such as oxygen poisoning and barotrauma. Therefore, when HBO is used to relieve tumor hypoxia, personalized treatment is necessary to achieve optimal efficacy without noticeable side effects.

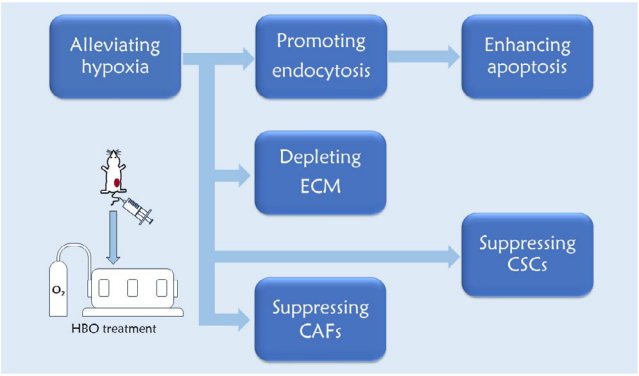

Figure 5. Schematic illustrating the main effects of HBO in nanomedicine-based chemotherapy. Abbreviations: CAFs: cancer-associated fibroblasts; CSCs: cancer stem-like cells; ECM: extracellular matrix.

2.2. HBO-Facilitated Chemodynamic Therapy

Chemodynamic therapy (CDT), which utilizes Fenton or Fenton-like reactions to yield •OH in tumor tissue, is a widely used novel cancer therapy with the advantages of high tumor selectivity, few side effects, and the ability to induce strong immunogenic cell death (ICD).[46–52] However, the therapeutic effect of CDT is limited by the H_2O_2 content in the tumor tissue, which is insufficient for realizing effective CDT.[46,52,53] Therefore, increasing the level of H_2O_2 is a promising strategy to improve the efficacy of CDT.

Glucose oxidase (which can be abbreviated as GOD or GOx) is an oxidoreductase that catalyzes glucose oxidation to generate H_2O_2 in the presence of oxygen (as well as H_2O). Hence, GOD can be used to increase the content of H_2O_2 in the tumor tissue. Given that oxygen is needed for glucose oxidation catalyzed by GOD and that HBO can improve the oxygen content in the tumor region, developing CDT-based nanomedicines with GOD and combining these nanomedicines with HBO is an excellent approach to enhance the treatment efficacy of CDT. For example, Xiong et al. designed a pH-sensitive multifunctional cascade bioreactor HCG, which was fabricated through the one-step self-assembly of copper ions (Cu^{2+}), GOD, and a hydrazone-bond-linked hydroxyethyl starch and DOX conjugate (HPD) (**Figure 6**).[54] Subsequently, HCG was combined with

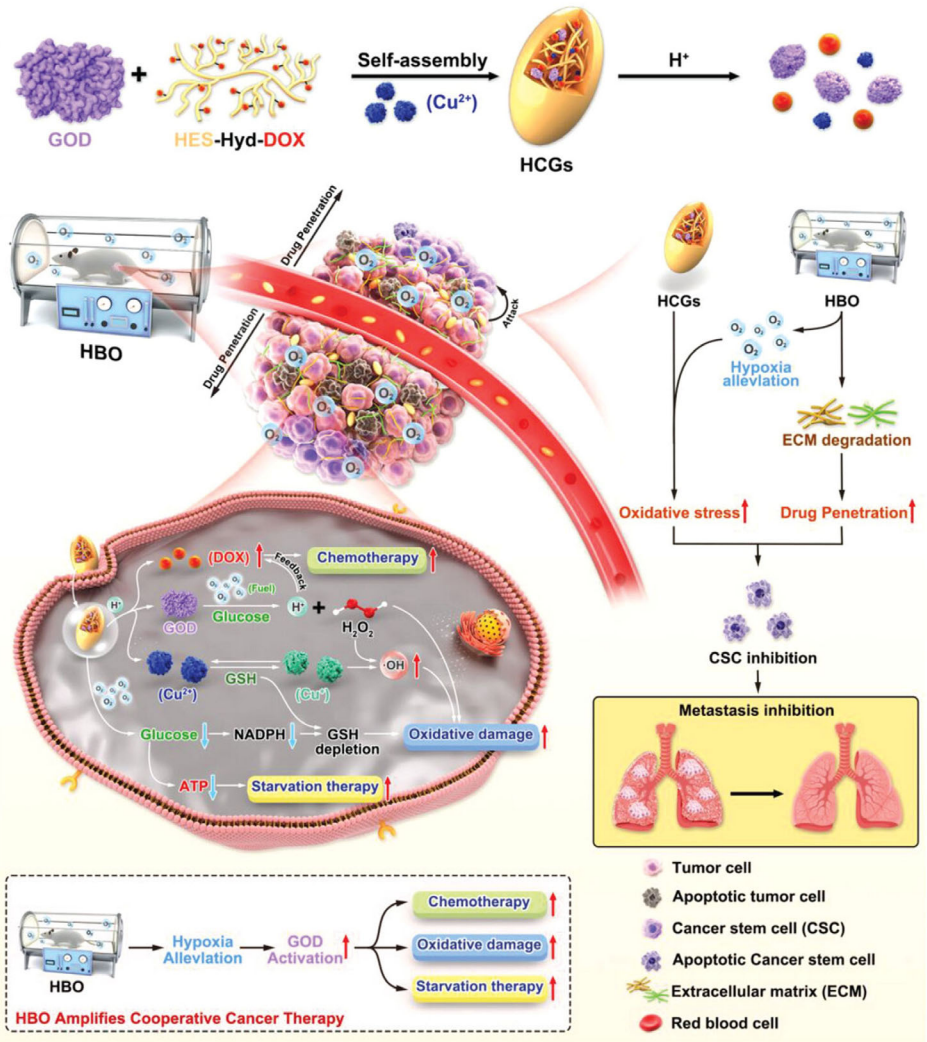

Figure 6. Schematic illustrating the production and therapeutic mechanism of HCG and the adjuvant effect of HBO. Reproduced with permission.[54] Copyright 2023, Wiley-VCH.

HBO to boost chemodynamic therapy/starvation therapy/chemotherapy. In this nanoplatform, HPD served as the framework and stabilizer of HCG and enabled acid-responsive DOX release for chemotherapy. Cu^{2+} could be effectively reduced to Cu^{+} by glutathione (GSH), which is overexpressed in tumor cells. Cu^{+} could then catalyze H_2O_2 in tumor cells to produce •OH with high cytotoxicity for efficient CDT. The oxidation of glucose and the production of gluconic acid and H_2O_2 catalyzed by GOD decreased the pH of tumor tissues, promoting acid-responsive DOX release of HPD and generating H_2O_2 for facilitating Cu^{+}-mediated CDT. Moreover, HBO could overcome the intrinsically hypoxic TME to activate the GOD-driven bioreactor HCG and diminish excessive tumor ECM to facilitate the exposure of CSCs to HCG. During the treatment, 4T1 cells treated with HCG and HBO showed lower viability, ATP content, and pH than those under hypoxic conditions. This was attributed to the supply of adequate O_2 to the tumor cells in the presence of HBO, facilitating GOD-mediated catalytic reactions and starvation of cancer cells with the generation of gluconic acid. Moreover, the HBO-treated tumor cells showed a significantly higher ROS level than those in the hypoxia group because HBO could activate GOD, improve the production of H_2O_2, and drive the subsequent Cu^{+}-mediated Fenton-like reaction to generate •OH. Considering that CSCs play crucial roles in cancer initiation, proliferation, invasion, recurrence, and metastasis, the authors evaluated the ability of HCG to eliminate CSCs. When treated with both HCG and HBO, breast cancer stem cells (BCSCs) exhibited substantially decreased viability compared with those incubated under hypoxic conditions. Meanwhile, the IC_{50} was 0.51 μg/mL and 1.66 μg/mL (based on DOX) for the "HCG + hypoxia + HBO" (hereinafter referred to as "HCG + HBO") group and the "HCG + hypoxia" (hereinafter referred to as "HCG") group, respectively, indicating that HBO assisted HCG in extinguishing BCSCs. Subsequently, the in vivo antitumor effect of HCG was further enhanced when HBO was supplemented, and the tumor inhibition rate increased

from 46.7% in the HCG group to 68.0% in the "HCG + HBO" group. Furthermore, more apoptotic tumor cells and fewer proliferating tumor cells were observed in the "HCG + HBO" group than in other groups. To explore the treatment mechanism of "HCG + HBO", the authors examined some critical biomolecular indicators after treatment. HIF-α was significantly downregulated after HBO treatment, revealing that tumor hypoxia was alleviated successfully. Subsequently, HCG led to a sharp increase in H_2O_2 levels in tumor cells (3.1 times higher than that in the control group), which implied that HBO also activated the catalytic oxidation of GOD in vivo by relieving tumor hypoxia. They then explored ROS levels in tumor tissues. As expected, the "HCG + HBO" group exhibited a higher ROS level than that in other groups. These results showed that HBO had a strong ability to alleviate tumor hypoxia and activate GOD within HCG, exacerbating oxidative stress in tumor tissues. The "HCG + HBO" treatment could also effectively eradicate CSCs in vivo because HBO could not only relieve tumor hypoxia but also degrade the ECM in tumor tissues to facilitate the exposure of CSCs to HCG, thus efficiently suppressing tumor growth and metastasis. Furthermore, the "HCG + HBO" group showed lower pulmonary metastasis than did other groups due to the decrease of CSCs in this group. This work employed HBO as the activation factor of a GOD-driven bioreactor and provided a new strategy for controlling the activation of nanomedicines via exogenous stimulation (i.e., HBO). Considering that GOD (or other enzymes, such as lactate oxidase and cholesterol oxidase) could also increase H_2O_2 levels in tumors with the assistance of HBO, more studies on combining HBO with GOD-containing drugs to realize efficient CDT may be reported in the future.

Collectively, HBO can act as an enhancer of CDT-based nanomedicines with GOD by providing oxygen to the tumor region, enhancing the oxidation of glucose, and promoting the generation of H_2O_2 for CDT. Compared to other tumor hypoxia-relieving strategies, HBO can modulate the CDT efficacy of nanomedicines containing GOD or other enzymes on demand during the treatment period. However, because HBO can improve the oxygen content not only in the tumor region but also in other tissues and organs, GOD (or other enzymes such as lactate oxidase and cholesterol oxidase) may overproduce H_2O_2 out of the tumor; thus, CDT-based nanomedicines with GOD may also produce •OH outside the tumor, which may lead to injury to normal tissues and organs. Therefore, the safety of combining CDT-based nanomedicines containing GOD and HBO should be considered before clinical application.

2.3. HBO-Facilitated Phototherapy

Phototherapy can be divided into two categories: PDT and photothermal therapy (PTT). PDT uses a photosensitizer (PS) and laser illumination to generate ROS for tumor treatment. When activated by NIR or visible light, the PS is changed to an excited state, mediating the generation of ROS and eliminating tumor cells.[55] Hence, the efficacy of PDT relies on the oxygen concentration in tumor tissues and is limited by hypoxia in tumor tissues.[4] As an adjunct therapy to alleviate tissue hypoxia, HBO can be employed to enhance the efficacy of PDT.[28,56,57] For example, the effect of PDT on the ablation of deep-seated tumors is limited by tumor hypoxia and the lack of sufficient PSs in cancer cells that are away from tumor blood vessels. To overcome this disadvantage, Li et al. developed a therapeutic strategy combining upconversion nanophotosensitizers (UNPSs) with HBO to reshape the ECM for potentiated tumor PDT (**Figure 7**).[56] UNPSs have two components: upconversion nanoparticles (UCNPs) as the light transducer and rose bengal (RB) as the ROS-generating PS. UCNPs can act as light transducers to activate RB because they can convert NIR light into ultraviolet (UV) or visible light. When UNPS-based NIR-induced PDT was combined with HBO, the tumor exhibited remarkably delayed growth, and the tumor tissues displayed noticeable cell necrosis and apoptosis. These results confirmed that HBO markedly elevated the efficacy of UNPS-based NIR-mediated PDT. Subsequently, the authors explored the mechanism of HBO-assisted PDT. They found that the content of HIF-1α in the groups treated with HBO was lower than that in other groups as expected, and the generation of ROS by UNPSs under NIR illumination was promoted when HBO was applied. Moreover, the amount of collagen fibers in the ECM of mice in the "UNPSs + NIR + HBO" group was 14.6 and 9.9 times less than that in the "phosphate-buffered saline (PBS)" group and the "UNPSs + NIR" group, respectively, and the penetration depth of UNPSs in the "UNPSs + NIR + HBO" group was 230 μm, which was deeper than that without HBO. These studies revealed that HBO-facilitated PDT is related to ROS-induced dissociation of collagen in tumors. The use of HBO improved the concentration of oxygen within tumors and thus enhanced the generation of ROS produced by UNPSs with NIR irradiation in the TME. The excessively generated ROS eliminated tumor cells and broke down collagen in the TME. Subsequently, in tumor tissues the perfusion of blood was enhanced and the interstitial fluid pressure was reduced, resulting in improved infiltration of UNPSs and oxygen diffusion in solid tumors. These cooperative effects ensure better elimination of tumor cells in solid tumors, resulting in better treatment effectiveness than that achieved by the application of PDT alone. This study provides an important reference for employing HBO to enhance the efficacy of nanophotosensitizer-mediated PDT.

PTT is an irradiation-dependent therapy that exploits photothermal agents to produce adequate heat via light irradiation to ablate tumors.[58,59] Combining HBO with probiotic-mediated PTT is an effective strategy for enhancing its effects. For example, Xiao et al. used an engineered probiotic Nissle 1917 (termed EcN-T), which could massively produce tyrosinase when exposed to NIR light to generate melanin in tumor tissues to facilitate PTT (**Figure 8**).[60] Owing to the inherent tumor hypoxia targeting ability of EcN-T, the probiotic could accumulate and quickly proliferate in tumor tissues, leading to the production of tyrosinase for melanin biosynthesis within the tumor after NIR light exposure. To overcome the limitation that the oxidative polymerization of L-tyrosine by tyrosinase for melanin production is suppressed by the hypoxia in TME, HBO was administered to elevate the oxygen content in tumor tissues to enhance melanin generation. The melanin content in the tumor tissues of the mice subjected to EcN-T therapy with HBO was 3.6 times higher than that in the PBS group, which demonstrated the ability of EcN-T in enhancing melanin biosynthesis with the assistance of HBO, providing an excellent basis for the application of EcN-T and

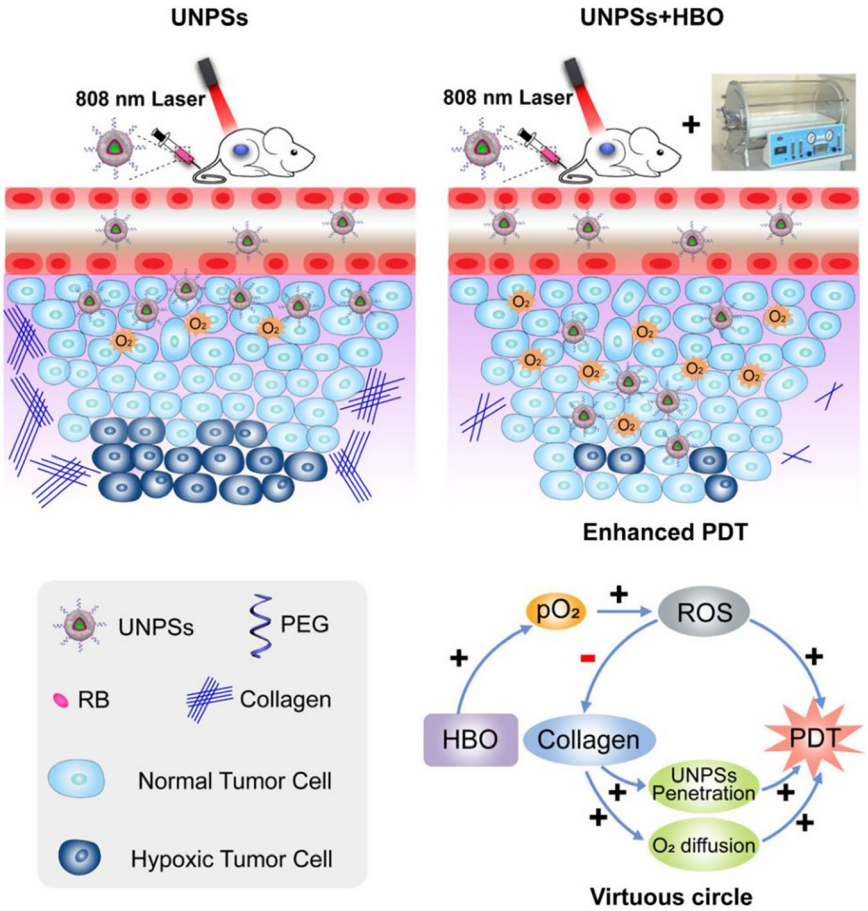

Figure 7. Schematic illustrating HBO-facilitated PDT mediated by UNPSs. Reproduced with permission.[56] Copyright 2018, American Chemical Society.

HBO in PTT. Moreover, to explore whether HBO influenced the proliferation of EcN-T, the authors separated EcN-T from tumor-bearing mice before and after HBO treatment and spread it on lysogeny broth plates. They observed that the EcN-T concentration in the tumor was higher after HBO treatment than that without HBO treatment (2.83×10^9 CFU g^{-1} vs 1.22×10^9 CFU g^{-1}), which indicated that the proliferation of EcN-T could be facilitated by HBO treatment. Subsequently, the antitumor effect of EcN-T was investigated. The tumor temperature in the group of "EcN-T + HBO + NIR" increased markedly to 55 °C within 10 min, and such a remarkable PTT effect of "EcN-T + HBO + NIR" led to a tumor inhibition rate of 99.3% because of the higher production of melanin in tumors. Furthermore, compared with the tumor tissues in other groups, the tumor tissues in the "EcN-T + HBO + NIR" group exhibited a noticeably lower tumor cell density and increased tumor cell apoptosis, which was consistent with the above result. This study employed HBO to enhance the efficacy of EcN-mediated PTT, providing a strategy to enhance engineered probiotic-mediated therapy.

Considering that heating the tumor at 40–42 °C can accelerate the blood flow and increase the partial pressure of oxygen within tumor,[61] combining mild PTT with HBO may be a potential strategy to enhance the effect of chemotherapy. Therefore, Zeng et al. employed TMZ/PSi NPs and HBO to suppress the growth of gliomas and decrease glioma stem-like cells.[62] They noticed that when treated with TMZ/PSi NPs, PTT, and HBO, the viability of NCH-421K cells (a glioma stem cell line) was remarkably reduced, indicating that PTT and HBO boosted the sensitivity of glioma stem-like cells to TMZ/PSi NPs. In vivo antitumor experiments also demonstrated that TMZ/PSi NPs combined with PTT and HBO exhibited a higher tumor inhibition rate than those exhibited by other groups. Moreover, glioma proliferation was lower in the "TMZ/PSi NPs + HBO + PTT" group than in the other groups. Collectively, these results illustrated that the combination of HBO and PTT can boost the efficacy of TMZ/PSi NPs for glioma treatment.

In summary, HBO is an effective adjuvant therapy for PDT. HBO can more effectively decrease the dense ECM in tumors, promote the penetration of PSs, and enhance the efficacy of PDT than some other strategies to relieve tumor hypoxia because HBO can promote the decrease of dense ECM in tumors via two different pathways (decreasing collagen directly and promoting the generation of ROS). However, the efficacy of one-time HBO treatment is weak and not persistent. Thus, to realize effective PDT, repeated HBO treatment is sometimes required, which is likely to cause side effects, such as oxygen poisoning or barotrauma. In addition, although the efficacy of PTT is not limited by

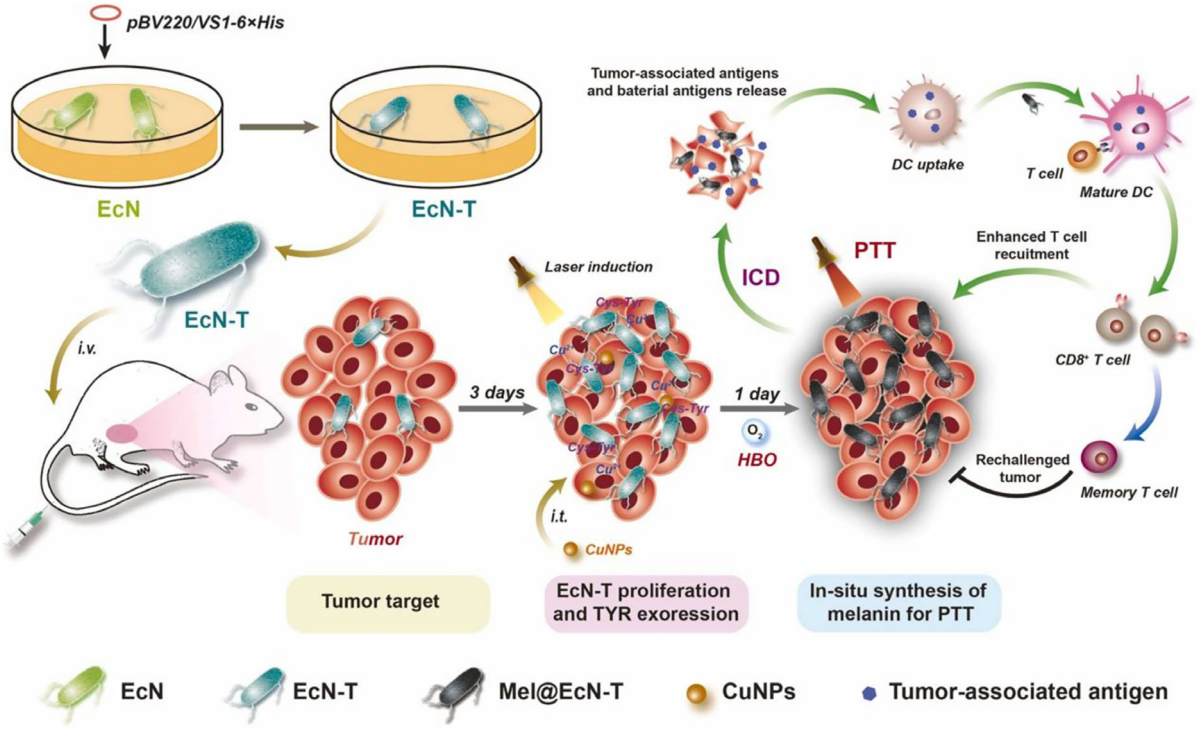

Figure 8. Schematic illustrating HBO-facilitated EcN-mediated PTT. Reproduced with permission.[60] Copyright 2022, Elsevier.

hypoxia in tumors, the combination of HBO and PTT can play a significant role in enhancing chemotherapy, implying that combining chemotherapy with HBO and PTT is another promising strategy for achieving satisfactory cancer treatment outcomes.

2.4. HBO-Facilitated Cancer Immunotherapy

Immunotherapies such as chimeric antigen receptor (CAR)-T cell therapy and immune checkpoint blockade (ICB) therapy, including programmed cell death protein 1 antibody (PD-1 Ab) therapy, have achieved significant progress in some cancer treatments.[63,64] However, the therapeutic efficacy of these strategies is remarkably weakened by hypoxia and immune suppression induced by hypoxia in the tumor tissue.[65,66] In addition, the infiltration of CAR-T cells or PD-1 antibodies is prevented by the dense ECM in solid tumors. Given that HBO can alleviate tumor hypoxia and promote ECM degradation,[42,45] Liu et al. used HBO to enhance PD-1 Ab-induced immunotherapy against a wide spectrum of solid tumors with abundant stroma, such as HCC, PDAC, and triple-negative breast cancer (TNBC) (**Figure 9**).[67] They found that HBO facilitated the antitumor efficacy of PD-1 Abs in all the types of tumors mentioned above, and the median survival was considerably lengthened. Moreover, the most noticeable tumor suppression efficacy was observed in subcutaneous H22 tumors treated with "HBO + PD-1 Ab" without the induction of notable toxicity. Thus, HBO enhanced the antitumor efficacy of PD-1 Ab in stroma-rich solid tumors, and combining PD-1 Ab with HBO was confirmed safe. The authors also found that after HBO treatment, the generation of collagen I, fibronectin, and collagen fibers declined remarkably, with a significant decrease in solid stress. Thus, the HBO-mediated modulation of abnormal mechanical TME was validated to occur by consuming collagen I, fibronectin, and collagen fibers in the ECM and releasing the solid stress of tumors. The accumulation of PD-1 Ab in tumor tissues with HBO treatment was higher than that without HBO treatment, and the extravasation and penetration of PD-1 Ab with HBO treatment were 2.6 times higher than those without HBO treatment, probably because of the HBO-mediated degradation of ECM. The effect of HBO on the infiltration of lymphocytes into the tumor was also explored. HBO treatment increased the infiltration of $CD4^+$ and $CD8^+$ T cells and lymphocytes into orthotopic H22 tumor tissues. Because hypoxia is a major factor that induces immunosuppression in solid tumors,[68] the authors also evaluated the influence of HBO on the TME and the immune responses induced by T cells. After HBO treatment, the ratio of M1 to M2 macrophages increased, and the number of regulatory T (Treg) cells decreased remarkably. Immunosuppressive cytokines like TGF-β and interleukins-10 (IL-10), which are mainly generated by Tregs, myeloid-derived suppressor cells, and M2 phenotype tumor-associated macrophages, reduced significantly in both tumor tissues and sera, and stimulatory cytokines like interferon-γ (IFN-γ) and IL-2 increased in the presence of HBO. These findings illustrated that HBO reprogrammed the TME from immunosuppressive to immunostimulatory. Furthermore, PD-1 Ab combined with HBO induced highly potent cytotoxic T lymphocytes in terms of activation, proliferation, and tumor eradication. This study thus revealed that HBO treatment represents a robust approach capable of reprogramming the immunosuppressive TME and inducing intense antitumor immune responses to boost the efficacy of immunotherapy.

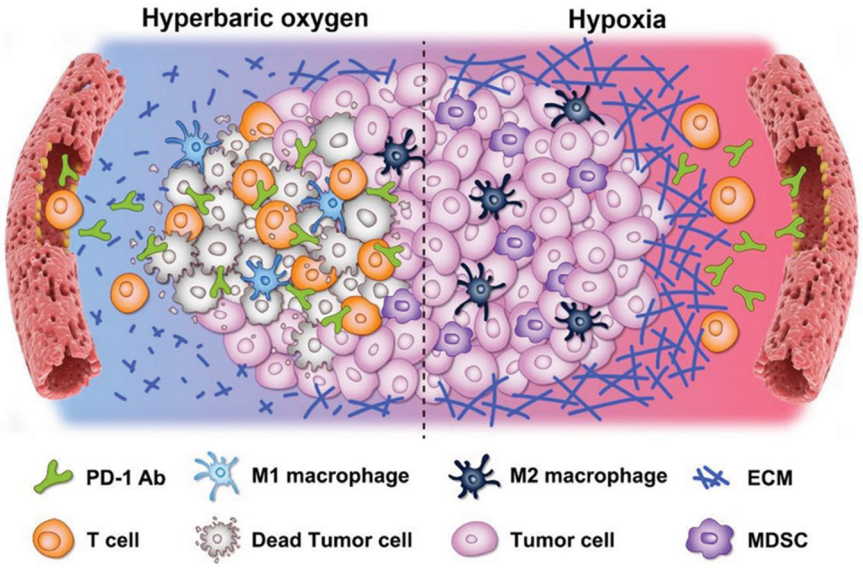

Figure 9. Schematic illustrating the HBO-facilitated PD-1 Ab therapy via immunosuppressive TME regulation and excessive ECM depletion. Reproduced with permission.[67] Copyright 2021, Wiley-VCH.

The activation of the cyclic guanosine monophosphate-adenosine monophosphate (GMP-AMP) synthase-stimulator of interferon genes (cGAS-STING) axis could also promote the efficacy of PD-1 Abs.[69] However, cGAS expression is inhibited by hypoxia in solid tumors. Li et al. combined teniposide and HBO to achieve maximum cGAS-STING activation in HCC.[70] They observed that teniposide-mediated cGAS-STING activation was remarkably inhibited but recovered upon relieving the hypoxia. When HBO was administered with teniposide, HIF-1α degraded owing to the alleviation of hypoxia, and the expression of the indicator of the cGAS-STING signaling activation was higher than that in the teniposide group, indicating that HBO assisted teniposide in efficiently triggering cGAS-STING signaling in tumors by relieving hypoxia. To demonstrate the local immune activation of tumors induced by teniposide and HBO, the authors identified the immune cells that infiltrated the tumor tissue. The infiltration rate of M1-like macrophages increased, whereas that of M2-like macrophages decreased significantly. Moreover, the maturation of dendritic cells (DCs) increased, suggesting that HBO could enhance teniposide-mediated, cGAS-STING-dependent nuclear factor kappa-B (NF-κB) and type I interferon (IFN-I) signaling activation in HCC cells, which could recruit and activate DCs. Meanwhile, the infiltration of cytotoxic T cells was enhanced after "HBO + teniposide" treatment, and the function and proliferation of cytotoxic T cells also potentiated substantially compared with those in other groups. Finally, the growth of tumors in the "HBO + teniposide + PD-1 Ab" group was remarkably suppressed compared with that in the groups without HBO, illustrating that HBO sensitized HCC cells to "PD-1 Ab + teniposide".

In addition, combining ICB therapy with nanomedicines, which can lead to the ICD of tumor cells, is another strategy to enhance the efficacy of immunotherapy.[71,72] Li et al. designed a CDT-based nanoadjuvant platform (Se@OMV-GOx-HA), whose efficacy could be enhanced by HBO to facilitate programmed death ligand 1 antibody (PD-L1 Ab)-induced ICB therapy.[73] By introducing Na_2SeO_3 during the culture of EcN (a commonly used probiotic), the authors obtained selenium-containing NPs (SeNPs) in the form of outer membrane vesicles (Se@OMV). Se@OMV was then modified with GOx and hyaluronic acid (HA) to yield the final product Se@OMV-GOx-HA. In the presence of GSH and H_2O_2, Se@OMV served as a nanoenzyme that promoted electron transfer from GSH to O_2 to generate $\bullet O_2^-$. GOx also catalyzed the generation of H_2O_2. HBO alleviated hypoxia in the tumor to promote the production of H_2O_2 catalyzed by GOx, thus supplying O_2 and H_2O_2 for the generation of $\bullet O_2^-$ induced by Se@OMV, leading to intense ICD. Moreover, facilitated by HBO, the infiltration of cytotoxic T cells increased remarkably and the efficacy of PD-L1 Ab-induced ICB therapy was enhanced significantly. In this study, HBO was adopted to enhance the efficacy of the combination of CDT and PD-L1 Ab, revealing that combining HBO with a CDT-based nanomedicine is a promising strategy for enhancing the therapeutic effect of PD-L1 Ab. However, to the best of our knowledge, no study has employed HBO to boost the efficacy of immunotherapies other than PD-1/PD-L1 Ab therapy. Given that the infiltration of T cells is remarkably increased due to the depletion of excessive ECM and that some key processes of T cells, including activation and proliferation, and their functions such as tumor annihilation, are also enhanced when combining PD-1 Ab with HBO,[67] we conjecture that other kinds of immunotherapies, such as cancer vaccines, may also benefit from HBO, actualizing more effective cancer treatments.

The immunosuppressive TME, which is partly caused by hypoxia, can be more effectively regulated by strategies using HBO than some other strategies for mitigating tumor hypoxia. This is because the additional oxygen provided by HBO dissolves in the plasma, and oxygen molecules can easily diffuse into deep-seated tumors and mitigate hypoxia. Nevertheless, HBO may exacerbate the side effects of immunotherapy. For example,

immune-related pneumonitis is one of the side effects of ICB,[74] which may be aggravated by HBO. Thus, when combining HBO with immunotherapy, the side effects should be monitored to evaluate whether HBO is suitable for enhancing the efficacy of immunotherapy.

3. Conclusion and Perspectives

In this minireview, we introduce the recent research progress in HBO-facilitated cancer treatment. In the discussed studies, HBO played a role in relieving tumor hypoxia by increasing the oxygen content in the blood and inducing the degradation of excessive ECM, thereby promoting the permeation of therapeutic drugs, especially nanomedicines. Consequently, the treatment efficacies of chemotherapy, CDT, phototherapy (PDT and PTT), and immunotherapy could be enhanced (**Table 2**). Compared with other strategies that can alleviate tumor hypoxia, HBO, which is employed to relieve tissue hypoxia, has the advantages of low cost, simple operation, direct and controllable oxygen supply, noninvasiveness, and wide clinical application potential (**Figure 10**, also illustrating some disadvantages of HBO). Hence, HBO is a potential option for relieving hypoxia and amplifying therapeutic effects in clinical cancer treatment.

Although HBO can boost the therapeutic effects of multiple cancer treatment modalities, challenges do exist in its clinical application. Chemotherapy remains a major modality for cancer treatment, and small-molecule drugs are the most widely used chemotherapeutics. However, the side effects of small-molecule drugs such as the cardiotoxicity of DOX may be significantly amplified by HBO. Thus, before utilizing HBO to enhance cancer chemotherapy, extensive preclinical research is required to evaluate the safety of combining HBO with small-molecule drugs. Second, although commercialized nanomedicines, such as Doxil and Abraxane, were found to benefit from HBO with negligible side effects, only animal experiments were used in these investigations. This means that the situation may be different when applying commercialized nanomedicines and HBO to humans. Third, although HBO facilitates the biosynthesis of engineered probiotics, it can also enhance their proliferation.[60] Therefore, inappropriate HBO treatment may cause excessive proliferation of probiotics in vivo, resulting in unknown consequences. In summary, preclinical and clinical trials are needed to confirm the safety of the combination of HBO and nanomedicines/engineered probiotics in animals or humans before clinical use. Finally, given that HBO is a safe strategy for enhancing the efficacy of cancer treatment, combining HBO with other therapeutic modalities such as nuclide-based radiotherapy, sonodynamic therapy, magnetic hyperthermia therapy, and electrodynamic therapy is also worth exploring. Additionally, among all types of immunotherapies, only PD-1/PD-L1 Ab therapy has been combined with HBO. Thus, it is still necessary to explore whether other immunotherapies, such as cancer vaccines, can benefit from the assistance of HBO. We hope that this review

Table 2. Summary of the effects of HBO in different therapeutic modalities.

Therapy type	Agent	Cancer type	Effect of HBO	References
Chemotherapy	Sorafenib	HCC	Enhancing apoptosis	[33]
	IR-780	Bladder cancer	Increasing cellular uptake and promoting ROS generation	[34]
	Doxil	HCC, TNBC	Modulating cell cycle arrest and intracellular DOX concentration; decreasing collagen deposition at the tumor ECM.	[42,44]
	Abraxane	TNBC, PDAC	Exhausting ECM by suppressing CAFs, degrading collagen I and fibronectin, normalizing tumor vasculature, and promoting Abraxane efficacy in CSC eradication.	[44,45]
CDT	Cu^{2+}, GOx, and DOX	TNBC	Enhancing the generation of H_2O_2 and gluconic acid, promoting the release of DOX, and enhancing CDT induced by Cu^{+}.	[54]
Phototherapy	UCNPs and RB	TNBC	Promoting the production of ROS, enhancing the degradation of ECM, and promoting cell necrosis and apoptosis induced by ROS	[56]
	Engineered EcN	Hepatoma	Stimulating the proliferation of EcN and providing EcN with oxygen to produce melanin	[60]
	TMZ and PSi NPs	Glioma	Boosting the sensitivity of glioma stem-like cells to TMZ	[62]
Immunotherapy	PD-1 Ab	HCC, PDAC, and TNBC	Enhancing the accumulation of PD-1 Ab and T cells in tumor, regulating immunosuppressive TME, and eliciting robust immune responses	[67]
	Teniposide and PD-1 Ab	HCC	Assisting teniposide in efficiently triggering cGAS-STING signaling pathway and enhancing antitumor immunity induced by PD-1 Ab	[70]
	Se@OMV, GOx, and PD-L1 Ab	TNBC	Providing oxygen to produce H_2O_2 and facilitate $\bullet O_2^-$ generation and enhancing the efficacy of PD-L1 Ab.	[73]

Abbreviations: CAFs: cancer-associated fibroblasts; CDT: chemodynamic therapy; cGAS-STING: cyclic GMP-AMP synthase-stimulator of interferon genes; CSCs: cancer stem-like cells; DOX: doxorubicin; ECM: extracellular matrix; GOx: glucose oxidase; HCC: hepatocellular carcinoma; PDAC: pancreatic ductal adenocarcinoma; PD-1 Ab: programmed cell death protein 1 antibody; PD-L1 Ab: programmed death ligand 1 antibody; PSi NPs: porous silicon nanoparticles; RB: rose bengal; ROS: reactive oxygen species; Se@OMV: Se-loaded outer membrane vesicle; TME: tumor microenvironment; TMZ: temozolomide; TNBC: triple-negative breast cancer; UCNPs: upconversion nanoparticles.

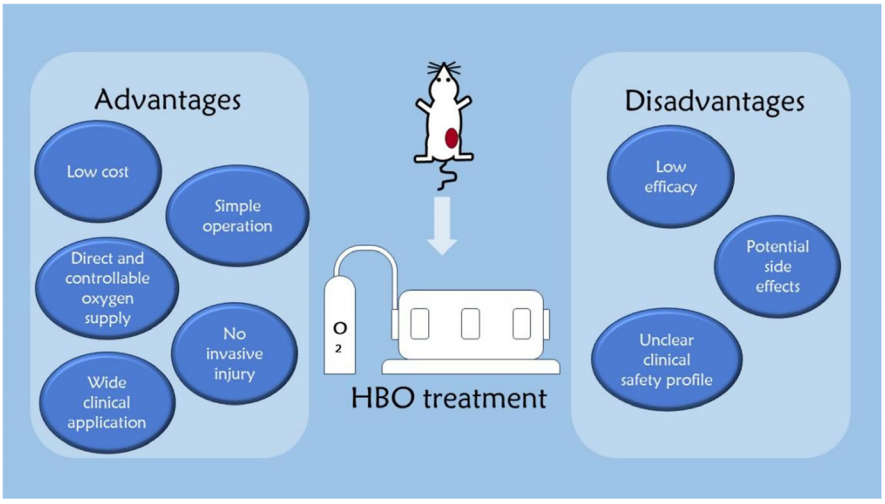

Figure 10. Schematic summarizing the main advantages and disadvantages of HBO.

provides references for further preclinical and clinical trials, enabling the combination of HBO and cancer therapy, especially the nanomedicine-mediated therapy, to be approved for clinical cancer treatment and benefit more patients with cancer.

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Conflict of Interest

The authors declare no conflict of interest.

Author Contributions

F.G.W. conceived the review topic. Z.H.L. wrote the manuscript. F.G.W., Z.H.L., and X.P.Z. revised the manuscript.

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