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Precision gas therapy by ultrasound-triggered for anticancer therapeutics

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Abstract

In recent years, ultrasound, as an external stimuli that can activate different types of naonocatalysts for therapy, has attracted extensive attention. One characteristic that makes ultrasound a particularly attractive trigger stimulus for nanomedicine is that it can be applied to the deep regions of the body noninvasively in a focused way. Different biological effects can be achieved by integrating ultrasound with nanocatalysts, and nanodroplets. Gas therapy, as a green antitumor treatment, has attracted substantial attention. The development of nanotechnology and nanomedicine has made gas therapy more precious by controlled release under internal, and outside factors and targeted delivery. In this article, an overview of ultrasound-based gas therapy on antitumor therapy has been provided. First, we explored the mechanism of ultrasound-triggered gas release. Second, we list the common gas release pathways and their mechanism in response to ultrasound activity. Third, exemplary instances of gas-generating facilities under ultrasound controllable are explored, with an emphasis on their originality and guiding principles. The impact of the gas-generating platform as a tumor therapy has also been considered. Finally, the difficulties and future prospects for this effective therapeutic approach are examined.

KEYWORDS
cancer therapy, gas-generating platform, gas therapy, ultrasound

1 | INTRODUCTION

In clinics, chemotherapy is regarded as the standard of care for cancer. With a 70% increase in use over the past 10 years, it is commonly used in cancer treatment. However, chemotherapy has several negative effects. Following systemic antitumor drug administration, traditional chemotherapy kills not only rapidly proliferating tumor cells, but also harms normal live cells, resulting in significant side effects as nausea, exhaustion, diarrhea, cardiotoxicity, fertility problems, and so forth. Moreover, after receiving multiple chemotherapy treatments, most patients may be afflicted with multidrug resistance (MDR) after repeated chemotherapy treatment. Up to date, the

MDR is the "bottleneck" in cancer chemotherapy.[1] As a result, chemotherapy for cancer generally has underwhelming therapeautic results. Chemotherapy for cancer has a relatively low success rate. With the development of technology, many novelty methods have been designed to augment the antitumor therapy efficiency. For example, the chemodynamic therapy (CDT),[2–5] sonodynamic therapy (SDT),[6–10] photothermal therapy (PTT),[11–13] photodynamic therapy (PDT),[14–17] radiotherapy (RT),[18] immunotherapy,[19–21] and starvation therapy (ST).[22] However, limited to the tumor microenvironment and the complexity, and heterogeneity of the cancers, each of the modality aboved has its drawbacks and advantages. In this regard, it is urgently necessary to figure out how to design novel and precise treatment strategies with few harmful medications.

As is well knowledge, a variety of gaseous molecules including nitric oxide (NO),[23] oxygen (O_2),[24] hydrogen sulfide (H_2S),[25] hydrogen (H_2),[26] and carbon monoxide (CO)[27] play a crucial role in many biological processes. Particularly, these molecules act as messengers that can cause specific physiologic or biochemical alterations in cells, tissues, or organisms.[28] Notably, several of them have unique therapeutic effects for a variety of diseases, including cardiovascular diseases, Alzheimer's disease, infections, cancer, neurotransmission, and others, as a result of their physiological regulation functions.[29] Especially, the gas plays an important role in anti-Warburg, thus protecting normal cells from damage while hindering cancer cells growth.[18,30] So gas therapy, namely exogenous administration of gaseous molecules, is desired for tumor therapy.[31,32] Gaseous molecules have many advantages over highly cytotoxic chemotherapeutic agents in the treatment of cancer. First, gaseous molecules may not cause drug resistance, which is a serious problem with chemotherapeutic drugs. Next, chemotherapeutic agents are too cytotoxic to healthy cells. Gaseous molecules, on the other hand, are safer and hardly have any adverse effects on healthy tissues. Gas therapy has therefore been created as a novelty "green" cancer treatment technique. While it should be understood that gas in the body is essentially a concentration dependent "double-edged sword." The concentration of gas molecules in the body during gas therapy is crucial for highly effective and biosafe anticancer therapies. Too high a concentration of gas in the blood is likely to lead to a underlying risk of toxicity, while too low a concentration of gas in diseased cells/tissues will not achieve optimal therapeutic efficacy. Ideally, the administrated gases could selectively accumulate on the diseased tissue rather than in the blood, and their concentrations in the disease-concentrated regions would remain in the therapeutic window for a long time.[33]

In this article, we propose the concept of precision gas therapy, that is, highly efficacious and low-toxic gas therapy. Therefore, to achieve selective accumulation of gaseous molecules in tumor tissues is a great challenge. To overcome these limitations, how to achieve targeted gas delivery as well as smart gas release is the key scientific problem of targeted gas therapy. On the whole, the methods mainly include 1) targeted gas delivery, usually by surface modification of targeted molecules.[34,35] 2) using nanocarrier to load gas and gas releasing moleculars.[36] 3) imaging-monitored gas therapy and multimodal therapy.[37] 4) controlled gas release by nanocatalysis. Among them, stimuli-triggered smart delivery systems were designed. There are two kinds of stimuli, namely endogenous and exogenous stimuli. In addition, the former mainly includes pH,[14,38,39] H_2O_2,[40] GSH,[35] and glucose.[41] The latter mainly contains light,[4] heat,[42,43] X-rays,[44,45] magnetic resonance imaging,[46] and ultrasound. Ultrasound stimulation, in particular, has attracted much more interest owing to its advantage of high tissue penetration and easy focus on localized region of the body. This presentation will focus on the mechanisms of ultrasound-stimulated gas release, recent significant advances in the design of gas molecules triggering ultrasound release, and the gas therapy will be discussed in detail in this presentation (Figure 1), which aims to provide a systematic understanding on the ultrasound triggered gas release.

2 | MECHANISM OF ULTRASOUND-TRIGGERED GAS RELEASE

Ultrasound technology is used for diagnostic and therapeutic purposes in the clinical due to its cheap characteristics, deep tissue penetration, safety, non-invasiveness, and ease

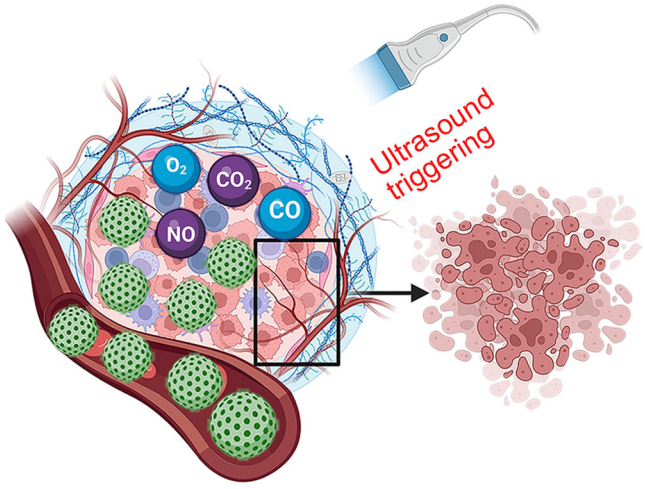

FIGURE 1 Schematic overview of ultrasound-triggered gas therapy. Under ultrasound irradiation, the gas released molecules are released gases, for example, NO, O_2, CO, CO_2, for tumor therapy.

of use.[47–49] Regarding uses of ultrasound-based therapy, it is possible to generate physical effects under the propagation of ultrasound, including acoustic fluid flow, pressure changes, cavitation, and heat therapy.[50,51] And sonication-responsive therapeutic agents deliver devices demand biocompatible components as carriers, enabling the release or activation of therapeutic drugs by specified protonation, hydration, phase changes, and changes in molecular or supramolecular conformation.[52] During ultrasound irradiation, the ultrasonically generated pressure oscillations affect the homeostasis of the drug delivery, concomitant thermal and mechanical effects are much more prominent for making further configurational changes.

2.1 | Mechanical effects

The sonication-induced mechanical influence, the most important underlying mechanism of the sonication effect, arises from steady cavitation resulting from the consecutive microbubbles oscillation or from inertial cavitation arising from the rapidly growth and burst of microbubbles.[53–56] As shown in Figure 2A, the solvent bubble underwent nucleation, growth, and collapse under the ultrasound.[57] Stable cavitation is commonly induced by ultrasound waves of low amplitude (power or intensity). The successive vibration of microbubbles produces the velocities in the flow that cause shear stress that disrupt the carrier, thus releasing the encapsulated drug.[58] It also creates transient pores in the cell membrane, causing the released drugs to flow into the cell.[59] Inertial cavitation appears when the strength of ultrasonication applied is sufficiently high. In particular, the collapse of microbubbles can produce shock waves under the condition of amplitudes more than 10,000 atmospheres.[60] In spite of the short duration of the burst wave, the resulting pressure ascent is enough to destroy drug carriers of low mechanical strength and cause them to release the cargo.[61] What's more, the microbubbles collapse neighboring the boundary experience nonuniformity, resulting in the shaping of high-velocity jet flow.[62] The shock waves generated by microjets could enhance the transparency of cell membranes and vascularity.[63]

Ultrasound can activate pharmaceuticals by rupturing the mechanochemically unstable connection within the carriers, as opposed to mechanically releasing the physically encapsulated drug. The majority of inorganic carriers are able to move a payload that is conjugated or adsorbed to the surfaces. Examples contain gold nanomaterials, carbon nanotubes, superparamagnetic iron oxide nanoparticles (SPIONs), and mesoporous silica particles (MSNPs). The payload is irreversibly removed by a cavitation period when exposed to low-frequency (20–90 kHz) ultrasound, as shown in Figure 2B.[52] When collapsing microbubbles produced by sonic cavitation are used in polymer mechanochemistry, they provide a mechanical elongational flow that stretches polymer chains and eventually causes the breakdown.[64] As a

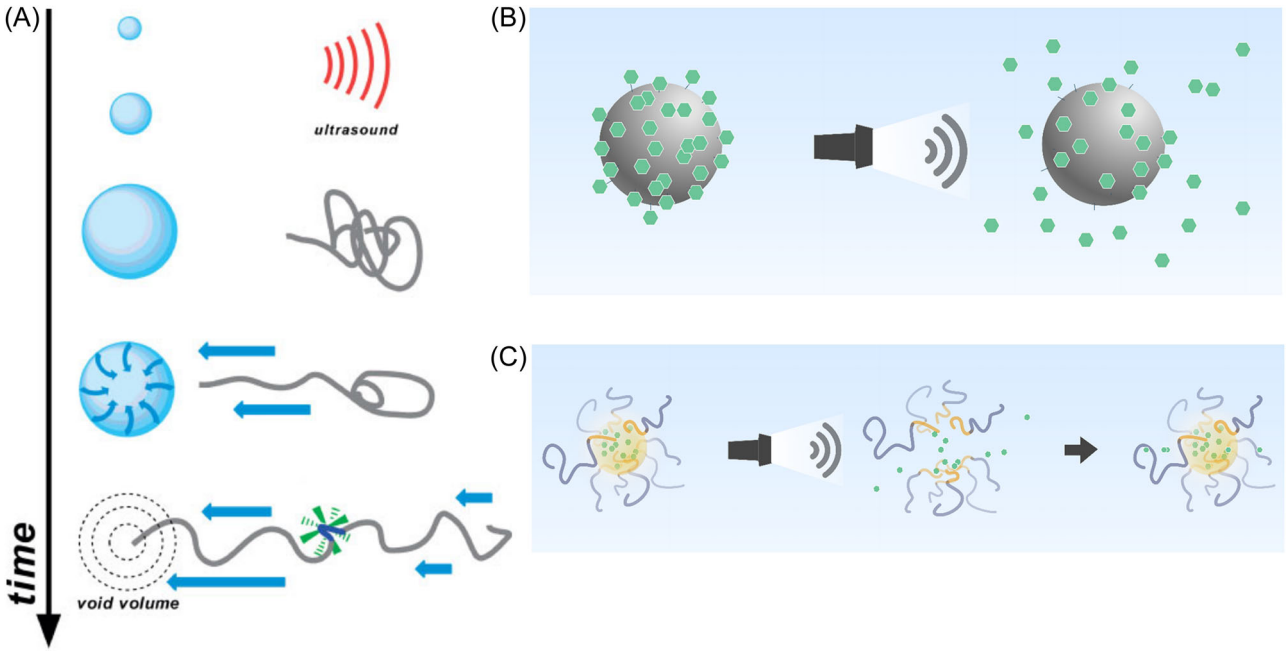

FIGURE 2 Mechanism of ultrasound-triggered gas release. (A) Cavitation-based ultrasound-triggered mechanochemistry schematic illustration. Reproduced with permission from reference.[57] Copyright 2012, Wiley. Irreversible (B) and (C) reversible releases of the payload from nanocarriers. Reproduced with permission from reference.[52] Copyright 2022, American Chemical Society.

result, some polymers' chemical characteristics can be modified at the level of molecular.[65] The idea was initially inspired by Staudinger's discovery of mechanical degradation of polymers in the 1930s.[66] Kost et al.[67] discovered that the ultrasound may trigger the small molecules release from extended chains of macromolecules later in 1989. Briefly, mechanosensitive polymers require the introduction of mechanical groups in the polymer chain, mechanically unstable bonds, a tension ring, or an isomerization bond in a force-sensitive molecular unit.[68] According to Moore et al.[69] reported, functionalized polyethylene glycol (PEG) was specifically broken at the weak azo bond in the chain center as a result of the ultrasound. Similarly, peroxide (O─O) bond, coordinated bonds, and disulfide (S─S) bonds have low dissociation energies and are susceptible to cleavage when subjected to successive molecular strain.[70] As shown in the Figure 2C, the polymeric micelles also temporarily release the payload when exposed to low-frequency ultrasound (20–90 kHz), but then reencapsulate the majority of the cargo after the ultrasound exposure has ended, suggesting a reversible release.[52] In contrast, it is difficult for sonomechanical force to cleave strong bonds with large dissociation energies, including carbon–oxygen (C─O) bonds, carbon–carbon (C─C) bonds, and carbon–nitrogen (C─N) bonds.[71]

2.2 | Thermal effect

During the transmission of ultrasonic wave in the media, part of the acoustic energy will be absorbed by the medium and converted into heat.[72] Additionally, the other two types of thermal effect can be produced via sonic cavitation. One is the persistent thermal effect brought on by the cavitation of bubbles during sustained oscillation, which can result in the sonic field region.[73] The other one is the immediate thermal effect, which occurs when a cavitation bubble suddenly bursts and causes localized overheating. When the focused ultrasound (FUS) or high-intensity focused ultrasound (HIFU) settings are set at moderate sound pressures, prolonged irradiation times, and high-duty cycles, the temperature elevation typically happens.

Ultrasound-responsive thermosensitive drug delivery systems should keep stable at physiological temperature (about 37°C), while quickly releasing the drugs in the tumor region (about 40–42°C) heated locally by ultrasound to minimize unintentional damage to surrounding healthy cells caused by long-term hyperthermia.[74] These requirments call for at least one material component to change swiftly and nonlinearly as the temperature rises. Nanoparticles (NPs), liposomes, or polymer micelles are common examples of such drug delivery methods.[75,76] Sensitivity to sound waves typically causes phase transitions in the lipid composition or conformational changes in the lipid bilayer in liposomes.[43,77] For example, the Dreher group designed a lysolecithin lipid containing low-temperature-sensitive liposome (LTSL) to transport the chemotherapy medication doxorubicin (DOX).[37] Once the temperature surpassed the phase transition temperature (about 40–42°C), the LTSL disintegrated after being exposed to HIFU radiation. The outcome showed that the DOX column in tumors cured with LTSL after HIFU irradiation was 3.4 times higher than without HIFU.

2.3 | Sonochemistry

Sonochemistry is the use of ultrasound effects (thermal and mechanical effects) to speed up or trigger chemical reactions.[78–80] Sonochemistry has many advantages, for example, the likelihood of changing the reaction pathway to get new selectivity, and improving the reaction rate.[81] The induction of chemical reactions under inertial cavitation may be due to the production of reactive oxygen species, which initiates a series of subsequent reactions, nanoscale heating in the vicinity of imploding bubbles, mechanical effects such as acoustic microfluidics (also associated with cavitation), or a combination of all these effects. For example, hydrogen gas was instantly produced from water, when integrated with core–shell nanoparticles modified by aluminum-oleic through sonochemistry.[82]

3 | ULTRASOUND STIMULI-RESPONSIVE GAS RELEASE

The mechanical effects, thermal effects, and sonochemistry effects could be used to design different kinds of smart catalysts that are able to trigger a series of reactions upon exposure to stimuli. And liposomes,[83] micelles,[78] polymeric particles,[84] and hybrid particles[84,85] sensitive to ultrasound have been developed for that purpose. What's more, ultrasound, one of the exogenous stimuli, is a non-invasive irradiation source with practical controllability and a high penetrating tissue depth. So integrating these intelligent materials with ultrasound, different therapy effects have been achieved. Thus ultrasound is considered an important trigger for gas-generating platform (Table 1).

3.1 | Ultrasound stimuli-responsive NO release

Conventional ultrasonically stimulated NO release is mediated out by wrapping NO gas directly into the

TABLE 1 Summary table of gas release under ultrasound.

Gas	Mechanism	References
NO	Bursting of NO microbubbles under the effect of ultrasonic cavitation	[86, 87]
	Activating NO donors under ultrasound	[88–96]
O_2	Bursting of O_2 microbubbles under the effect of ultrasound	[97–100]
CO	Activating CO-producing molecules under ultrasound	[101–104]
CO_2	Activating CO_2-producing molecules under ultrasound	[105, 106]

microbubbles, the main mechanism of which may be the bursting of microbubbles under the effect of ultrasonic cavitation.[86,87] For example, the perfluorocarbon (PFC) incorporated NO was fabricated, with centers synthesized by a disulfide-tagged amphiphilic block copolymer, which acts as a GSH-degradable macromolecular emulsifier during the oil-in-water emulsification process of PFC. The manufactured PFC nanodroplets are colloidal stable and capable of encapsulating NO and model drugs. When exposed to ultrasound and GSH, the incorporated drug molecules are released synergistically, while NO molecules are released passively but rapidly.[107] In addition, gas encapsulated liposomes also have been used for delivery. When combined with ultrasound, the gas-containing liposomes could achieve controllable gas release.[108] Expect for the directly encaspulated NO in to the chemistry, activating NO donors triggered by ultrasound is as well as an important method for ultrasound controllable NO production.

S-nitrosothiols (RSNO)-based donors, L-arginine (L-Arg), and *N*-diazeniumdiolate (NONOate)-based are the majority of NO donors.[88] Ultrasound-triggered NO donor, S-nitrosothiols (RSNO)-based donors, was designed on the surface of HSA to form SNO–HSA. And the paclitaxel drugs were encapsulated in the SNO–HSA, which are composed of NO-generating nanoplatforms, SNO–HSA–PTX (Figure 3A(a)). Interestingly, upon ultrasound irradiation, the groups of -SNO would rupture homolytically for NO release (Figure 3A (b)).[89] Similarly, Zhao et al.[90] recently synthesized a dual-responsive nanoplatform triggered by pH/ultrasound. More precisely, zeolitic imidazolate framework 8 (ZIF-8) was designed as a delivery tool for drugs due to its large numbers of surface area, adjustable pore size, and high loading ability. The homotypic cancer cell membrane coated ZIF-8 was simultaneously loaded with S-nitrosoglutathione (GSNO) and chlorin e6 (Ce6). Upon the ultrasound activated, the nanocomplex can lead to NO produced from GSNO and ROS generation from the sonosensitizers Ce6 when then nanotheranostic get to tumor tissues through the increased penetration and retention effect (Figure 3B). Additionally, the potential creation of highly reactive peroxynitrite (ONOO–) or other reactive nitrogen species (RNS) may improve the therapeutic potential of gas. In addition, the production of ROS during blood circulation was inhibited due to the large number of Ce6 loaded in ZIF-8, which may induce being aggregated and quenched. However, the acidic tumor microenvironment promoted the release of Ce6, effectively enhancing the efficacy of SDT. The experiments in vivo were further shown that the combined gas therapy and SDT had better therapy results than any one of the other single treatment modules. It is worth mentioning that O_2 depletion during SDT could exacerbate tumor hypoxia, which in turn affects the clinical therapy efficacy; however, NO release could modulate blood perfusion condition and conquers tumor hypoxia. What's more, the interactive interaction with NO and ROS from SDT generates stronger oxidants (e.g., RNS), which suppress tumor growth further. Ji group[91] employed a similar approach to create a platform targeted to mitochondria and ultrasound-responsive for delivery both of O_2 and NO, using human serum albumin as a carrier for the NO donor to incorporate IR780 sonosensitizer and perfluorodecalin (an ultrasound contrast agent) for theranostic applications. Amazingly, the in situ-produced ROS can also be employed to initiate gas release.[92,93]

L-arginine (LA), an internal source of NO donor, was added to the mesopores and lumen of modified HMSNs by electrostatic affinity loading. The platform can be relayed for delivery upon ultrasound excitation. In the first step of the process, ultrasound-augment infiltration promotes the transmission of nanoparticles by the tumor tissue vasculature. The next procedure is get by meditation of nanomaterials into the cancer cells. Ultrasound used locally was used to activate H_2O_2 in tumors of Panc-1 to generate high ROS production, which interacted with LA molecules effectively and produced NO to kill tumor cells.[94]

He group.[95] found that the photosensitive NO donor (*N*,*N*′-di-sec-butyl-*N*,*N*′-dinitroso-1,4-phenylenediamine (BNN6)) was also can be utilize to ultrasound stimuli. Ultrasound employment could lead to the NO radicals free from BNN6, the reason may because of the ultrasound luminescence and the heat and pressure generated under

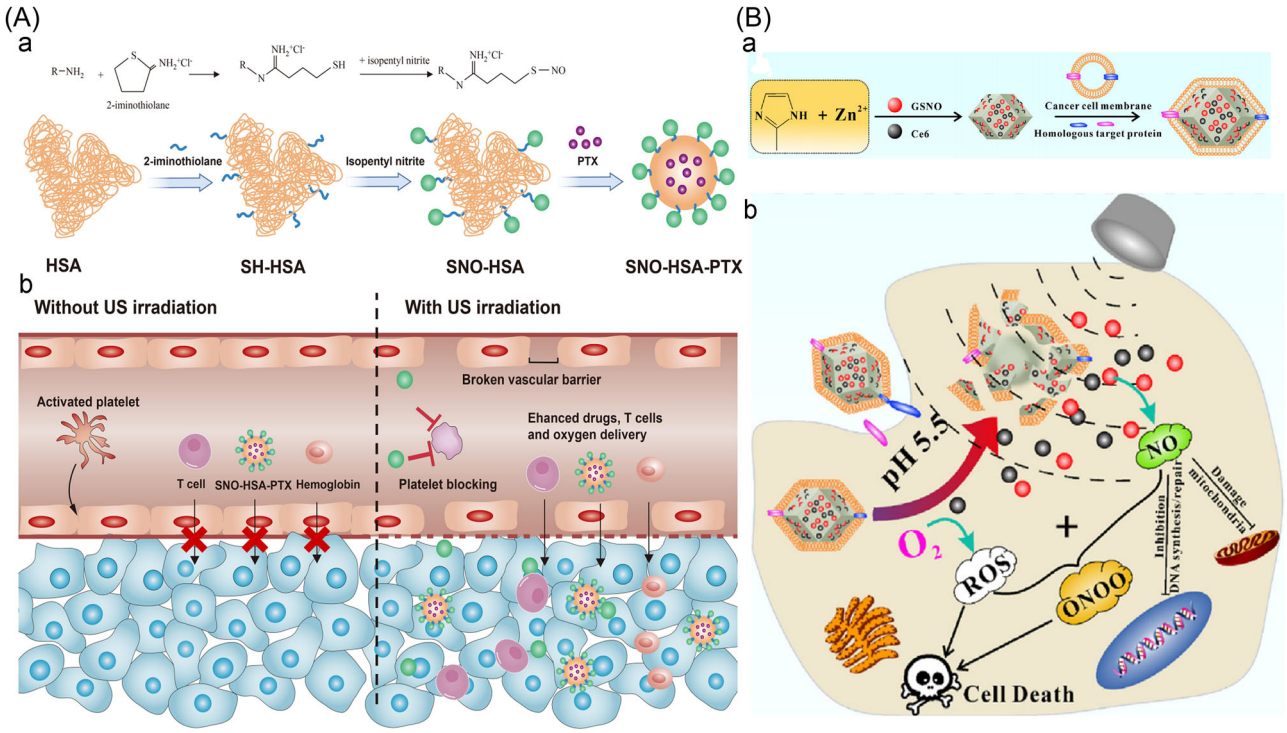

FIGURE 3 (A) Schematic representation of augmented efficacy of NO-releasing nanoagents mediated T cells function and drug accumulation. (a) Schematic presentation of the design of SNO–HSA–PTX nanomaterials. (b) The NO produced by SNO–HSA–PTX under ultrasound irradiation by inhibiting activation of platelet. Reproduced with permission from reference.[89] Copyright 2021, Dove Medical Press. (B) (a) The schematic synthesis of GCZ@M. (b) Schematic illustration of GCZ@M for gas-sonodynamic combined therapy. Reproduced with permission from reference.[90] Copyright 2020, Elsevier.

ultrasound imply. Concretely, they designed hMSNs packed with ultraparamagnetic iron oxide nanoparticles (SPIONs) for magnetic resonance (MR)-guided imaging. NO-releasing BNN6 molecules were used to fulfill the cavities of SPION@hMSN with a BNN6 molecule loading of 623 mg per gram of silica nanoparticles. The suppressing tumor cell growth ability could be augmented through either increasing the concentrations of nanomedicine or the ultrasound power.

Notably, the release of NO from SNO conjugates in the presence of ultrasound may also be influenced by a number of factors, including sonoluminescence, heat, and high pressure.[52] The polymeric micelles, which are self-assembled from amphiphilic copolymers. And it had the core-shell structure, whose core is hydrophobic and shell is hydrophilic. Micellar nanoparticles made from poly(ethylene glycol)-b-poly(ε-caprolactone) (PEG-b-PCL) diblock copolymers were used to payload NO-produced 1,3-bis (2,4,6-trimethylphenyl) imidazolylidene nitric oxide (IMesNO) and anticancer drug of doxorubicin (DOX). HIFU irradiation can activate IMesNO donors, which can elongate tumor blood vessels and promote DOX accumulation in tumor tissues via the EPR effect (Figure 4A,B).[96] On the whole, liposomes, microbubbles, hybrid nanoparticles, and micellar nanoparticles have been demonstrated as nanocarriers for the controllable delivery of GSMs successfully, and these delivery tolls show great influence on improving drug permeability and cellular uptake upon exposure to ultrasound. When combined with SDT, it will not only enrich the possible activation mechanisms but also improve the therapeutic efficacy.

3.2 | Ultrasound stimuli-responsive O_2 release

To date, many oxygen (O_2) supplementation strategies have been developed, generally conforming to the following two methods: 1) use of catalysts (iron and manganese) or reactions between enzymes and hydrogen peroxide (H_2O_2),[110] which was limited to the intracellular H_2O_2 concentration. 2) incorporation of O_2-saturated perfluorocarbon (PFC) or hemoglobin compounds.[97–99] 3) Metal-organic framework (MOF) nanocarriers for gas storage and on-demand release under stimuli.[111] By increasing the oxygenation in the region of tumor, the released O_2 can not only eliminate the hypoxic microenvironment in the tumor but also increase the effectiveness of photodynamic therapy (PDT), sonodynamic therapy (SDT) and radiotherapy

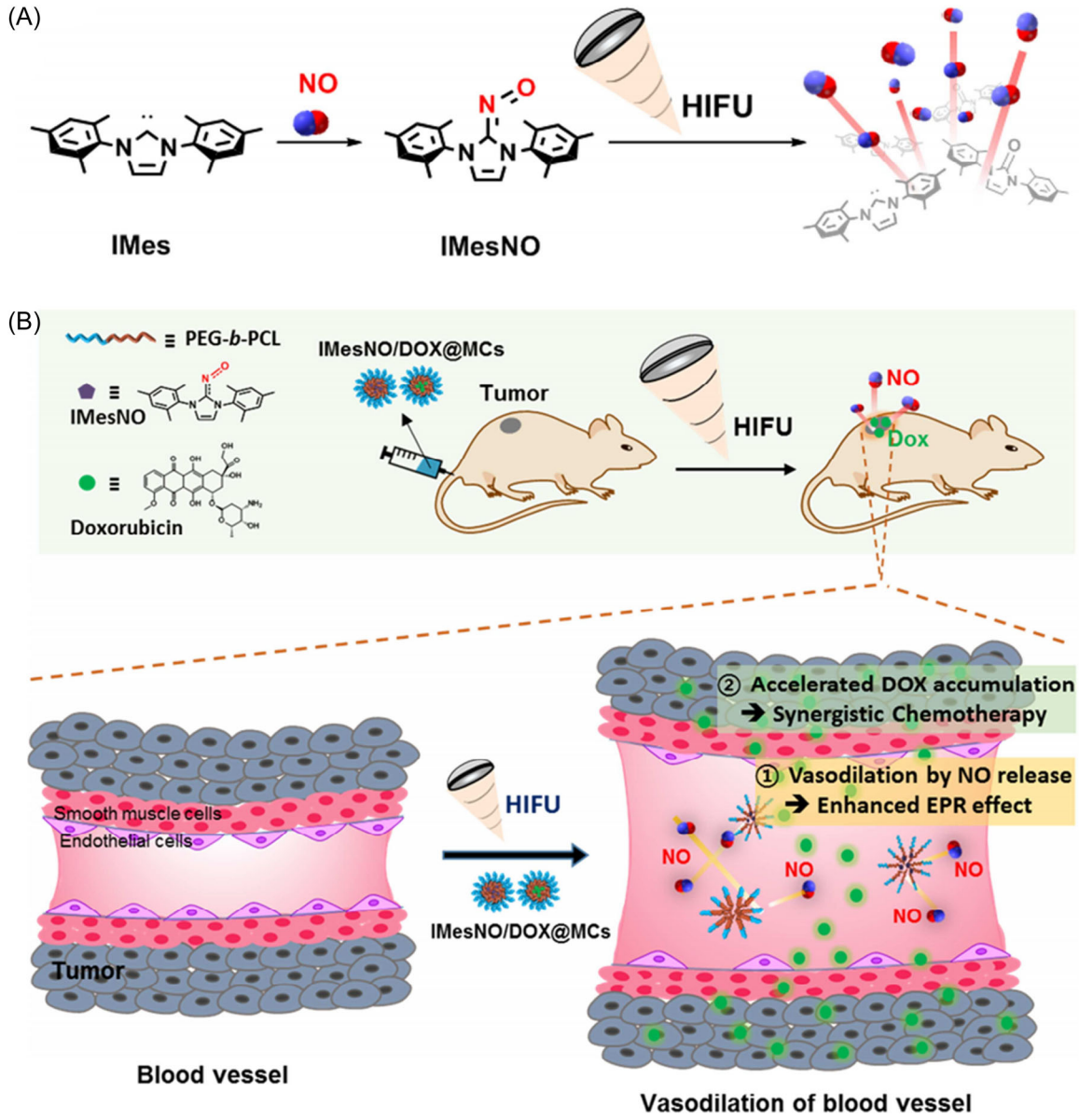

FIGURE 4 (A) Schematic illustration of IMesNO synthesis and NO release from IMesNO upon HIFU irradiation. (B) Schematic illustration of IMesNO/DOX@MCs with HIFU irradiation for anticancer therapy. Reproduced with permission from reference.[96] Copyright 2019, Elsevier. HIFU, high-intensity focused ultrasound; IMesNO, 1,3-bis(2,4,6-trimethylphenyl) imidazolylidene nitric oxide.

(RT). The release of gas molecules could be controlled by US stimulation. And it could be used to trace the microbubbles. For instance, the nanoengineered nanoplatforms, acouscyte/O_2, were synthesized. In this design, an oxygen-saturated PFC and Temoporfin (acoustic sensitizer) were wrapped in multilayer liposomes (C-ML/HPT/O_2), and then C-ML/HPT/O_2 were loaded into live neutrophils (Figure 5A). To increase the targeted cancer ability, the cRGD was integrated. As shown in Figure 5B, when the nanoagents injected in the animal, the cRGD was recoginized by αvβ3, thus increasing the utilization and being avoided clearing by reticuloendothelial system. What's more, upon ultrasound irradiation, the nanoagents could release O_2 and drugs due to the acoustic transition property (Figure 5B).[100]

3.3 | Ultrasound stimuli-responsive CO release

When carbon monoxide (CO) enters the body in excess, it is characterized as a toxic gas that can cause poisoning by decreasing the hemoglobin's ability to carry oxygen. However, recent studies have shown that a small amount can be employed in a number of

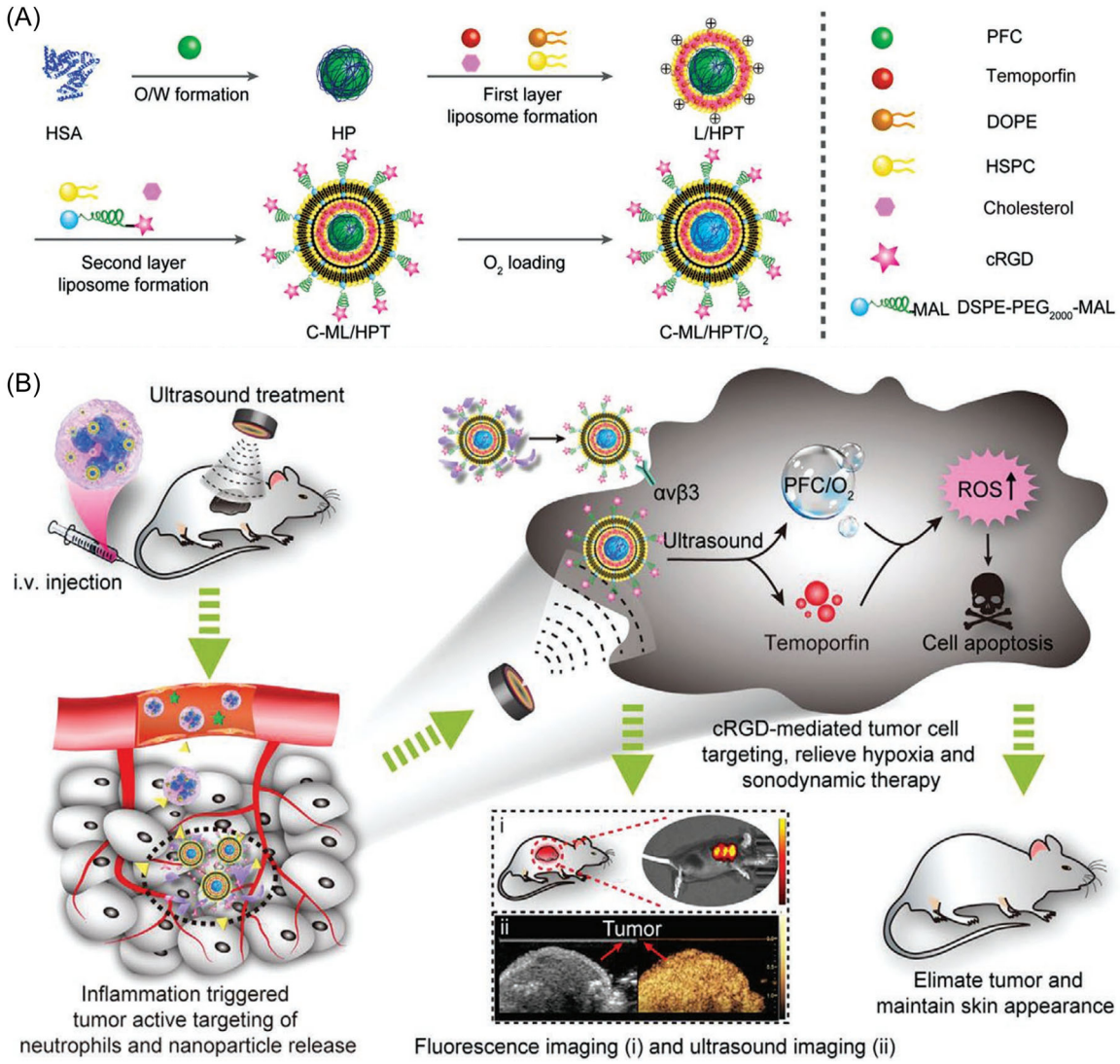

FIGURE 5 (A) Schematic presentation of C-ML/HPT/O_2 design. (B) Schematic illustration clarifying the employment of C-ML/HPT/O_2 with ultrasound for anticancer therapy. Reproduced with permission from reference.[100] Copyright 2022, Wiley-VCH VERLAG GMBH.

biomedical disciplines, such as anti-inflammation, antitumor therapy, and stroke therapy.[40,109,112] Therefore, it is crucial to create a controlled CO administration strategy as soon as possible to ensure the effective delivery and controllable release of CO on demand. In recent years, CO-producing molecules (CORMs) have recently been identified for spatiotemporal CO release, displaying more effective pharmaceutical benefits than gaseous CO.[42,113,114] Metal carbonyl complexes have been employed as the CORMs to transport CO in cancer regions.[115] A unique cyanine-appended Re(I)-tricarbonyl compound has been reported to release CO under ultrasound irradiation (Figure 6A).[101] In this study, the authors appended Cyanine moieties in the compound to amplify the p–p conjugation plane, and add its sonosensitivity for the release of CO. The Re-Cy released the three CO together under ultrasound irradiation, which was approved by the gas chromatography and the CO probe. The FDA-approved pluronic-based micelles for medication delivery are other examples of ultrasound-mediated drug nanocarriers. For example, hydrophobic tricarbonyldichlororuthenium(II) dimer (CORM-2) was incorporated into Pluronic F-127 micelles and demonstrated low degrees of CO release in the presence of cysteine.[103] By utilizing the ultrasonic-responsive feature of Pluronic micelles, low-intensity nonfocused ultrasound, in contrast, caused a four-fold CO release. Recently, Sun et al.[102] developed an ultrasound stimuli-responsive nanocarrier for CO controllable delivery, which could alleviate the SDT-induced hypoxic microenvironment efficiently (Figure 6B). Ultrasound stimulation could not only increase the accumulation of the nanoparticles in the tumor cells and tissues, but also induce the 2,2′-azobis

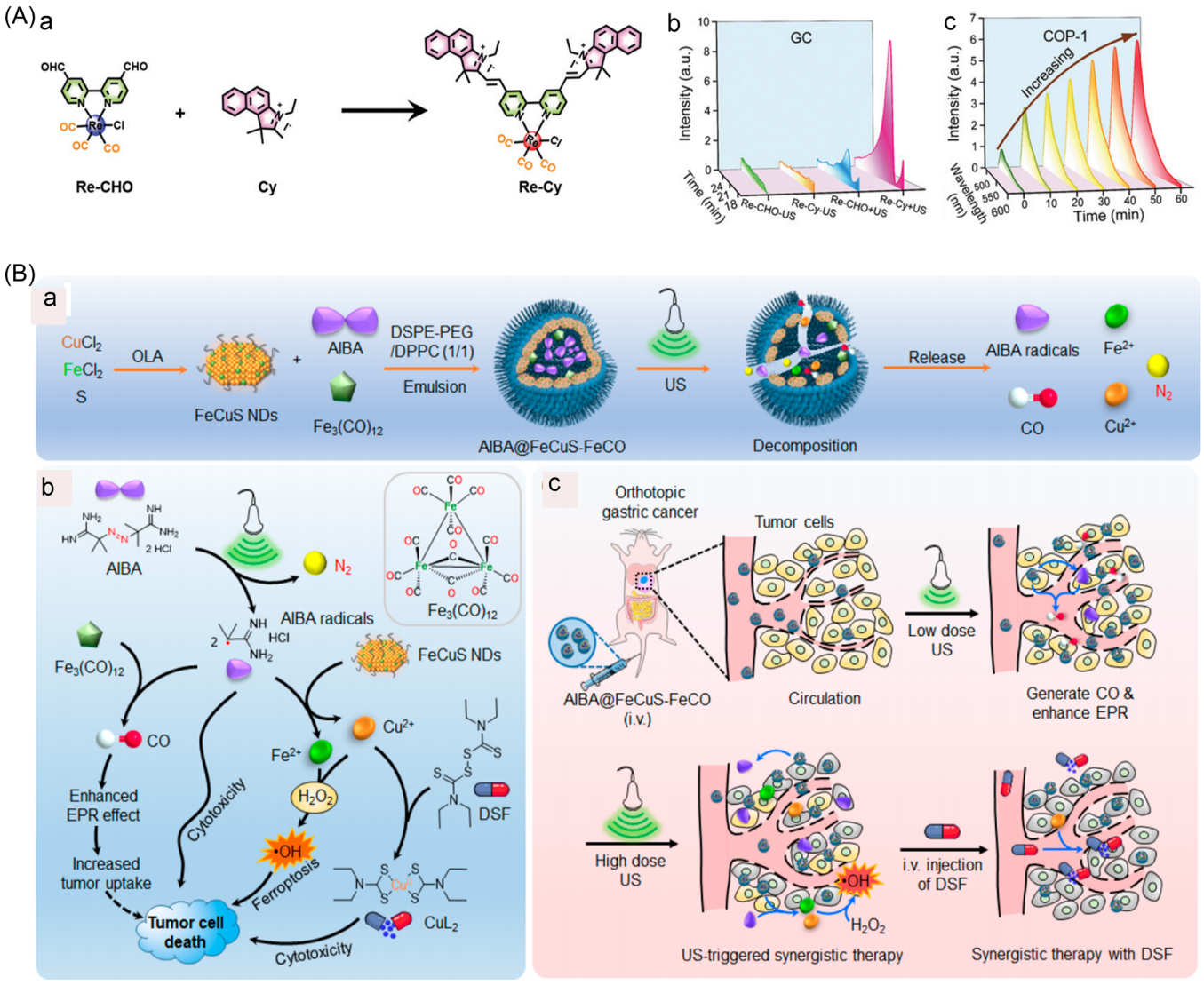

FIGURE 6 (A) An ultrasound-triggered cyanine-rhenium(I) complex for CO therapy. (a) Schematic illustration of Re-cy synthesis. (b) Gas chromatograms demonstrating the CO production from Re-Cy/Re-CHO in the absence or presence of ultrasound. (c) Ultrasound-induced CO release from Re-Cy monitored by the COP-1 probe. Reproduced with permission from reference.[101] Copyright 2022, Royal Society Chemistry. (B) An ultrasound activated AIBA@FeCuS-FeCO for CO therapy. (a) Presentation of the design of AIBA@FeCuS-FeCO and the capacity to increase ultrasound-activated degradation and produce AIBA radicals, CO, N_2, Fe^{2+}, and Cu^{2+}. (b) Proposed mechanism of AIBA@FeCuS-FeCO and DSF to lead to tumor cell death by ultrasound synergistically activated therapy. (c) Cartoon presentation the common process of AIBA@FeCuS-FeCO and DSF for synergistically ultrasound-activated therapy of orthotopic gastric tumors in vivo. Reproduced with permission from reference.[102] Copyright 2021, American Chemical Society.

(2-methylpropionamidine)dihydrochloride's (AIBA) dissociation, which generates AIBA radicals owing to their outstanding thermal properties. The produced AIBA radicals in situ can further stimulate the disintegration of the CO donor of $Fe_3(CO)_{12}$. Then the Fe^{2+} and Cu^{2+} generated from Fe-doped CuS nanomaterials coordinate the Fenton reaction to produce highly toxic hydroxyl radicals (•OH). The synergistic combination of these activities led to the elimination of xenograft tumor cells and increased survival of tumor-bearing animals.

Guo group designed a originality targeted ultrasound release carrier of CO (TARC-CO) for controllable delivery CO. Under the ultrasonic irradiation, the amount and location of CO release could be flexibly controlled and managed, thus leading to a safer CO-based therapy. The TARC-COs could also be used as ultrasound contrast agents and followed visually to observe the dynamic process of CO administration through ultrasound imaging. The stimulation of cancer cell death, suppression of cell proliferation, and restriction of vascular development in tumors were the last ways in

which TARC-COs were clearly shown to possess exceptional antitumor effects under ultrasound triggering.[104]

3.4 | Ultrasound stimuli-responsive CO_2 release

CO_2 molecule itself does not have a specific function in disease treatment, but the process of CO_2 production has recently been explored for theranostics.[116] And its controllable release demonstrated high therapy efficacy.[117] Especially, the ultrasound-triggered gas-generating nanoplatforms have practical controllability and high tissue-penetrating depth. Therefore, the ultrasound-triggered CO_2 generating nanoplatforms based on the inertial cavitation are also concluded in this review. L-Arginine was incorporated into hollow mesoporous silica nanoparticles for suction and stabilization of CO_2, when was further released into the surrounding environment from LA molecules by changing the pH and/or temperature.[105] As seen in the panc-1 tumor xenograft, the therapeutic low-intensity ultrasound waves caused these CO_2 bubbles released has been demonstrated, which produced a variety of bioeffects including cavitation, mechanical effect, shock waves, and instant necrosis of cancer cells. These effects also simultaneously destroyed the blood vessels of the tumor. The great therapeutic biosafety of this CO_2-boming effect meant that it exclusively affected the tumor tissue at the designated ultrasound-irradiation spot and would not harm healthy tissues or organs. By producing CO_2, this effect of interstitial cavitation was further realized. Mesoporous calcium carbonate nanoparticles (MCC NPs) loaded with hematoporphyrin monomethyl ether (HMME) as a sonosensitizer were used to create a pH/ultrasound dual-responsive CO_2 generator.[106] Meanwhile, hyaluronic acid with tumor-targeted properities was modified onto MCC nanoparticles' surface, endowing the composite nanosystem with high tumor-targeting properties and minimizing premature drug release. Overall, the nanoplatform of HMME/MCC-HA takes advantages of the synergistic integration of therapeutic inertial cavitation and SDT to bring a multimechanism antitumor effect, including apoptosis/necrosis and vascular disruption of cells. Due to the ideal targeting efficiency by precisely locating the tumor region, HMME/MCC-HA was disintegrated under the dual action of TME and external ultrasound stimulus, accompanied by CO_2 production and bursting effect, which leads to the irreversibility of cavitation-regulated cell necrosis, together with the occlusion of blood supply, providing a "bystander effect." At the same time, ROS produced by HMME targeted the effective apoptotic pathway of SDT in the tumor region. Therefore, the combination of apoptosis/necrosis with multiple mechanisms resulted in a prominent tumor treatment efficacy with minimal adverse effects on major organs. In addition, the echogenic performance of CO_2 gas enabled the nanoplatform to serve as a powerful ultrasound contrast agent for the detection of cancer lesions. After intravenous injected the nanoagents 3h, the CO_2 bubbles produced under pH/ultrasound dual-responsive. Meanwhile, the enhanced accumulation of tumor region is achieved through CD44 receptor-mediated endocytosis effect. The experiments in vivo demonstrated that HMME/MCC-HA could inhibit tumor growth remarkably with the V/V0 of 0.87 ± 0.13. These results demonstrated the good therapeutic effect with a multimechanism strategy based on the HMME/MCC-HA nanoplatform (Figure 7A–C).

3.5 | Ultrasound stimuli-responsive codelivery of gas

Expect for the ultrasound stimulation for single gas release, the ultrasound could trigger the release of two kinds of gases. In this context, the Guo group designed type ultrasound-responsive nanoparticles for the codelivery of gases. To be specific, the albumin-based NO donor (HAS-NO) were synthesized firstly, then the sonosensitizer, IR780, was added to the HAS. After that, perfluorodecalin was added to synthesize the nanocomplex IPH-NO. In this system, the IPH-NO could not only produce O_2, but also NO, thus relieving hypoxia in the tumor, reversing the tumor microenvironment immunosuppression, and enhancing the sonodynamic therapy for immune activation.[91]

4 | ANTITUMOR THERAPY EFFECT OF ULTRASOUND-BASED GAS GENERATING PLATFORM

The gases, such as NO, O_2, CO, and CO_2 were employed as effective anticancer agents.[118] For one thing, the gases could be incorporated into the nano/microbubbles, and then released controllable in the local tissue of cancer under the ultrasound stimulus.[119] For example, the CO_2 itself does not have treatment efficacy, but during the period of CO_2 bubble production triggers drug payloaded into the CO_2 nanobombs release.[120] And the small molecular weight gas could diffuse into the deeper tumor regions and permeate through biomembranes without needing any transport mechanism actively. For another, the gases could experience a changeable to become

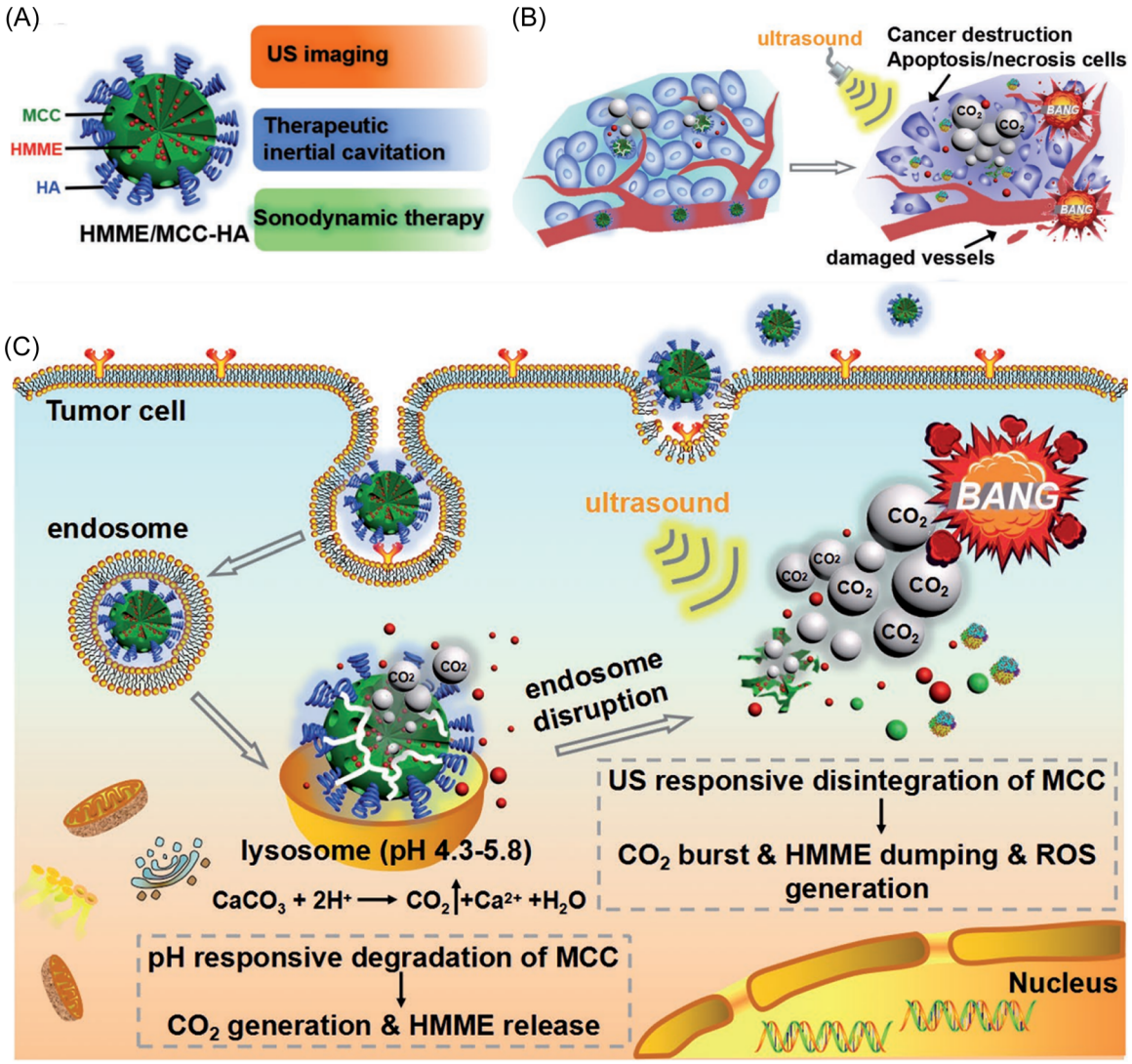

FIGURE 7 (A) The design of HMME/MCC-HA. (B) The mechanisms of causing cell death. (C) HMME/MCC-HA realized pH/ultrasound dual-responsive decomposition of MCC, CO_2 bubbling, and drug releasing behaviors in cancer cell, triggering cell death ultimately induce tumor cell death through ultrasound-activated synergistic therapy. Reproduced with permission from reference.[106] Copyright 2017, Wiley.

active, for example, the catalase transforms the H_2O_2 in the tumor microenvironment to O_2, when it is fixed in the mesoporous organosilica nanoparticles to form into hybrid catalytic nanocatalysts. The hybrid nanocatalysts are sensitive to the H_2O_2 in the tumor, thus accelerating the continuous O_2 generation, which could result in tumor ablation upon high-intensity focused ultrasound. The PFC-dissolved O_2 indicated the efficient capacity of oxygen loading. Based on this, the nano-PFC was designed as the carrier of O_2. To stabilize the PFC droplets, human serum albumin was used. Upon the ultrasound irradiation, the PFC droplets dissolved O_2 could release O_2 rapidly in the tumor, which would relieve the hypoxia environment of tumor, thus augmenting the RT effect.[99]

Related research works have shown that CO is a distinguished biological gasotransmitter related to mitochondria, which is the place of intracellular oxidative phosphorylation, aerobic respiration, and synthesis adenosis triphosphate.[121–123] Inhibiting tumor cells growth with CO accelerated significantly the stage of mitochondrial respiration secondly, which is the major stage of oxygen consumption, thus forcing tumor cells to deplete more oxygen to generate energy,[124] and then cause mitochondria depletion and formation of reactive oxygen species (ROS), which resulted in activating proapoptotic influence to cause tumor cells death. From this point of view, the two rhenium(I) tricarbonyl compound sono-ReCORMs (Re-NMe_2 and Re-NO_2) using different displaced ligands for gas-sonodynamic

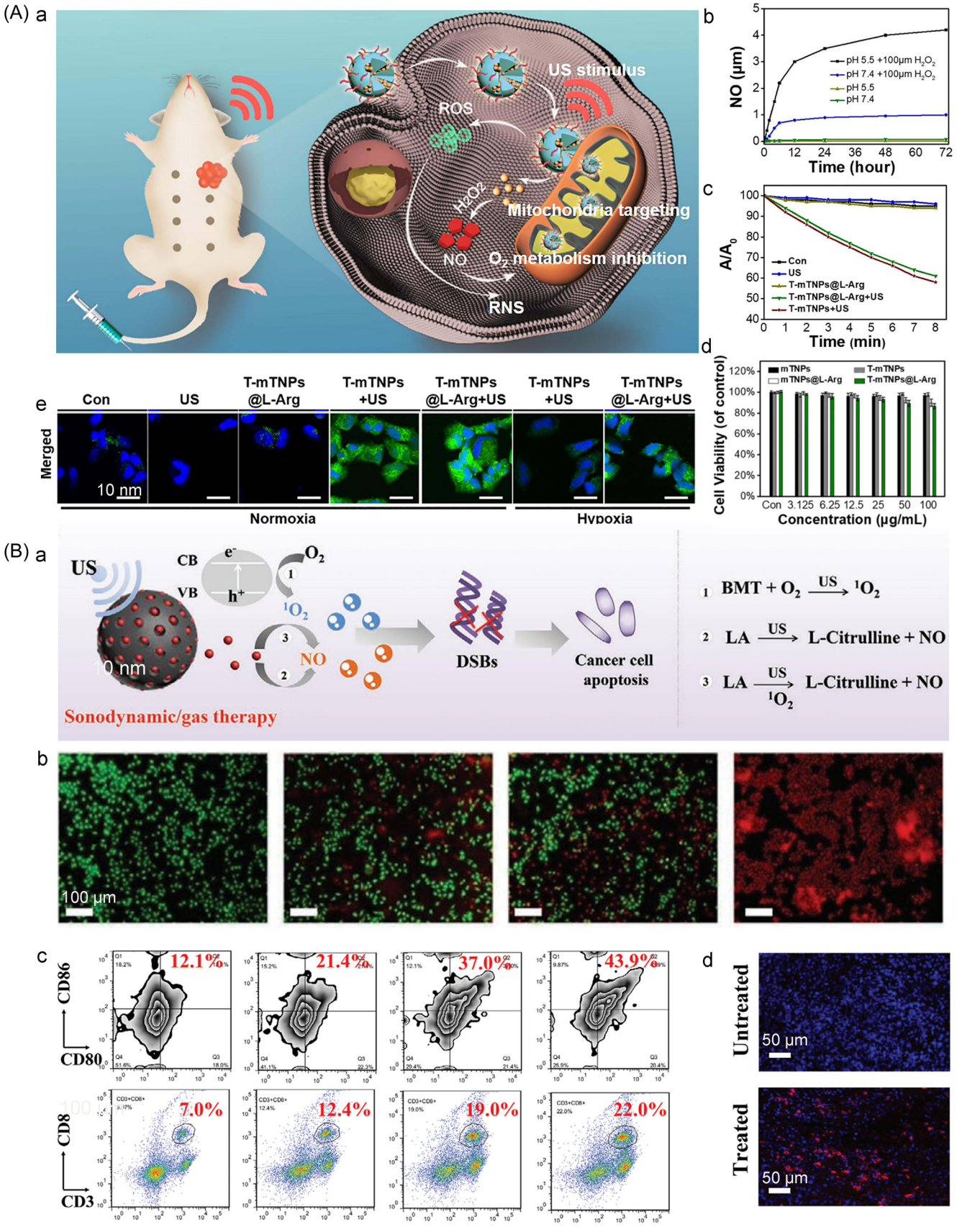

FIGURE 8 (See caption on next page)

synergistic therapy have been investigated.[125] The rhenium tricarbonyl complexes could not only produce $^1O_2$, but also yield CO under the ultrasound stimuli. What's more, Re-NMe_2 had a better catalytic property than $ReNO_2$. In both the experiments in vitro and in vivo, the group of combination ultrasound with $ReNMe_2$ had a much better antitumor effect than Re-NMe_2 group and ultrasound only group. It is worth noting that hypoxia could cause more cancer cell death. Expect for the ultrasound could directly trigger CO release for tumor therapy. The synergistic sonodynamic therapy and CO triggered by internal stimuli have also been reported. For example, a multifunctional biomimetic nanosystem owned SDT, CO gas therapy efficiency, and indoleamine 2,3-dioxygenase inhibition has been designed.[126] In this study, gold nanoparticles were designed on the black phosphorus quantum dots-doped mesoporous silica frameworks (Au-BMSNs) to achieve the function of SDT. Afterward, the CO-release molecules CORM-401[127] were payloaded into the Au-BMSNs for the H_2O_2-responsive drug delivery system (CAu-BMSNs). To avoided the devour by rethiculoendothelial and enhance the targeted ability, the macrophage membrane were extructed to decorate the CAu-BMSNs. Finally, IDO blocking signal was combined for achieving SDT-CO therapy-immune therapy to inhibit primary tumor growth, relapse, and hinder lung metastasis. In different cancer models, the authors figured out that the nanosystem could suppress tumor progression by ultrasound-stimulus in situ ROS and CO release in the tumor. What's more, the immune cell death induced by the nanosystem could trigger antitumor immune response and found a long immunological memory through integrating with IDO inhibitor by transforming systemic central memory T cells into effector memory T cells and decreasing Treg populations, which could suppress lung metastasis and protect tumor rechallenge from rechallenging in vivo.

As another significant gas transmitter, NO has been demonstrated to influence a variety of physiological processes such as apoptosis, angiogenesis, immune response, and neurotransmission.[93,128,129] And its' hindering tumor growth efficiency could be due to the "anti-Warburg effect."[130] Wang's group designed a nanocomplex, named T-mTNPs@L-Arg for synergistic NO gas therapy and SDT for breast cancer (Figure 8A(a)).[131] The authors loaded the L-arginine (NO donor precursor)into the mesoporous and decorated it with triphenyl phosphonium for mitochondria targeting. T-mTNPs@L-Arg could release NO and ROS under ultrasound (Figure 8A(b,c)). The ROS concentration was also verified at the cell level (Figure 8A(e)) and its antitumor efficiency has also been demonstrated in vivo (Figure 8A(d)). Combined with ultrasound, the gas-generating platforms could supply precise intracellular delivery of a high gas concentration for cancer therapy. In this study,[132] L-Arg (as a NO prodrug), was utilized for gas therapy, and BMT, as a sound sensitizer, was used for SDT. Amazingly, BMT could trigger the production of $^1O_2$ after US stimuli, which next promoted L-Arg oxidation to produce a large number of NO (Figure 8B(a)). The excess ROS (NO and $^1O_2$) could result in the overexpression of a series of inflammatory factors (e.g., p53 gene and cytochrome C) and increase the production of cytotoxic substances (e.g., peroxynitrite), thus resulting in mitochondrial/cellular DNA double-strand damage, eventually causing the apoptosis of both primary and metastasis cancer cells (Figure 8B(b–d)).

5 | SUMMARY AND OUTLOOK

Gas therapy has attracted much more interest owing to their effective therapeutic treatment and biosafety. However, the concentration of the gas directly affect their therapy efficiency. In recent years, the gas release molecular has been developed for instantly releasing gas under different stimuli. Among different stimuli, ultrasonic arts is severed as a tool for clinical diagnostic and treatment because of its reliable security, deep tissue infiltration, low incidence of side effects, nonionizing radiation, and noninvasive. In our work, we sum up the mechanism of ultrasound-triggered gas therapy, the recent achievements of ultrasound-responsive gas-generating platform in tumor therapy applications.

FIGURE 8 (A) T-mTNPs@L-Arg for synergistic SDT-nitric oxide gas therapy of breast cancer. (a) Schematic illustration of T-mTNPs@L-Arg therapy in vivo. (b) Cumulative NO generation at different treatments. (c) ROS generation detected by DPBF probe. (d) Cell viability of MCF-7 cells with ultrasound stimulus. (e) The ROS concentration in the MCF-7 cells stained with DCFH-DA with different treatments. Reproduced with permission from reference.[131] Copyright 2022, Dove Medical Press. (B) Ultrasound-triggered BMT@LA nanovaccine for SDT-NO immunotherapy-gas therapy with enhanced antitumor efficacy. (a) Schematic illustration of BMT@LA synergistic therapy in vivo. (b) The live/dead cell fluorescence after different treatments. (c) Flow cytometric analyses of mature DC cells, CD8 + T cells, and CD4 + T cells in the spleen of different groups. (d) The images of lung tissues after different treatment groups, metastatic nodules were indicated by red circles Reproduced with permission from reference.[132] Copyright 2021, Wiley-VCH VERLAG GMBH. NO, nitric oxide; ROS, reactive oxygen species; SDT, sonodynamic therapy.

Although in infancy stage, this hopeful situation can be substantial far and advanced in the below situations.

First, the mechanism of gas antitumor therapy need to be explored further to improve their treatment efficacy, specially, the gas treatment depend on their concentration. Neither too low concentration nor high concentration of gas is failed to meet the expected therapy effect.

Second, while there are many different forms of stimuli-mediated donor catalysis for gas signal molecules, such as the MOF as carriers, and the liposome nanocarriers for carrying the gas in the tumor, only a small number of them have been demonstrated to be ultrasound triggering. To develop novelty ultrasound responsive donors next, it is critical to comprehensively explain their composition and activation mechanisms upon ultrasound function systematically. Moreover, ultrasonic exposure can indirectly activate the molecular donors of gas signals through generating ROS, sonoluminescence, etc. So this presents another opportunity to create brand new ultrasonic stimulation, SDT, and gas signal molecular therapy. Above all, the effectiveness of the antitumor treatment can be increased by combining ultrasonic stimulation, SDT, and gas signal molecular therapy.

Third, it should be pointed out that gas signal molecular dose not work function isolately under the real pathological and physiological conditions. Therefore, there is still much more to be understood the subtle interaction between different gas signal molecules.[133]

Last but not least, although some progress has been made in the design of various ultrasound-responsive gas release, only a few of them have been transformed to clinical trials. In addition, while some newly gas-generating nanogenetrators show promising therapy effect, the preparation is complex, thus limiting their clinical applications. Therefore, there still needs to be develop nanogenerators repeatability, efficiency, and stability for clinical translation.

Overall, employing ultrasound as an external stimulus for gas treatment release is an exciting area for investigation. This interdisciplinary attitude necessitates ongoing contributions from materials scientists, chemists, biologists, and others to hasten the practical application of this intelligent catalysis.

AUTHOR CONTRIBUTIONS

Fangxue Du: Methodology (lead); resources (lead); writing—original draft (lead). **Ruiqian Guo**: Resources (equal). **Ziyan Feng**: Resources (equal). **Ziyao Wang**: Resources (equal). **Xi Xiang**: Methodology (equal). **Bihui Zhu**: Funding acquisition (equal); writing—review & editing (supporting). **Raul D. Rodriguez**: writing—review & editing. **Li Qiu**: Investigation (equal); methodology (equal); supervision (equal); writing—original draft (equal); writing—review & editing (lead). All authors have read and approved the final manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATMENT

No data sets were generated or analyzed during the current study. Thus, data sharing is not applicable to this article.

ETHICS STATEMENT

This study did not involve human participants and/or animals or informed consent. Thus, ethical clearance is not applicable to this article.

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