**Abstract**

Gas therapy, an emerging cancer treatment method of inflammation-related diseases, has recently received substantial attention. The rapid advances in nanomedicine and nanotechnology have made gas precision treatment possible through tumor targeted delivery and controlled release of therapeutic agents. Single therapeutic is often inevitably accompanied with limited therapy efficacy. Gas therapy combined with other treatment methods can sensitize different therapy modes to augment cancer therapy. Understanding the mechanism through which gas enhances other therapeutic modalities will enable the design of reasonable strategies for clinical cancer therapy. In this review, we summarize novel gas-based nanomedicines, focusing on gas-based nanomedicine carriers, along with the release of gas molecules and the mechanisms of gas enhanced therapy. We describe the design of novel gas-releasing nanoplatforms and the underlying synergistic mechanisms against cancer. Moreover, we describe the current challenges and outlook for future prospects in novel gas-based nanomedicines for gas therapy in cancer.

**KEYWORDS**
controlled release, gas therapy, nanomedicine, stimuli-responsive, therapy mechanism

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**1 | INTRODUCTION**

Cancer is the deadliest disease threatening human health worldwide. Traditional radio-/chemo-therapeutic drugs have frequently been demonstrated to have low efficiency and high non-specific toxicity to normal tissues, which cause pain to patients. Rapid advances in nanomedicine and nanotechnology have provided various therapeutic nanoplatforms in both clinical trials and current practical applications. On the basis of these well-designed nanoplatforms, some novel nanomedicines have recently been proposed for more efficient therapeutics, notably emerging novel gas-based nanomedicines that selectively kill cancer cells and protect normal cells against...
non-specific damage by reducing the side effects of traditional therapies through the virtue of the anti-inflammatory effect of gases.\textsuperscript{3–6}

Several types of gaseous molecules, such as nitric oxide (NO), hydrogen sulfide (H\textsubscript{2}S), carbon monoxide (CO), and H\textsubscript{2} have the function of regulating vasodilatation, neurotransmission, anti-inflammatory, and anti-oxidative reactions in the physiological and pathophysiological processes.\textsuperscript{7,8} Importantly, several gas molecules showed specific therapeutic effects in cardiovascular diseases, Alzheimer’s disease, infection, cancer, and neurotransmission owing to their physiological modulation functions.\textsuperscript{9}

Low concentration (<nM level) of NO/H\textsubscript{2}S/CO can protect cancer cells, thus favoring tumor cell proliferation, growth, and metastasis, whereas these gases with high concentration (≥nM level) have toxic to cancer cells.\textsuperscript{10} However, because of the limits of low solubility in water and untargeted diffusion around the body, achieving highly efficient and sustainable gas delivery is difficult. Therefore, it is highly important to realize the accurate gas release and efficient gas delivery for the clinical translation of gas therapy. This review summarized the recent significant development in the elaborately designed gas nanomedicine. Given the great progress in nanomedicine, some well-designed nanoplatforms, as gas-based nanomedicines, may achieve the aforementioned goal. In addition, these gas-transmitters can synergize other traditional cancer therapies, on the basis of the strength of nanomaterials, and provide broad and versatile opportunities in cancer therapy.

Given the important role of gas-based nanomedicines, this comprehensive review summarizes recent developments in novel gas-based nanomedicines for cancer therapy in the following four aspects (as shown in Figure 1): (1) gas carriers, (2) stimuli-responsive gas prodrug, (3) in situ gas-generating nanomedicines, and (4) gas-based nanomedicine for enhanced cancer therapy. In the gas-based nanomedicines, we introduce two gas-releasing strategies from the viewpoints of stimuli-responsive gas prodrug and in situ gas-generating nanomedicines. Gas therapy is a low-toxicity and high-efficacy therapy strategy that can sensitize cells to chemotherapeutic drugs, thus effectively killing cancer cells and realizing the combination between gas therapy and traditional therapy. Given the efficient therapeutic effect, we provide a detailed summary of the mechanisms of a series of gas-based nanomedicines in the enhancement of cancer therapy in Section 4. Finally, future challenges and potential inspirations for gas-based nanomedicines are also discussed to further promote their clinical applications.

\textbf{FIGURE 1} Scheme of novel gas-based nanomedicines for cancer therapy. Reproduced with permission.\textsuperscript{74} Copyright 2017, American Chemical Society. Reproduced with permission.\textsuperscript{88} Copyright 2018, Wiley-VCH. Reproduced with permission.\textsuperscript{66} Copyright 2011, Royal Society of Chemistry

2 \hspace{1em} GAS CARRIERS

The burgeoning green strategy of gas therapy has played a very important role in cancer therapy, owing to its low toxicity and high efficiency. However, the low water solubility and high tissue penetration are the main reasons making most gas molecules being difficult to control. With the development of functional nanomaterials, gas-based nanomedicines have emerged through well-designed drug delivery systems to realize targeted delivery and controlled release of gas molecules. We here summarize four types of gas nanocarriers for precision nanomedicine-mediated gas therapy: nanoliposomes, inorganic nanoparticles (NPs), metal-organic framework (MOF) nanomaterials, and polymer NPs (as shown in Figure 2).

2.1 \hspace{1em} Nanoliposomes

Liposomes are the first successful nano-drug delivery system that is translated into clinical applications. First described in the 1960s by Bangham et al., liposome has been shown to have benefits in the medical and cosmetic industries.\textsuperscript{11} Liposomes are composed of phospholipids, which self enclose, forming spheres of lipid bilayers surrounding an aqueous core.\textsuperscript{12} Modification of polyethylene glycol (PEG) to liposomes can prevent the reaction with plasma proteins and escape the capture of mononuclear
phagocytes.\textsuperscript{13–15} Therefore, PEGylated liposomes endow NPs with ultra-long circulation compared with free drugs. Recent studies have shown that different types of liposomal encapsulation of various agents with different physicochemical properties can effectively deliver drugs to lesions and enhance cancer therapy effects.\textsuperscript{16–19} H\textsubscript{2} is relatively safe, with no danger of blood poisoning at fairly high concentrations and without the tumor-promoting effects compared with those of NO, CO, and H\textsubscript{2}S gases. Liposomes can be used as nanoreactors for in situ photocatalytic hydrogen generation. In an in situ hydrogen therapy, the product H\textsubscript{2} diffuses across the lipid bilayer through a catalytic cycle of polymer dots and counteracts the reactive oxygen species (ROS) in diseased tissues.\textsuperscript{20} However, the stability of liposomes is low, and the development of nanocarriers with excellent stability is urgently needed.

2.2 Polymeric NPs

Polymeric NPs have been investigated in therapeutic delivery applications because of their success in solving poorly soluble, rapid renal clearance, systemic toxicities, and improving delivery.\textsuperscript{21} The most frequently used polymer-based NPs for decades have been PEG, polyethyleneimine, poly(lactic acid-co-glycolic acid (PLGA), and its related homopolymers.\textsuperscript{22} Among these, PLGA and its related homopolymers as the US Food and Drug Administration approved nanocarriers have been wildly used in the biomedical field.\textsuperscript{23} PLGA has the characteristic of degradation, and its degradation products are non-toxic H\textsubscript{2}O and CO\textsubscript{2}, which can be eliminated by the body. One important targeted strategy is surface modification, which plays a key role in biocompatibility and the treatment of disease.\textsuperscript{24} Recently, polymer-drug conjugates, polymer micelles, and nanogels have been investigated to protect drugs against rapid clearance and enzymatic digestion, and enable controlled release under the surface modification.\textsuperscript{25–27} Polymer-drug conjugates, one of the first classes of anti-cancer nanomedicines, could be developed as a single agent or a component of combination therapy in clinical cancer therapy. The first therapeutic polymer-drug conjugates have been shown to increase drug cytotoxicity and decrease cardiotoxicity by modifying biodistribution.
in preclinical studies, thus providing a promising way of circumventing multidrug resistance (MDR).28

Polymeric micelles, as natural carriers, mimic the biological transport system in structure and function, fulfilling several tasks of selective delivery of ideal carriers at different levels. A hydrophilic shell helps the micelles remain unrecognized in the blood circulation, and a virus-like size (<100 nm) prevents the reticuloendothelial system from the uptake of them, resulting in some passive accumulation in the specific organization.29–32 Compared with polymer-drug conjugates, polymeric micelles have relatively higher physicochemical stability. The size of typical polymeric nano-micelles is 20–100 nm, thus providing an advantage for polymers and nanomaterials. Foster et al. have reported the amphiphilic block copolymer micelles functionalized by S-arylthiooxime, which can release H2S and are used to study the effect of H2S on the growth and proliferation of cancer cells. These H2S-releasing micelles, compared with other common H2S donors, significantly decrease the survival of HCT116 cells and provide a new strategy for studying the biological effects of H2S.33

Nanogel is a sub-micron size cross-linked hydrogel particle with high water content, excellent colloidal stability, and flexibility to control drug release.34–37 These characteristics provide broad prospects for the application of hydrogels in tissue engineering, biomedical implants, bio-nanotechnology, and drug delivery. In addition, some environmentally responsive groups introduced into the 3D cross-linking network of NPs have been found to endow nanogels with excellent stimuli-responsive properties.36,38 Among them, degradable nanocarriers enabling both controlled drug release and high biosafety are crucial to their clinical translation. Our group has developed a new type of biodegradable zwitterionic nanogel based on poly(sulfobetaine methacrylate) with excellent sufficient drug release in a reductive environment. The equal cationic and anionic groups endow nanogel superior long circulation time, thereby increasing the tumor accumulation for cancer therapy.39 With the development of gas therapy, an ultraviolet-visible responsive nanomedicine formula was proposed by Fan et al.40 N, N′-di-sec-butyl-N,N′-dinitroso-1,4-phenylenediamine (BNN6) and doxorubicin hydrochloride (DOX) were coloaded into monomethoxy (polyethylene glycol)-poly(lactic-co-glycolic acid) (mPEG-PLGA) and the nanomedicine shows good stability under physiological conditions but decomposes in response to ultraviolet-visible irradiation for NO gas release. The generated NO gas breaks the NP structure and facilitates the loaded DOX molecules releasing and realizing the gas/drug effect by reversing MDR under the functional of NO. Therefore, polymer NPs can serve as functional nanocarriers with degradable and long circulation time performance for degradable long circulation time performance for cancer gas therapy.

2.3 Inorganic NPs

Inorganic nanomaterials have high chemical/physiological stability and multifunctionality, and have shown remarkable potential in combating cancer. The incorporation of their unique properties has expanded alternative platforms for drug delivery. Among the most promising inorganic NPs being developed are iron oxide, silica, and carbon NPs.

Iron oxide NPs, the typical metallic material, have been successful, owing to their superparamagnetism effect, which can generate imaging contrast by magnetic resonance and be concentrated at specific target sites in diseased tissues by an external, high-gradient magnetic field.41–43 Numerous studies have reported the development of superparamagnetic iron oxide NPs as a magnetic resonance imagining (MRI) agent in clinical applications in the past decade.44,45 In addition, magnetic NPs, as a magnetic fluid hyperthermia donor, also increase the temperature of the tumor site to induce the cytotoxicity of cancer cells, which is a promising new technology for cancer treatment.46–49 Current research on iron oxide NPs has opened up broad prospects for the application of diagnostic reagents in magnetic resonance imaging and drug delivery. Delivering anti-cancer drugs to targeted locations by coupling functionalized iron oxide NPs is one of the most interesting research areas as a kind of cancer treatment strategy.50 Moreover, two different oxygen radicals were generated by the disproportionation of hydrogen peroxide (H2O2) under the action of Fe2+/Fe3+. Therefore, the Fenton reaction has been proven to be a new platform for ROS generation.51,52 Ding et al. developed pH-sensitive porous magnetite supra-particles, which allow loading of artemisinin and easy degradation to ferrous ions under acid environment to improve the cytotoxicity of cancer cells.53 The recent emerging gas therapy is limited due to the low water solubility and strong tissue penetration.54–55 For overcoming the rate of therapeutic gas releasing, magnetic iron oxide was selected as a carrier for covalent surface-bound CO-releasing molecules (CORMs), which trigger the release of CO under an alternating magnetic field based on its inherent magnetic hyperthermia.56 In addition, superparamagnetic iron oxide is an excellent MRI contrast agent that can guide precision gas therapy.57 Despite the potential biomedical applications of iron oxide NP-related nanocarriers, possible changes in iron homeostasis, oxidative stress, and cellular responses are the main critical issues that limit their clinical applications.50
Silica and carbon are two classical inorganic nonmetallic NPs widely used in catalytic and biological fields. Silicon is a necessary element with a role in metabolic processes as the second-largest element on earth. Most people approximately absorb about 20–50 mg of silicon per day and the ingested silicon is found in the form of silicic acid in the blood plasma. Orthosilicic acid, which is mainly absorbed by humans, is present in many tissues including the bone, tendons, aorta, liver, and kidney. Mesoporous silica NPs (MSNs) as a kind of silica-based NPs have been wildly used in biomedicine because of their high specific surface area, adjustable size, porosity parameters, high biocompatibility, and nontoxic degradation products in biorelevant media, thus providing a large reservoir for the packaging of guest goods. He and co-authors effectively coated the hydrophobic manganese carbonyl (MnCO) prodrug on the advanced hollow MSN carrier to achieve a new H2O2 responsive CO treatment nano-drugs. Afterward, a nanomedicine-based strategy of a mitochondria-targeted and intramitochondrial microenvironment-responsive prodrug (iron carbonyl [FeCO]-TPP)-loaded mesoporous silica nanomedicine (FeCO-TPP@MSN@HA) was proposed for mitochondrial-targeted CO therapy. The developed FeCO-TPP@MSN@HA nanomedicine could realize precise gas treatment by delivering carbon monoxide to the mitochondria of cancer cells. To improve cancer treatment outcomes, a CO-delivery nanomedicine (FeCO-MnO2@MSN) has been synthesized by introducing manganese dioxide (MnO2) NPs and FeCO into MSNs to achieve the synergetic gas/chemodynamic therapy under the response of tumor acidic microenvironment. Therefore, silica nanomaterials demonstrate excellent performance as drug carriers in biomedical applications and are expected to produce valuable pharmaceuticals in the future.

Carbon, a component present in millions of various compounds, is found in every living organism. Because a series of exciting carbon nanomaterials are being developed, carbon-based nanomaterials are wildly used in biomedical because of their favorable chemical and physical properties, including electrical, thermal, optical, and structural diversity, particularly in the biomedical imaging and cancer therapy areas. Given the existence of diverse allotropes of carbon, there are many types of carbon-based materials, such as diamonds and the newly discovered and promising carbon nanotubes, graphene oxide (GO), graphene quantum dots, and fullerene. Given the deeper appreciation and development of carbon-based nanomaterials, GO has been noted for its favorable chemical and physical properties, including electrical, thermal, optical, and structural diversity, particularly in the biomedical imaging and cancer therapy areas.

2.4 Metal-organic framework

MOFs are a new type of porous organic-inorganic crystal hybrid materials dominated by the self-assembly of metal atoms and organic units. They are widely used due to their various superior properties and functions. The orderly arrangement between linkers and metal ions endows MOFs with different pores, tunnels, and cages, thus suggesting a high potential for loading different cargo molecules. Furthermore, MOFs can have their surfaces further modified to increase their functionality. In addition, some lanthanide-containing metal oxides and/or light-emitting organic ligands can generate fluorescence or phosphorescence under ultraviolet light irradiation. Therefore, the choice of organic and inorganic components can enable modulation of the crystalline structure and chemical functionality of MOFs, thus supporting their use in a wide range of applications, including gas storage, catalysis, and drug loading. More importantly, various MOFs can be triggered by external stimuli (magnetic field, acid, temperature, and light), thus enabling their use in bioimaging and drug delivery.

Molecular imaging has become an emerging field of medicine, which uses auxiliary contrast agents to evaluate the effect of drugs. Recently, MOFs have received extensive attention in the field of bioimaging due to their easy cellular internalization, good dispersion stability, and high bioavailability. MOFs can be used as magnetic resonance contrast agents for MRI via coordinating superparamagnetic metal ions, and luminescent building blocks (ligand or metal ions) for optical imaging by incorporating fluorescent. For instance, Taylor et al. have reported Mn-based nanoscale MOFs with controllable morphology and demonstrated its potential for MRI contrast with extraordinarily high MR enhancement. In particular, the fluorescent ligands MOF provided play a key role in luminescent sensor and biological imaging, which improve the coordinated interactions of alterable fluorescence. Jin and coworkers have constructed a new Ti-based MOF (Ti-MOF) for loading CO prodrug (MnCO) to achieve CO releasing under the response of intratumoral H2O2 and CO monitoring through fluorescence imaging.
fluorescence annihilation effect after Ti-MOF loaded with MnCO and the fluorescence activation effect after Ti-MOF releases CO are used to realize real-time fluorescence monitoring of CO release. In addition, the high specific surface area and porosity enable loading and release of different cargoes, particularly therapeutic agents. In 2006, Férey and co-workers reported that MOFs could be used as a drug delivery system due to their remarkable capacity for drug loading and their controlled release behavior. Smart materials including stimuli-responsive MOFs have received substantial attention, particularly in the biomedical field used for controllable drug release. A nanoscale MOF based on porphyrin-palladium (Pd-MOF) was developed by Zhou et al. The highly dispersed palladium atoms were used to absorb hydrogen gas for photocoustic imaging-guided hydrogen-thermal therapy. Therefore, MOFs exhibit important advantages for outstanding applications in biomedicine, as compared with the traditional materials. More functional MOFs are expected to be designed and synthesized as superior gas-based nanocarriers for controlled gas release.

3 | STRATEGIES FOR GENERATING GAS

The development of nanomedicines to achieve precise control of gas release plays an important role in improving gas therapy efficacy. In this section, we summarize two kinds of gas-based nanomedicines from the viewpoint of gas release. Stimuli-responsive gas prodrug molecules release gas molecules, depending on the properties of nanocarriers, under different stimuli, such as pH, glutathione (GSH), H2O2, or NIR light (Figure 3). In situ gas-generating nanomedicines can generate gas molecules through photocatalytic reaction, chemically catalytic reaction, and enzymocatalytic action (Figure 4). The following two sections describe the strategies for devising gas-based nanomedicine and provide typical examples.

3.1 | Stimuli-responsive gas prodrug molecules

3.1.1 | pH

Nanosystems that respond to the tumor microenvironment (TME) have drawn extensive attention in recent years, due to their potential applications in precise treatment of cancer. Weak acidity is an important feature of malignant tumors and the design of pH-responsive nanomedicines could achieve precise gas targeting to tumors (Figure 3A). Metastable γ-phase manganese sulfide (MnS) NPs are promising for tumor pH-responsive H2S prodrugs. In light of this principle, He et al. have devised a nanomedicine based on metastable γ-MnS (MnS@BSA) for the combination of gas therapy and chemodynamic therapy based on the pH-responsive H2S prodrugs. The acidic TME could trigger the dissociation of MnS@BSA and thus release Mn2+ and H2S gas. In the meantime, the production of •OH radicals and pH-responsive H2S gas release realize the combination of chemodynamic therapy (CDT) and gas therapy. Free ammonia borane (AB) rapidly decomposes into H2 in the acidic phosphate buffer saline (PBS) and reflects high acid responsiveness. Recently, He et al. have used AB as a hydrogen prodrug and loaded it into mesoporous silica (AB@MSN) to achieve intratumoral high-payload delivery and in situ acid-triggered release of H2. Later, Zhang et al. designed a nanosystem based on biomembrane-coated polydopamine and AB was loaded into NPs under the interaction of hydrogen bonding for combined photothermal therapy and hydrogen therapy. Sulfur dioxide (SO2) is a double-faced gas molecule. As reported, SO2 is another promising therapeutic gas in a number of diseases and conditions after CO and NO. However, the limited gas penetration depth confines the in vivo and in situ delivery of SO2. Lu et al. have proposed a gas therapeutic based on SO2 prodrug, which can precisely control SO2 gas release under both photothermal and pH stimuli, thereby realizing the synergy of gas therapy and photothermal therapy. Besides, the mechanism of SO2 inducing cell apoptosis based on the nanoplatform has been found to involve the upregulation of intracellular ROS levels and the modulation of apoptosis-related proteins. Thus, this strategy may be worthy of further development for deep tumor therapy.

3.1.2 | Glutathione

GSH is another endogenous stimulus source to control gas release and a significant intracellular anti-oxidant. The level of GSH in cancer cells is higher than that in normal cells. Therefore, GSH-responsive gas release is possibly achieved by GSH-sensitive nanocarriers, such as MSNs, amphiphilic polymeric NPs, and organo-inorganic complexes. Li et al. have integrated a ratiometric photoacoustic (PA) probe (cyanine [CY]) with a GSH-activated H2S donor (polysulfide [PSD]) to form CY-PSD NPs for triple-negative breast cancer therapy. The PSD-based theranostic agent reacts with GSH and generates H2S by decomposed tetrasulfide bonding. Moreover, the generated H2S can be monitored by PA signals emitted by CY, thus resulting in cytotoxicity toward MDA-MB 231 cells (where MB refers to methylene blue) and further causing
tumor inhibition by inducing apoptosis (Figure 3B). Liu et al. have designed GSH-responsive NO-releasing mannan NPs (NO-mannan) for NO-enhanced photodynamic therapy (PDT). GSH triggers hydrophobic–hydrophilic transition of NO-mannan and in the meanwhile generates NO under the reductive hypoxic TME. Importantly, the NO-induced hypoxia relief enables NO-mannan to enhance PDT, thus potentially providing an applicable method for efficacious PDT treatment of cancer. To validate the anti-MDR of SO2 in cancer therapy, Shen et al. have designed a GSH-responsive SO2 polymeric prodrug as a nanocarrier. The obtained amphiphilic polymeric pro-
drug releases SO₂ rapidly in response to thiol compounds, as triggered by GSH, and the releasing rate of SO₂ is dependent on GSH concentration. SO₂ and DOX act in synergism to enhance anti-tumor effects against MCF-7 ADR cells both in vitro and in vivo. Therefore, it is promising to develop GSH-responsive gas-releasing nanomedicine.

3.1.3 Hydrogen peroxide

Hydrogen peroxide (H₂O₂) is fairly higher in the TME than in normal cells/tissues, which is another characteristic of tumors. Therefore, to ingeniously design H₂O₂-responsive gas-releasing nanomedicines is of practical significance. Jin and co-workers have developed a novel H₂O₂-responsive nanomedicine for CO therapy (Figure 3C). This work first demonstrated that MnCO could react with over-secreted H₂O₂ inside a tumor, thus causing in situ CO release through a new Fenton-like reaction. Subsequently, they constructed a new Ti-MOF for adsorption and coordination of CO-releasing nanocomplex manganese carbonyl to realize H₂O₂-responsive CO releasing. However, the limited (generally less than 20 μM) concentration of H₂O₂ in the TME made H₂O₂-responsive gas releasing not the best way. To address this critical issue, a cascade reaction was introduced in the TME. Glucose oxidase (GOx) oxidizes intratumoral glucose to toxic H₂O₂, and H₂O₂ further leads to oxidation of L-arginine (L-Arg) to NO. Therefore, a novel L-Arg and GOx co-loaded hollow mesoporous organosilica nanomedicine (L-Arg-HMON-GOx) has been constructed for combined cancer starvation-like/gas therapy without a need for external excitation. In addition, the depletion of intratumoral H₂O₂ could lead to the apoptosis of tumor cells, because ROS has a great impact on the development of potential cancer therapies through adjusting cellular
redox levels. Thereby, the design of dual pro-oxidation therapies is of great potential to be potent in selectively combating cancer cells.

3.1.4 Near-infrared light

In the past few years, many photo CORMs have been developed for precise temporal-spatial control of gas release, thanks to the non-invasive, inexpensive, and controllable characteristics of light. NIR light is a favorable choice, owing to its higher tissue penetrability and lower phototoxicity. To fulfill intracellular delivery of CO, He et al. have constructed a NIR-responsive nanosystem by trapping MnCO CORMs within a small GO nanosheet, which could load drug and collect/convert NIR light energy to promote the release of CO. A series of NIR-responsive stimulations were later reported. Our group has fabricated an intelligent NIR laser-triggered NO nanogenerator to treat MDR cancer by incorporating photothermal agents, which may provide insights regarding other NO-relevant medical treatments. Substantial hydrogen can be integrated and stabilized in the Pd atom to form Pd hydride. Therefore, Zhao et al. have developed PdH0.2 nanocrystals for photothermal agents, which may provide insights regarding other NO-relevant medical treatments. SO2, one important endogenous gasotransmitter, combats diseases by virtue of its vasorelaxant effect, anti-mycobacterial characteristics, and a combined treatment method for overcoming drug resistance in cancer chemotherapy. In studies of the mechanism of SO2 killing tumor cells, Li and co-workers have constructed SO2 prodrug-loaded rattle-structured silica-coated upconversion NPs based on NIR light-triggered SO2 generation. They have found that SO2 could increase intracellular ROS levels to cause the nuclear DNA of cancer cell damage and induce cell apoptosis. This NIR light-triggered gas nanomedicine may provide an outlook of advancing synergistic cancer therapy platforms.

3.1.5 Others

X-ray and ultrasound (US) can also be used for controlled gas release because of their high tissue penetration ability. Recently, Shi and co-workers have described a smart X-ray-activated NO-releasing upconversion nanoplatform that was sensitive to X-rays for cleaving the S-N bond of S-nitrosothiol (SNO) and then causing NO release (Figure 3E). However, high-dose X-rays (>5 Gy) were required, which may result in serious adverse effects and inevitably cause harm to normal tissues. To develop an NO delivery system with low-dose X-ray stimulation, Xue et al. have designed a novel soft X-ray-activatable persistent luminescence nanotransducer for tunable and endurable NO release. Though this nanoplatform utilized an ultralow dosage (down to 0.9 mGy) soft X-rays, it has successfully achieved persistent luminescence and continuous NO release for approximately 40 min after stopping X-ray irradiation. The tissue penetration depth of US reached 20 cm under a 1 MHz US wave and the US wave could facilely be focused on a small region of the body (Figure 3F). CO2 induces the necrosis of tumor cells via blocking the blood supply and inhibiting the growth of panc-1 pancreatic solid tumors. Zhang et al. have developed a novel physical treatment by using a nanobomb system based on CO2 bubbles. CO2 bubbles were quickly released by therapeutic US waves and the generated bubbles waves effectively induced panc-1 cells’ instant necrosis and blood vessel destruction within panc-1 tumors. X-rays and US-responsive nanomedicines may open new possibilities for therapy of deep tumors with alleviated adverse effects.

3.2 In situ gas-generating nanomedicines

The aberrant metabolism of cancer cells results in a TME with unique characteristics, such as over-production of lactic acid, and fairly higher concentrations of GSH and H2O2. In addition, the uncontrolled growth of cancer cells and structurally abnormal blood vessels in tumor tissues bring about hypoxic (oxygen-lacking) microenvironment in solid tumors. Therefore, the design of NPs with diverse nanostructures could produce chemical catalysis reactions under either the endogenous TME or exogenous physical stimuli. A variety of new nanoplatforms have been devised for in situ stimuli-responsive gas generation. This tumor-specific gas generation, including photocatalytic, chemically catalytic, and enzymocatalytic generation, will be delineated in the following parts.

3.2.1 Photocatalysis

Photocatalysis excites the electrons in the valence band to the conduction band under light irradiation, leaving holes in the valence band, thereby generating negative-electron (e-) and positive-hole (h+) pairs. The electrons and holes have reducing and oxidizing characteristics respectively, thus producing therapeutic gas under the TME to improve cancer therapy. HisAgCCN is a photactivated nanomaterial which can cause the conversion of endogenous CO2 to CO in vivo. Inspired by Ag3PO4 doped carbon-
dot-decorated C₃N₄ NPs (AgCCN), an excellent Z-scheme system to transform CO₂ to CO, Zheng et al. have constructed HisAgCCN by modified AgCCN as photocatalysts to transform tumor endogenous CO₂ to CO for enhancing chemotherapy (Figure 4A). Interestingly, HisAgCCN promotes mitochondrial biogenesis and aggravates oxidative stress in tumor cells, while reducing the side effects of chemotherapy to normal cells. Hydrogen has been identified as a potentially safer gas without blood poisoning risk in the anti-cancer field, as compared with NO, CO, and H₂S gases. To solve the problems of low water-soluble and poor hydrogen delivery, Sun et al. have synthesized a photoactivated H₂ nanogenerator comprising [FeFe]-hydrogenase, fluorinated chitosan (FCS), and gemcitabine (GEM). FCS was used to improve the transmembrane and transmucosal delivery of the nanogenerator. Meanwhile, GEM together with [FeFe]TPP realizes controlled H₂ release within tumors under laser (660 nm) irradiation, thus significantly enhancing the efficacy of intravesical instillation chemotherapy. The accumulated concentration of H₂ was locally generated from NPs through 660 nm laser (2 W/cm²) continuous irradiation for 5 h, thus showing the high stability of [FeFe]TPP and supporting photocontrolled release of H₂. Therefore, drug-free nanocatalysts may avoid toxic adverse effects and address drug content-limited therapeutic efficacy.

### 3.2.2 Chemical catalysis

Chemical catalytic reactions widely occur in tumors, thus generating abundant and special chemicals and products with tumor-specific theranostic effects. One of the typical catalytic reactions is the Fenton reaction, which uses bivalent iron ions (Fe²⁺) to catalytically generate toxic ⋅OH radicals in the presence of intratumoral H₂O₂. On this basis, a number of Fe-based nanoplatforms have been utilized as the Fenton reagent for CDT. Considering the overexpression of H₂O₂ in the TME, Jin et al. have designed an H₂O₂-responsive CO-releasing nanomedicine, MnCO@hMSN. The MnCO in the nanomedicine catalyzes H₂O₂ to ⋅OH. The oxidation and then competitively coordination with the manganese center of hydroxyl radical could lead to TME-specific release of CO. The nanomedicine exhibits good anti-tumor activity both in vitro and in vivo. Low concentrations of NO were always used in treating physiological diseases. High concentrations of NO could realize effectively cancer treatment. To deliver NO in a continuous manner, Li et al. have constructed a NO synthase (NOS)-like nanoplatform (NanoNOS) (Figure 4C). A mesoporous silica shell was used to protect the catalytic activity of gold nanorods. NanoNOS catalyzes nicotinamide adenine dinucleotide phosphate (NADPH), L-Arg, and O₂, thus generating NO in a three-step process through a cascade reaction. NADPH is oxidized by NanoNOS, thereby resulting in the production of O₂− and the subsequent dismutation of O₂ to H₂O₂ via SOD-like activity. The generated H₂O₂ subsequently accelerates oxidizing L-Arg and produces NO via a nonenzymatic pathway. Nanoreactors, acting as artificial cell-like devices that can initiate cascade reactions, have recently been investigated as potential therapeutics for deadly diseases. Mu et al. have introduced a unique planar MOF-based hybrid nanoplatform by the integration of ultrasmall gold NPs (Au NPs) and L-Arg as nanozyme and NO donor, respectively. The glucose-metabolic reaction generates H₂O₂ through the oxidation of Au, which drives biocatalytic cascades that convert L-Arg into NO. The chemical catalytic reaction may pave the way to exploring bioinspired nanoreactors for their cooperative anti-cancer effects.

### 3.2.3 Enzymocatalysis

Enzymes are natural and sustainable catalysts. Enzymatic processes are environmentally friendly and cost-effective, with high rates and selectivity. In recent years, biocatalysis has emerged as an important green chemical reaction in the biomedical domain. However, long-term operational stability is a major drawback, and it is hard to recover and reuse enzymes. Thanks to advances in nanotechnology, loading into nanocarriers is necessary to enhance the stability and recyclability of biocatalysts in comparison with free enzymes. Chandrawati et al. have developed an NO delivery platform by encapsulating β-galactosidase into polymeric carriers to control the amount and time of NO release via a biocatalysis mechanism for glaucoma therapy. After the degradation of the lipid vesicles, followed by the enmeshed enzyme and NO donor, β-galactosidase, NO is slowly released through the enzymatic activity of β-galactosidase. Using the strategy of delivering specific enzymes to the disease site, Shi et al. have proposed to deliver catalase to tumors, so that intratumoral H₂O₂ can be decomposed to O₂ under the catalysis of catalase. The authors have immobilized catalase in the large open pore channels of dendritic-structured mesoporous organosilica NPs (MON), forming a hybrid catalytic nanoreactor (Figure 4B). The in situ endogenously catalytic generation of O₂ bubbles enhances high-intensity focused US ablation, hence enabling much more precise and efficient surgery by means of high-intensity focused US ablation in future clinical applications. The efficacy of traditional PDT agents is to a large extent restricted by the low concentration of O₂ in the tumor region. To overcome the problem derived from tumor hypoxia, Chen et al. have developed an H₂O₂-activated O₂-releasing and
evolving PDT NP, which consist of a photosensitizer and catalase in the aqueous core, and a black hole quencher in the polymeric shell. They have also used enrichment of \( \text{H}_2\text{O}_2 \) in the tumor region, which penetrated the shell into the core and was then catalyzed to \( \text{O}_2 \) by catalase. This strategy uses catalase to trigger an increase in \( \text{H}_2\text{O}_2 \) for gas therapy, thus providing a method through which enzymatic catalysis causes no significant cytotoxicity to normal cells which express low \( \text{H}_2\text{O}_2 \).

4 | GAS-BASED NANOMEDICINES FOR ENHANCED CANCER THERAPY

Gas therapy is drawing attention in nanomedicine as a safe and enhanced therapeutically efficient technique. However, a single therapeutic effect is inevitably accompanied by limited efficacy. Often, tumors cannot be completely eliminated by individual gas therapy. Therefore, this therapy is often combined with other therapeutic methods, like chemotherapy, photothermal therapy, and PDT. Understanding the mechanism of gas enhancing other therapeutic modalities will aid in designing reasonable strategies for clinical cancer therapy. In the sections below, we generalize the mechanisms of gas-based nanomedicines enhancing cancer therapy in detail. These mechanisms are also listed and summarized in Table 1.

4.1 | NO-based nanomedicines

NO, a free-radical gas, is endogenously generated from L-Arg by NOSs and has attracted considerable attention. A recent study has shown that NO has a biphasic effect (pro- and anti-tumor) on cancer development. Low levels of NO are beneficial to cell growth and anti-apoptotic responses, and cell cycle arrest and apoptosis can be easily induced by high levels of NO conversely. The positive effect at low doses of NO activates the cyclic guanosine monophosphate pathway, a critical mediator of the long-term proliferation response. As NO concentrations increase (>1 \( \mu \text{M} \)), hypoxia-inducible factors (HIFs) are stabilized, and the accumulation of p53 is hindered effects associated with suppressed cell proliferation. Hypoxia in tumor cells is considered the main reason for poor therapeutic effects. To relieve hypoxia in tumor cells, Zhang et al. have designed a Bi-SNO NP that served as a valid hypoxic radiosensitizer by triggering NO release via X-rays to enhance the efficacy of radiotherapy. Additionally, HIF-1a expression in tumors declined after injection of Bi-SNO and treatment, thus demonstrating that NO alleviates the tumor cellular hypoxic conditions. Furthermore, NO mediates angiogenesis, epithelial-mesenchymal transition, and metastasis. Sung et al. first demonstrated that a NO-based nanomedicine can efficiently reprogram the tumor vasculature and immune microenvironment to overcome the resistance of cancer therapy by normalizing tumor vessels, ameliorating the immunosuppressive TME, suppressing tumor metastases, and improving the anti-cancer effectiveness of three treatment modes—chemotherapy. Our group has fabricated NIR laser-triggered NO nanogenerators for reversing MDR in cancer (Figure 6A). The generated NO molecules have been shown to have chemosensitizing effects by suppressing the expression of an efflux pump protein (P-glycoprotein), thus successfully achieving MDR reversal. Recently, researchers have been inspired by this finding to develop delivery systems combined with NO and drugs. Moreover, Kim and co-workers have revealed the mechanism underlying the reversal of MDR for chemotherapy mediated by NO (Figure 5A). NO overcomes MDR by decreasing the DNA repair and detoxification, strengthening nuclear drug transport, inhibiting the expression of HIF and nuclear factor-\( \kappa \)-B (NF-\( \kappa \)-B), and/or inactivating drug efflux proteins. Therefore, a combination of NO and drug delivery systems is expected to augment chemotherapy for clinical applications.

4.2 | CO-based nanomedicines

CO was first described by John Haldane for its physiological effects on the human body through its binding. Its strong affinity for hemoglobin (>220-fold greater than that of oxygen) has caused CO to be viewed as a silent killer. With in-depth studies on CO, potential clinical therapeutics have received greater attention in the form of inhaled gaseous therapy. Extensive preclinical evidence in large and small animals has suggested that CO and CORMs have beneficial effects on cardiovascular disease, sepsis and shock, kidney and liver injury, cancer, and acute lung. CORMs provide a secure approach to control CO release as an advanced cancer therapy. Recent studies have found that CO can be used for anti-angiogenic therapy in triple-negative breast cancer by decreasing vascular endothelial growth factor (VEGF) expression and inhibiting phosphorylation of VGEF receptor 2 and downstream proteins to decrease the migration and tube formation capacity of the endothelial cells. Hypoxia is usually lower in early-stage tumors than in advanced tumors, and CO increases mitochondrial biogenesis and accelerates mitochondrial oxygen consumption (Figure 6B). On this basis, Li et al. have developed a cooperative anti-cancer therapeutic approach involving bioreductive chemotherapy and CO-mediated pro-apoptotic gas therapy. They have synthesized Prussian blue NPs as a photothermal
**TABLE 1**  Mechanism summary of different types of gases for cancer treatment

| Gas | Mechanism | Refs. |
|-----|-----------|-------|
| NO | • Activate the cyclic guanosine monophosphate (cGMP) pathway.  
    • Stabilize hypoxia-inducible factor (HIF-1).  
    • Suppress the accumulation of p53.  
    • Reprogram the tumor vasculature to overcome resistance to cancer therapy.  
    • Ameliorate immune microenvironments to suppress metastasis.  
    • Downregulate the expression of P-gp protein to overcome MDR. | 133,135,139,113,129 |
| CO | • Downregulate the expression of VEGF.  
    • Inhibit the phosphorylation of VEGFR2.  
    • Decrease the migration of downstream proteins and the tube formation ability of endothelial cells.  
    • Increase mitochondrial biogenesis.  
    • Accelerate mitochondrial oxygen consumption.  
    • Induce ferroptosis. | 146,144,147,148,157 |
| H2S | • Enhance cancer glycolysis.  
    • Cause intense intracellular acidification.  
    • Downregulate downstream anti-apoptotic proteins.  
    • Suppress the NF-κB and STAT3 pathways.  
    • Inhibit oxidative stress. | 159,160,161,107 |
| H2 | • Reduce hydroxyl radicals;  
    • Perturb redox homeostasis and cause redox stress.  
    • Enhance VDAC1 phosphorylation.  
    • Disrupt mitochondrial membrane potential.  
    • Inhibit mitochondrial function.  
    • Inhibit ATP synthesis.  
    • Downregulate the expression of P-gp protein to overcome MDR. | 166,167,113,173 |
| O2 | • Improve hypoxia. | 124,175 |
| SO2 | • Downregulate the expression of P-gp protein to overcome MDR. | 105,176 |

Abbreviations: ATP, adenosine triphosphate; MDR, multidrug resistance; NF, nuclear factor; STAT3, signal transducer and activator of transcription 3; VEGF, vascular endothelial growth factor; VEGFR2, vascular endothelial growth factor receptor 2.

CO-generating reagent created the hypoxic environment in tumor cells and activated the hypoxia-bioreducible chemical of tirapazamine, which synergizes with CO-mediated pro-apoptotic effects for enhancing anti-tumor efficacy. In addition, CO-induced mitochondrial depletion also leads to ROS production and apoptosis of cancer cells. To our knowledge, mitochondrial damage activates mitophagy and autophagy induced by adenosine triphosphate (ATP) shortage for self-protection. Wang and co-workers have designed a durable and biocompatible metal carbonyl complex delivery nanoplatform (Fe(CO)\(_5@Au\)) by placing iron pentacarbonyl (Fe(CO)\(_5\)) inside an Au nanocage to achieve CO-induced autophagy for improving cancer therapy (Figure 5B). The released CO damages mitochondria and subsequently initiates autophagy. The nanomaterial accumulates in autolysosomes and results in their destruction during autophagy, thus achieving synergistic effects in cancer cells. In addition, Zhang et al. have developed a US-driven biomimetic nanosystem with excellent synergistic antitumor effects, which has shown excellent effective suppression of tumor growth through US/H\(_2\)O\(_2\)-generated \(^1\)O\(_2\) and CO-induced cell apoptosis and mitochondrial dysfunction. Recently, our group has reported a versatile CO/thermo/chemotherapy nanoplatform (FeCO-DOX@MCN) for the combined treatment of CO-induced ferroptosis. FeCO-DOX@MCN nanomedicine efficaciously kills cancer cells, and the released CO extremely increases the sensitivity of cells to chemotherapeutics. Importantly, cell viability is obviously developed when a typical inhibitor of ferroptosis (ferrostatin-1) is added, thus indicating that ferroptosis was an important factor for CO to increase the sensitivity of cancer cells to chemotherapeutic agents. Therefore, we conclude that CO influenced cellular behavior by increasing mitochondrial biogenesis and driving mitochondria, thus increasing ATP and ROS production.
4.3 H$_2$S-based nanomedicines

H$_2$S is recognized as a third endogenous gas-transmitter, along with NO and CO, which have dual roles in promoting and inhibiting cancer. Goubern et al. have found that H$_2$S has a very high affinity to mitochondria as an energetic substrate at low micromolar concentrations, thus providing additional compelling evidence that H$_2$S participated in the regulation of the various physiological processes.

Recent studies have reported that H$_2$S leads to cancer cell death, as a poisonous molecule at high doses, without affecting the viability of normal fibroblast cells. Further studies have revealed the possible mechanisms of this anti-cancer effect. H$_2$S overdrives cancer glycolysis,
FIGURE 6  Gas-based nanomedicines for enhanced cancer therapy: (A) Reversal of multidrug resistance in cancer by near-infrared (NIR) laser-triggered nitric oxide nanogenerators. Reproduced with permission. Copyright 2017, Wiley-VCH. (B) Programmed reactive oxygen species (ROS)/CO-release of nanomedicine for synergetic chemodynamic-gas therapy of cancer. Reproduced with permission. Copyright 2019, Nature Publishing Group. (C) ZnS@ZIF-8 core-shell nanoparticles incorporating indocyanine green (ICG) and tirapazamine (TPZ) achieve H₂S-sensitized synergistic antitumor effects, on the basis of cascade photodynamic therapy (PDT)/chemotherapy. Reproduced with permission. Copyright 2020, Ivyspring. (D) Palladium nanocrystal-engineered metal-organic frameworks for synergistic hydrogen/photodynamic therapy. Reproduced with permission. Copyright 2021, Wiley-VCH. (E) Near-infrared light triggers sulfur dioxide gas for cancer therapy. Reproduced with permission. Copyright 2019, American Chemical Society. (F) Tumor microenvironment-responsive mesoporous MnO₂-coated upconversion nanoparticle for chemo-photodynamic therapy. Reproduced with permission. Copyright 2018, Wiley-VCH.

thus resulting in high metabolic acid production, which in turn results in intense intracellular acidification and subsequently cancer cell death. As can be seen in Figure 5C, Lee et al. have studied H₂S to the reaction of the viability of cancer and non-cancer cells in view of cancer cells’ glycolytic nature and metabolism. The released H₂S significantly increases glycolysis, thus leading to lactate overproduction and cancer cell death without notable intracellular acidification or cell death in noncancer cells, thus illustrating that H₂S enables selective anti-cancer therapy by targeting metabolic processes and pH homeostasis in cancer cells. In addition, H₂S downregulated the downstream anti-apoptotic proteins by inhibiting the NF-κB and signal transducer and activator of transcription
3 pathways, thus causing cancer cell apoptosis. To further verify the pharmacological mechanism of H$_2$S, Li et al. have developed a thiol-initiated H$_2$S therapy for triple-negative breast cancer, which consisted of PSD and CY. They have performed proteomics analysis and a detailed investigation of the anti-cancer mechanism of CY-PSD NPs. They have observed mitochondrial dysfunction through a suppressing energy supply and apoptosis initiation, and the suppression of oxidative stress caused by H$_2$S, thus resulting in significant cytotoxicity to cancer cells. In addition, PSD has been integrated with CY in a theranostic nanosystem capable of real-time monitoring of released H$_2$S to detect therapeutic concentrations and tumor targeting for precise cancer therapy. Studies have also found that excessive H$_2$S increases oxidative stress through suppression of the enzyme catalase in cancer cells, which leads to increased ROS levels, H$_2$O$_2$ over-production, and DNA damage. Therefore, many combined therapies based on H$_2$S have been designed, including H$_2$S-amplified chemotherapy, H$_2$S-amplified ROS-based therapy, and H$_2$S-primed chemodynamic therapy (Figure 6C). H$_2$S provides an extraordinary way for material design through combining other therapies as an enhanced cancer treatment strategy.

### 4.4 H$_2$-based nanomedicines

Hydrogen gas (H$_2$) has higher biosafety than NO, CO, and H$_2$S, as well as cancer-selective effects while protecting normal cells. A well-known mechanism has been attributed to the selective anti-oxidation property of H$_2$ through selective reduction of hydroxyl radicals. Typically, in the TME, redox homeostasis can be perturbed and which results in redox stress, thus leading to cell damage and apoptosis. However, in normal cells, H$_2$ plays a protective role by removing excess ROS and preventing oxidative damage. Therefore, the minimal adverse effects of their byproducts make H$_2$ therapy secure and efficient for clinical applications. Prevalent pathways for H$_2$ therapy in clinical settings are inhalation of hydrogen-containing air, oral intake of hydrogen-rich water, and injection of hydrogen-rich physiological solutions, the concentration of which is limited due to their very low water solubility. Therefore, It is necessary to find strategies for targeting the delivery of H$_2$ and precise treatment. For targeted hydrogen therapy, He and co-workers have fabricated an AB-loaded mesoporous silica nanomedicine (AB@MSN) and carboxymethyl cellulose (CMC)-stabilized Fe (Fe@CMC) NPs to achieve in situ acid-controlled release of H$_2$. Interestingly, they have found that hydrogen molecules attenuate the toxic adverse effects of chemotherapy and enhance its effectiveness by developing a novel hydrogen-gas producing prodrug. Many synergistic treatment strategies have been developed. Sun et al. have clarified the mechanism of hydrogen chemotherapy by investigating the metabolic behavior of intracellular drugs (Figure 5D). They have found that the combination of hydrogen with chemotherapeutic drugs enhances the phosphorylation of voltage-dependent anion channel 1 (VDAC1), and decreases mitochondrial membrane potential, inhibits mitochondrial function, and hinders ATP synthesis, thus leading to down-regulation of P-gp proteins for enhancing the drug transport capacity. Zhu et al. have used the anti-inflammatory effect of hydrogen to decrease the adverse effects of single thermal therapy on normal cells/tissues and enhance photothermal therapy. Recently, Zhu and co-workers have designed a nanoscale porphyrin MOF integrated with nanopalladium crystals for synergistic hydrogen/PDT (Figure 6D). Hence, H$_2$ is particularly prospective for tumor therapy as a tumor-specific therapeutic gas.

### 4.5 Other gas-based nanomedicines

Except for the aforementioned gases, oxygen (O$_2$) and SO$_2$ have been extensively explored in biomedical applications as well. The inherent hypoxia and inefficient O$_2$ supply in solid tumors are the main obstacles to cancer therapy. Tumor progression and proliferation contribute to higher H$_2$O$_2$ accumulation in the TME than in normal tissue, thus inspiring many researchers to use catalase to produce O$_2$ from H$_2$O$_2$ to improve therapeutic efficacy. Liu and co-workers have developed a multiscale hybrid catalytic by using MON with large open pore channels for immobilizing catalase, which exhibits sensitivity to the catalytic activity of H$_2$O$_2$. The generated O$_2$ strongly enhances the high-intensity focused US ablation. MnO$_2$ is an important reagent that reacts with H$_2$O$_2$ through a disproportionation reaction, forming O$_2$. Liu and co-workers have developed an intellectual biodegradable hollow MnO$_2$ (H-MnO$_2$) nano-platform for co-loading chlorine and doxorubicin to achieve oxygen sensitization for combined chemo-PDT. Zhang and co-workers have found that MB activates O$_2$ and induced lipid peroxidation, thus breaking liposomes, enlarging the contact area between CaO$_2$ and H$_2$O$_2$ and resulting in accelerated production of O$_2$ after short irradiation periods. Therefore, the authors designed a liposome-based NP with O$_2$ self-sufficient properties (LipoMB/CaO$_2$) for PDT against hypoxic tumors (Figure 5F). However, MDR occurs during several courses of chemotherapy, thus significantly decreasing the effectiveness of cancer treatment. SO$_2$, produced through the body’s metabolic processes, can be used for combating MDR in cancer therapy. Shen and
co-workers have designed a GSH-responsive polymeric prodrug of SO₂ to combat MDR in MCF-7 ADR cancer cells. The released SO₂ increases ROS in tumor cells and then causes oxidative damage, thus sensitizing MCF-7 ADR cells to DOX. Our group has prepared a high SO₂-loading nanosystem for overcoming the MDR to augment tumor accumulation and treatment efficacy through suppressing the expression of P-glycoprotein (Figure 5E). Therefore, gas therapy may provide a new strategy for cancer therapy.

5 | CONCLUSION AND OUTLOOK

Gas-based therapeutics is an emerging method for selective cancer killing while protecting normal cells. Many gas-releasing nanomedicines using multifunctional nanoplatforms have been designed for cancer treatment. In this review, we introduced the recent advances in gas therapy in detail. The designed stimuli-responsive nanocarriers are encouraging in healing malignant tumors with reduced risk of gas poisoning. Furthermore, some gas molecules have been combined with other therapeutic approaches. For example, NO molecules have been used to reverse MDR, and oxygen has been used to enhance radiotherapy and PDT. However, many challenges for gas-related applications remain, which require in-depth exploration. For example, most gas releasing platforms have short release times, thus weakening the therapeutic effect. In addition, developing nanomedicines with the on-demand gas release is important. With the rapid development of gas therapy-related basic research, increasing novel gas-based nanomedicines have been designed. However, many unknown areas exist regarding the biological effects of nanomaterials on cells or the body. The nanomaterials used in the clinic are usually very simple and differ from the described functional nanomaterials. Therefore, a long path to the use of novel gas-based nanomedicines in clinical settings remains, and treatment strategies that are simple and easy to implement should be exploited to achieve clinical gas therapy. The mechanisms of gas therapeutic effects are incompletely understood, thus limiting the application of gas therapy to some extent. The detailed mechanisms of gas therapy require further investigation and exploitation. In addition, the inhibition of cancer-related inflammation has shown great potential in preventing or suppressing cancer. The concentration-dependent influence of gasotransmitters (NO, CO, H₂S, H₂, etc.) on inflammation, either pro- or anti-inflammatory effect, remains a complex problem, while these gases often display anti-inflammatory effects at certain concentrations. Overall, gas therapy is a fast-growing field emerging in nanomedicine, and efforts should be made to understand the mechanisms and develop applications to accelerate the adoption of gas therapy in clinical settings.

ACKNOWLEDGMENT

This work was supported by the National Natural Science Foundation of China (Nos. 51933002 and 51872188) and the Program of Shanghai Academic Research Leader (20XD1400400).

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ORCID

Qianjun He https://orcid.org/0000-0003-0689-8838
Wuli Yang https://orcid.org/0000-0003-0384-9213

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he joined the Laboratory of Molecular Imaging and Nanomedicine, Fudan University. His current research focuses on gas-based nanomedicines and their applications in combination therapy of cancer.

Wuli Yang in the Department of Macromolecular Sciences, Fudan University. Her current research focuses on gas-based nanomedicines and their applications in combination therapy of cancer.

### Author Biographies

**Xianxian Yao** received her M.S. degree from University of Shanghai for Science and Technology in 2017 and obtained her Ph.D. degree at Fudan University. Since then, she has been studying as a postdoctoral under the guidance of Prof. Wuli Yang in the Department of Macromolecular Science, Fudan University. Her current research focuses on gas-based nanomedicines and their applications in combination therapy of cancer.

**Qianjun** He received his B.S. and M.S. degree respectively in Polymer and Inorganic Material Sciences at the Wuhan Institute of Technology, and obtained his Ph.D. (2010) and then became an Assistant Professor at the Shanghai Institute of Ceramics, Chinese Academy of Sciences. In 2012 he was appointed as a Marie Curie Fellow at the University of Leeds, UK. In 2014, he joined the Laboratory of Molecular Imaging and Nanomedicine, National Institute of Biomedical Imaging and Bioengineering, National Institutes of Health.
Wuli Yang received his B.S. degree in 1995, M.S. degree in 1998, and Ph.D. degree in 2001 from Fudan University. He joined the Department of Macromolecular Science at Fudan University in 2001 as a lecturer and was promoted to associate professor in 2003. In 2010, he was promoted to full professor. His research focuses on emulsion polymerization, functional inorganic nanoparticles, functional polymeric composite microspheres, and biomedical nanoparticles for diagnostic and drug delivery.