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## Gas-mediated reinforcement of cancer therapies: emerging strategies and future perspectives

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Cancer therapy has made notable progress in moving towards more precise, intelligent and personalized treatment modes. However, current approaches such as chemotherapy, phototherapy, sonodynamic therapy, and immune therapy still suffer from limitations, hindering their application in clinical practice. Gasotransmitters have long been recognized as key regulators in cancer pathology, and the development of novel therapeutic agents with gas-releasing ability aiming to establish new therapeutic modes has garnered considerable attention. In this perspective, we aim to summarize the critical roles of gaseous molecules in cancer biology and their potential mechanisms for enhancing the efficacy of dominant treatment modalities. We also provide insights into recent advances in integrating gas therapy with conventional treatments to overcome current challenges and improve therapeutic outcomes, ultimately paving the way for the development of next-generation treatment paradigms.

## Introduction

Cancer has emerged as one of the leading causes of global mortality, posing a serious threat to human health due to its complexity, heterogeneity and high fatality rate.<sup>1</sup> Current cancer treatment strategies include surgery, chemodynamic therapy (CDT),<sup>2,3</sup> radiotherapy (RT),<sup>4</sup> phototherapy (including photodynamic therapy (PDT) and photothermal therapy (PTT)),<sup>5,6</sup> thermal ablation therapy,<sup>7</sup> immunotherapy,<sup>8</sup> sonodynamic therapy (SDT),<sup>9</sup> and starvation therapy.<sup>10</sup> Although these strategies have shown considerable therapeutic efficacy, significant limitations persist. For instance, surgical resection often fails to completely remove tumor tissue, leading to recurrence. RT and CDT suffer from poor tumor selectivity, which can lead to systemic toxicity in healthy tissues and the development of therapeutic resistance. In addition, phototherapy is hindered by uneven photosensitizer distribution and inadequate tissue penetration, culminating in suboptimal therapeutic efficacy within selected tumor regions. Moreover, although immunotherapy demonstrates great therapeutic potential, it is frequently associated with immune-related adverse events

(irAEs) and suffers from limited patient response rates.<sup>11,12</sup> Therefore, the development of more effective and versatile cancer treatment approaches remains an urgent unmet need.

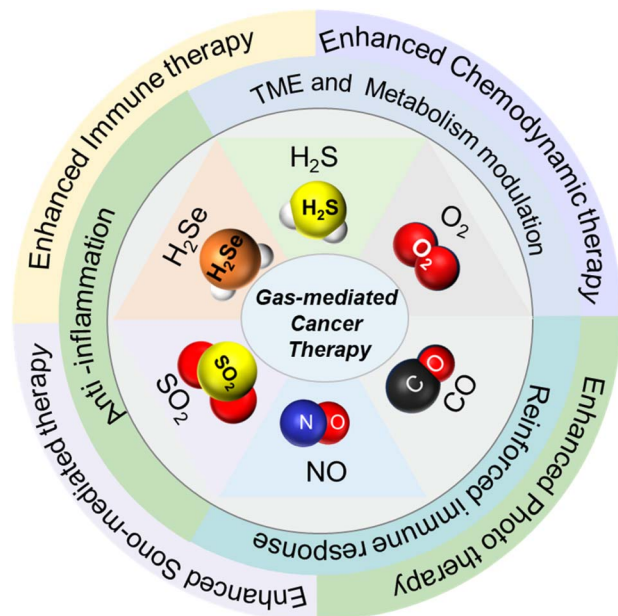
Gas therapy (GT) has emerged as a promising therapeutic modality that utilizes bioactive gaseous molecules to regulate pathological processes and exert therapeutic effects. In recent years, several physiologically significant gases, including gasotransmitters, such as nitric oxide (NO),<sup>13</sup> hydrogen sulfide (H<sub>2</sub>S),<sup>14</sup> and carbon monoxide (CO),<sup>15</sup> as well as other biocompatible gases, such as hydrogen (H<sub>2</sub>)<sup>16</sup> and oxygen (O<sub>2</sub>),<sup>17</sup> have attracted increasing attention as emerging agents in cancer therapy. Notably, the gasotransmitters often exhibit concentration-dependent biphasic effects, acting as a “double-edged sword” in both physiological and pathological contexts.<sup>18</sup> For example, H<sub>2</sub>S, produced *via* multiple endogenous metabolic pathways, induces minimal side effects in normal cells at low concentrations.<sup>19</sup> However, elevated levels of H<sub>2</sub>S in tumor tissues disrupt mitochondrial homeostasis and induce apoptosis, primarily through the inhibition of cytochrome c oxidase (complex IV, COX IV) in the electron transport chain (ETC). This suppression of mitochondrial bioenergetics impairs the biosynthesis of biomacromolecules and ultimately inhibits tumor proliferation.<sup>20</sup> Similarly, both NO and CO can inhibit COX IV and other mitochondrial enzymes, further suppressing cellular energy metabolism.<sup>21</sup> Despite considerable advances in gaseous therapeutics for tumor treatment, clinical translation remains challenging due to the need for precise regulation of the dosage and delivery strategies as improper administration may lead to severe respiratory toxicity and systemic side effects.<sup>22</sup> Furthermore, single-agent gas therapy regimens are often insufficient to achieve complete tumor eradication.

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**Scheme 1** Illustration of a novel gas-mediated cancer therapy modality, and its proposed synergistic therapeutic mechanism. Gas molecules exhibit unique therapeutic potential in oncology through diverse mechanisms of action, including anti-inflammatory effects, immune response potentiation, tumor microenvironment (TME) remodeling, and metabolic reprogramming.

Encouragingly, the integration of GT with other therapeutic modalities has emerged as a promising strategy, offering synergistic effects that enhance anticancer efficacy and provide a compelling direction for future development. When combined with CDT, RT, phototherapy, immunotherapy, or ferroptosis, gas molecules act as effective adjuvants. For instance: (1)  $O_2$  enhances the efficacy of PDT or SDT by alleviating tumor hypoxia;<sup>23</sup> (2) NO reacts with ROS to generate highly reactive cytotoxic species, such as highly toxic peroxynitrite ( $ONOO^-$ ), thereby improving the therapeutic efficacy of PDT or SDT;<sup>24–26</sup> (3) CO and NO can reverse multidrug resistance (MDR) *via* distinct mechanisms, thereby restoring chemosensitivity.<sup>27</sup> Overall, integrating GT with existing anticancer modalities may significantly potentiate their therapeutic outcomes (Scheme 1).

In this perspective, we first outline representative biotherapeutic gases (e.g., NO, CO, and  $H_2S$ ), then focus on their synergistic mechanisms in tumor therapy. Our goal is to elucidate their anticancer pathways, while highlighting their unique advantages and inherent limitations. Finally, we summarize recent advances in combining GT with other treatment modalities. This perspective does not aim to provide exhaustive coverage of the field, as many recent reviews have already done so,<sup>28–31</sup> but instead offers a focused discussion of key themes currently under research.

## NO, CO, $H_2S$ , and beyond: biological roles and therapeutic potential

### NO

NO was first identified as a signaling mediator produced by endothelial cells.<sup>32</sup> Since then, research has demonstrated that

NO exerts multiple regulatory effects on tumor pathophysiology. Endogenous NO is mainly produced by nitric oxide synthases (NOS), namely endothelial NOS (eNOS), neuronal NOS (nNOS) and inducible NOS (iNOS).<sup>33</sup> Notably, the biological effects of NO vary depending on its site of production, concentration and target. At physiological concentrations, NO mediates antioxidant-type responses *via* cyclic guanosine monophosphate (cGMP)-dependent pathways, thereby protecting cells against oxidative damage and apoptosis.<sup>34</sup>

Recently, attention has shifted to the anti-tumor activity of NO. Several studies have demonstrated that a high local concentration of NO can suppress tumor progression by inhibiting mitochondrial enzymes and inducing DNA damage, thereby restricting the tumor growth.<sup>35</sup> Mechanistically, this process involves the concurrent production of NO (*via* iNOS) and superoxide radical ( $O_2^{\cdot-}$ , *via* NADPH oxidase) in activated tumor-associated macrophages. These species react to form  $ONOO^-$ , a highly potent cytotoxic molecule that kills tumor cells.<sup>36</sup> These mechanisms can be further enhanced by immunostimulatory therapeutic strategies and can synergize with other ROS-dependent therapies to improve the therapy outcome.<sup>37</sup>

### CO

CO, closely interrelated with NO, also plays an intricate role in cellular signaling. Endogenous CO is produced from the breakdown of heme, which is catalyzed by heme oxygenase 1 (HO-1).<sup>38</sup> CO plays a crucial vasodilatory role and interacts with the NOS–NO signaling axis in the cardiovascular system.<sup>39</sup> Unlike NO, which is a free radical, CO is a relatively stable molecule that is not easily consumed by intracellular metabolites. This stability suggests that CO may compensate for reduced NO bioavailability and locally regulate NO production as needed.<sup>40</sup>

CO also exhibits pleiotropic effects on cancer progression. At low concentrations, CO promotes tumor growth through the CO/HO-1 system.<sup>41</sup> However, at high concentrations exceeding a specific threshold, it can suppress tumor growth by inhibiting mitochondrial activity, inducing excessive ROS production and downregulating major protein expression, thereby reducing the tumor cell proliferation and survival.<sup>42,43</sup> Additionally, CO modulates cancer metabolism by inhibiting the Warburg effect, forcing tumor cells to consume more oxygen and ultimately leading to cell death.<sup>44</sup>

### $H_2S$

Although long regarded as a toxic gas,  $H_2S$  is now recognized as a key member of the gasotransmitter family, playing important roles in cell signaling and cancer biology. Endogenous  $H_2S$  is primarily generated by three enzymes: cystathionine  $\beta$ -synthase (CBS), cystathionine  $\gamma$ -lyase (CSE), and 3-mercaptopyruvate sulfurtransferase (3-MST).<sup>45</sup> Similar to NO and CO, low concentrations of  $H_2S$  exert cytoprotective and antioxidative effects, whereas elevated levels impair mitochondrial function, leading to cytotoxicity and cell death.<sup>46,47</sup> This effect is primarily attributed to its inhibition on COX IV, which disrupts



mitochondrial electron transport, triggers pro-oxidant response, and induces DNA-damaging impacts.<sup>48</sup>

Beyond their independent effects, many physiological processes require the coordinated signaling pathways between H<sub>2</sub>S and NO to be completed.<sup>49</sup> These gasotransmitters share considerable overlapping molecular signaling pathways including PI3K/Akt and MAPK, and their interplay modulates cancer cell survival, proliferation, and the immune response.<sup>50</sup> Deciphering these interactions, particularly the downstream signaling crosstalk among H<sub>2</sub>S, NO, and CO, may provide novel therapeutic strategies for cancer treatment.<sup>51</sup>

### Other gas

Beyond the three canonical gaseous signaling molecules, several others have emerged as promising therapeutic agents, such as O<sub>2</sub>, H<sub>2</sub>, sulfur dioxide (SO<sub>2</sub>) and hydrogen selenide (H<sub>2</sub>Se). O<sub>2</sub> is essential for cellular metabolism, driving nutrient oxidation and energy production.<sup>52</sup> Its depletion may cause severe apoptotic and necrotic cell death,<sup>53</sup> making it critical to maintain partial oxygen pressure (*p*O<sub>2</sub>) within physiological ranges for cellular homeostasis. In clinical practice, owing to its excellent biosafety profile, O<sub>2</sub> is commonly administered not only as a life-saving intervention for tissue hypoxia but also as an adjuvant to enhance O<sub>2</sub>-dependent antitumor therapies.<sup>54</sup> H<sub>2</sub>, a safe and non-toxic agent, exhibits broad-spectrum anti-inflammatory and ROS scavenging properties, making it readily applicable in clinical settings.<sup>55</sup> Previously dismissed as merely a pollutant, SO<sub>2</sub> has recently gained attention for its therapeutic potential, functioning as a vasodilator, anti-mycobacterial agent, and chemosensitizer to combat drug resistance in cancer treatment.<sup>56–58</sup> H<sub>2</sub>Se, a structural and functional analogue of H<sub>2</sub>S, is now proposed as an emerging gasotransmitter.<sup>59</sup> Endogenously, H<sub>2</sub>Se serves as a precursor for the downstream biosynthesis of selenoproteins.<sup>60,61</sup> It acts as a highly effective nucleophile and reductant, neutralizing ROS to mitigate oxidative stress. Selenium-containing compounds also demonstrate therapeutic potential in cancer treatment. Under aerobic conditions, excessive H<sub>2</sub>Se promotes ROS generation through glutathione (GSH) consumption, leading to DNA damage and apoptosis in cancer cells.<sup>62,63</sup> Additionally, H<sub>2</sub>Se has been reported to alleviate chemotherapy- and radiotherapy-induced side effects, improving clinical outcomes.<sup>64</sup>

### Clinical translation of gas-based cancer therapies: potential and challenges

Therapeutic applications of medical gases have gained increasing attention, with early efforts focusing primarily on direct inhalation.<sup>65</sup> For example, O<sub>2</sub> is routinely administered in clinical practice to alleviate hypoxia, while H<sub>2</sub> is administered for its anti-inflammatory properties. These approaches are generally safe for non-toxic gases. However, caution is required with NO, CO, and H<sub>2</sub>S, as exposure beyond safety thresholds can lead to severe toxicity. Therapeutically effective gas concentrations typically range from nanomolar (nM) to micromolar (μM). The established safety threshold concentrations for gas

inhalation are 1.02 μM (25 ppm) for NO, 4.09 μM (100 ppm) for CO, and 0.41 μM (10 ppm) for H<sub>2</sub>S. Importantly, when targeting cardiac tissue, the CO concentration should not exceed 30 nM (0.84 ppm).<sup>30</sup> The inherent physicochemical properties of these gases critically influence their biological behavior. For example, the free radical property of NO confers its half-life in the blood to be only a few seconds, which is due to its rapid binding with hemoglobin. In contrast, CO is more stable and therefore has a longer blood half-life, persisting for several minutes.<sup>44</sup> H<sub>2</sub>S falls in between, with its high reactivity, resulting in a half-life of seconds to minute-scale.<sup>19</sup>

These pharmacological challenges have driven innovations in gas delivery systems, paralleling expanding clinical investigation. For example, a Phase 1b trial (NCT05351502) is currently evaluating a low-volume, ultra-high concentration of nitric oxide (LV-UNO) in combination with PD-1 inhibitors. The study assesses the overall response rate (ORR), duration of response (DOR), and immune-related responses in patients with tumors. Another ongoing trial (NCT05607407) explores an indirect H<sub>2</sub>S modulation strategy using methimazole in progressive glioblastoma, aiming to improve treatment outcomes and extend survival. These examples illustrate the potential advantages of integrating GT with established cancer treatment modalities. In the following sections, we discuss the mechanisms through which these gases contribute to tumor therapy, highlighting their diverse roles across different biological contexts.

## Potential mechanisms of gas delivery that reinforce synergistic anti-tumor effects

### Inflammation modulation and cancer development

Inflammation is closely associated with tumor initiation and progression.<sup>66</sup> The infiltration of inflammatory cells into the tumor stroma has been consistently observed in both preclinical models and clinical settings. However, the precise relationship between inflammation and tumorigenesis remains incompletely understood. Chronic inflammation, a prolonged and dysregulated process, drives simultaneously tissue destruction and repair. Crucially, it contributes to tumor development across all stages, from initiation and promotion to progression.<sup>67</sup> Several mechanisms underlie this process. Infiltrating inflammatory cells generate elevated levels of ROS and reactive nitrogen species (RNS),<sup>68</sup> which disrupt redox homeostasis and induce genotoxic damage. Within this inflammatory microenvironment, abundant survival and proliferative signals enable the persistence of mutated or damaged cells, thereby promoting tumorigenesis.<sup>69</sup> Furthermore, tumor progression is further driven by cytokines, chemokines, and eicosanoids, which collectively support the proliferation of transformed cells.<sup>70,71</sup>

Addressing the chronic inflammation offers a promising therapeutic strategy for tumor intervention. Accumulating evidence indicates that gaseous mediators are inherently involved in cellular signaling and play key roles in regulating



inflammatory responses. For instance, H<sub>2</sub>S suppresses the nuclear factor  $\kappa$ B (NF- $\kappa$ B) pathway and downregulates chemokines such as interleukin-6 (IL-6) and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), thereby exerting anti-inflammatory effects.<sup>19,46</sup> Similarly, CO exhibits therapeutic anti-inflammatory properties by inducing HO-1 production and regulating inflammatory signaling pathways, including MAPK and the NF- $\kappa$ B.<sup>72</sup> Notably, inflammation not only precedes tumorigenesis but also shapes the adaptive immune response, influencing both its magnitude and specificity. This underscores inflammatory modulation as a robust therapeutic approach to restrain tumor progression.

### Enhanced immunogenic cell death

Immunity, originally referring to protection or exemption from a particular disease, has now evolved into the foundation of immunotherapy, which is becoming a paradigm for cancer treatment.<sup>73</sup> Compared with traditional chemotherapy, immunotherapy enables the precise identification and elimination of neoplastic cells, while minimizing off-target effects and systemic inflammation. This approach fundamentally relies on the ability of T lymphocytes to mount effective antitumor responses. Current therapeutic strategies regulate antitumor immunity through three principal mechanisms: enhancing dendritic cell antigen presentation, stimulating effective protective T-cell responses, and overcoming immunosuppression within the tumor microenvironment (TME).

Immune suppression represents a major obstacle for effective tumor immunotherapy. For instance, the hypoxia TME promotes the accumulation of adenosine, which inhibits effector T-cell function.<sup>74</sup> Interestingly, recent studies have shown that H<sub>2</sub>S promotes the differentiation of central memory T cells (T<sub>cm</sub>), a phenotype associated with enhanced antitumor responses and long-term persistence.<sup>75</sup> Experimental evidence shows that H<sub>2</sub>S-treated T cells or those engineered to over-express CBS (an H<sub>2</sub>S-producing enzyme) demonstrated superior tumor control in melanoma and lymphoma models. Mechanistically, this effect depends on the NAD<sup>+</sup>-Sirt1-Foxo1 axis and improved mitochondrial function.

In addition, H<sub>2</sub>S-mediated protein S-sulphydration has emerged as a critical regulator in tumor-associated macrophages (TAMs), which typically drive immunosuppression and tumor progression. Activation of the CTH-H<sub>2</sub>S axis has been associated with the repolarization of TAMs toward the anti-tumorigenic M1 phenotype, potentially blocking their tumor-promoting activities in breast cancer.<sup>76</sup> Moreover, both CO and H<sub>2</sub>S compromise mitochondrial integrity, resulting in the cytosolic release of mitochondrial DNA. This event enables NO and H<sub>2</sub>S to function as a gas immunoadjuvant that activates the cGAS-STING pathway, a central driver of innate immune responses.<sup>77</sup> These findings underscore the significant role of gaseous signaling molecules in immune therapy. A deeper understanding of their interplay with adaptive immune responses could open new avenues for advancing cancer immunotherapy.

### Targeting tumor metabolism

Tumor metabolism reprogramming is a hallmark of cancer survival and adaptation to hostile environments.<sup>78</sup> This process typically involves three fundamental requirements: (i) rapid ATP production, (ii) enhanced macromolecule biosynthesis; and (iii) maintenance of redox balance to sustain proliferation and mitigate oxidative stress without inducing cell death.<sup>79</sup> Metabolic heterogeneity in cancer can be traced back to the discovery of aerobic glycolysis in cancer, also known as the Warburg effect.<sup>80</sup> A proposed explanation is that glycolysis provides key intermediates for biosynthetic pathways, facilitating the synthesis of nucleotides, amino acids, and lipids.<sup>81</sup> Meanwhile, compensatory respiration through the tricarboxylic acid (TCA) cycle has also been observed.<sup>82</sup> These findings collectively underscore the critical role of carbohydrate metabolism in energy production. Consequently, targeting the carbohydrate metabolism of cancer cells or disrupting their energy supply has emerged as a promising therapeutic strategy.<sup>83</sup>

Conventional chemotherapeutic agents that inhibit metabolic enzymes or complexes are often limited by their toxicity to normal tissues. Recent studies, however, highlight the role of gaseous signaling molecules (such as H<sub>2</sub>S and NO) in cancer metabolism. Exogenous H<sub>2</sub>S enhances glucose metabolism and lactate accumulation by impairing proton export, resulting in intracellular acidification. This acidic stress disrupts homeostasis and triggers apoptotic cell death.<sup>84</sup> NO, a byproduct of cellular metabolism, exerts context-dependent roles in tumor biology. On the one hand, NO impairs mitochondrial respiration and increases glutamine consumption in the TCA cycle, promoting tumor progression and chemotherapy resistance. Thus, inhibiting NO synthesis in stromal cells may suppress tumor-supportive effects and improve therapeutic outcomes.<sup>85</sup> On the other hand, NO-mediated post-translational modifications,<sup>86</sup> particularly S-nitrosation, exhibit tumor-suppressing properties in highly glycolytic or hypoxic cancer cells. These dual roles of NO underscore the importance of precision dosing and combinatorial strategies in NO-based therapies. Further studies are essential to evaluate NO donors and small molecule regulators, as targeting NO metabolism could disrupt tumor survival networks and provide novel therapeutic avenues.

### Tumor microenvironment remodel

TME encompasses the complex ecosystem surrounding a tumor, including various cell types, extracellular matrix components, signaling molecules, and blood vessels. The heterogeneity of cancer cell metabolism often leads to dysfunctional blood flow and heightened inflammation. Moreover, hypoxic, acidic, nutrient-deprived, electrolyte imbalance, and elevated oxidative stress are commonly observed in the TME.<sup>87</sup> While these intrinsic characteristics of the TME contribute to drug resistance and hinder therapeutic efficacy, their distinct differences from normal tissues also present opportunities for precise drug delivery and targeted therapy.<sup>47,88</sup> Notably, the delivery of TME-remodeling agents to tumor sites has emerged as a promising strategy to convert non-responsive "cold" tumors into immunologically active "hot" tumors.



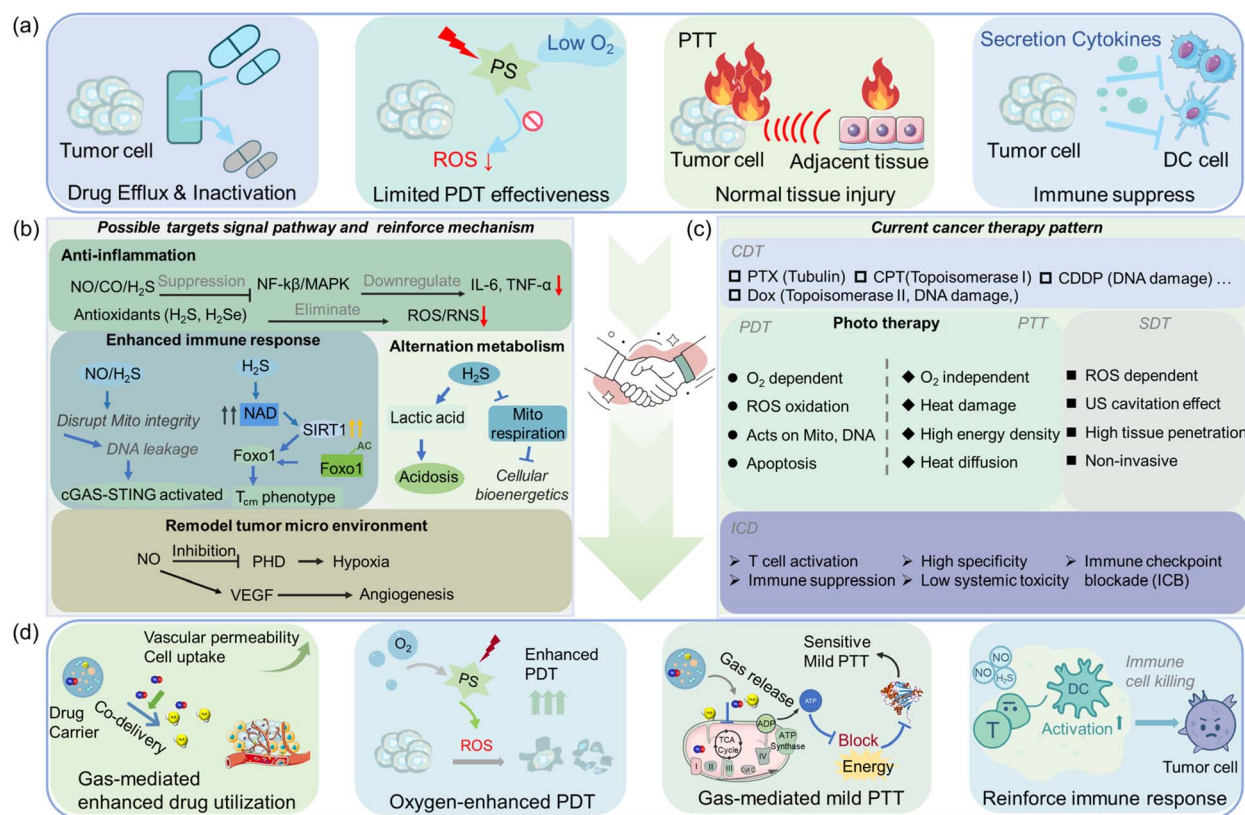
NO functions as a bell-shaped effector molecule in the TME, exerting both pro- and anti-tumorigenic effects. Elevated NO levels in TME promote tumor progression and migration by upregulating caveolin-1 expression, as observed in melanoma, breast, and prostate cancer.<sup>89,90</sup> NO also regulates angiogenesis in the TME and has been exploited as a therapeutic target. Specifically, inhibiting the expression of NOS1 can sensitize glioma tumors to radiotherapy.<sup>91</sup> Beyond tumor initiation, stroma-derived NO has also been observed to have tumor-suppressive effects.<sup>92</sup> These studies highlight the divergent roles of NO in the TME.

Although experimental research in this field is still in its early stages and is further complicated by the pleiotropic effects of signaling molecules on tumor progression, such mechanistic insights highlight the unique and versatile roles of gasotransmitters in modulating tumor biology and demonstrate considerable promise as therapeutic agents (Fig. 1b). However, considering the multifaceted nature of cancer progression and the limitations of single-modality treatments (Fig. 1a), increasing research efforts have shifted toward integrating GT with both conventional and emerging therapeutic strategies. In

the following sections, we will discuss how gaseous signaling molecules can synergize with established treatment modalities, including CDT, PDT, PTT, SDT, and immunotherapy (Fig. 1c), to enhance therapeutic efficacy and overcome resistance mechanisms (Fig. 1d).

## Gas delivery combined therapy

Significant progress has been made in the development of cancer therapy, including CDT, PDT, PTT, immune therapy, and sono-therapy. However, current strategies still suffer from several limitations and require further optimization to address clinical challenges. The integration of GT with traditional therapeutic modalities has emerged as a promising solution. Gas molecules reinforce the treatment efficacy through three primary mechanisms: (1) directly participating in cell signaling pathways to induce cancer cell apoptosis; (2) acting as adjuvants to create a favorable microenvironment that augments the effectiveness of other therapies; (3) modulating target proteins to render the tumor cell more vulnerable to current therapeutic approaches, thereby reducing the side effects.



**Fig. 1** Schematic of the proposed mechanism illustrating how novel gasotransmitters reinforce conventional cancer therapeutic strategies. (a) Limitations of traditional tumor treatment modes; (b) potential mechanisms of gas molecules in enhancing tumor treatment outcomes; (c) characteristics of traditional tumor treatment modes; (d) enhanced outcome of gas therapy in synergy with traditional treatment modalities. PS, photosensitizer; NF-κB, nuclear factor kappa B; MAPK, mitogen-activated protein kinase; IL-6, Interleukin-6; TNF-α, tumor necrosis factor-alpha; cGAS, cyclic GMP-AMP synthase; STING, stimulator of interferon genes; NAD, nicotinamide adenine dinucleotide; SIRT1, silent information regulator 1; Foxo, forkhead O transcription factors; T<sub>cm</sub>, central memory T cells; PHD, prolyl hydroxylase domain; VEGF, vascular endothelial growth factor; PTX, paclitaxel; CPT, camptothecin; CDDP, cisplatin; Dox, doxorubicin; ICB, immune checkpoint blockade; TCA, tricarboxylic acid cycle; ADP, adenosine diphosphate; ATP, adenosine triphosphate; DC, dendritic cell; CDT, chemodynamic therapy; PDT, photodynamic therapy; PTT, photothermal therapy; SDT, sonodynamic therapy; ICD, immunogenic cell death.

### Gas-enhanced chemodynamic therapy

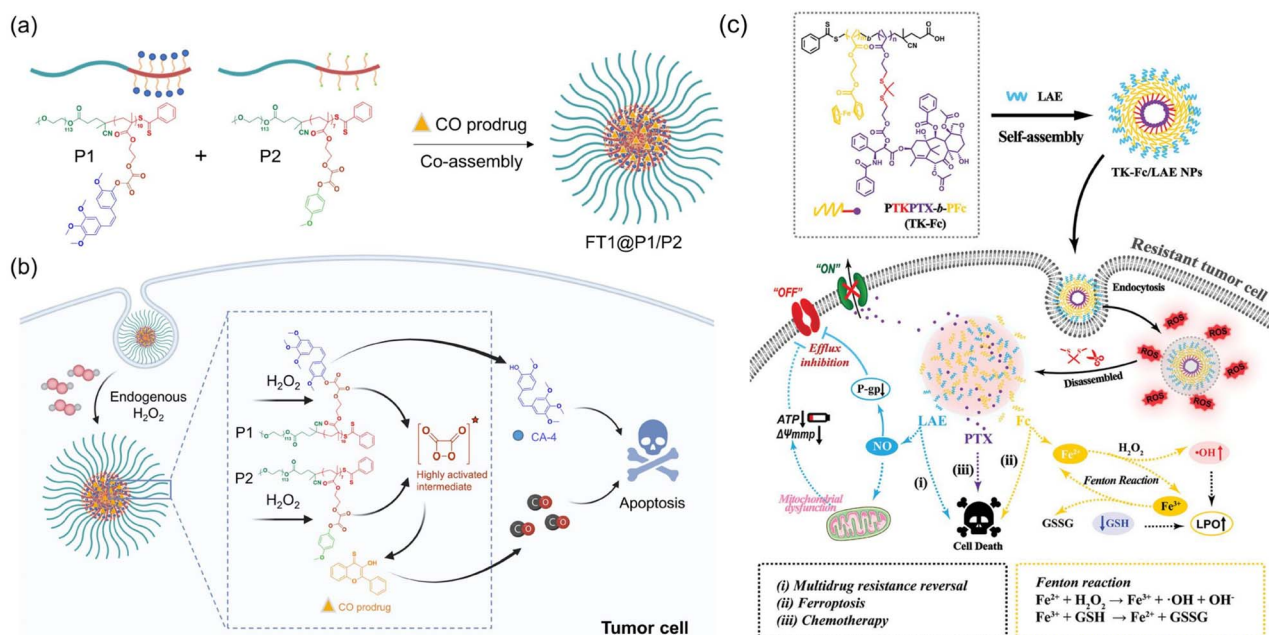
Combining GT with CDT represents an effective strategy to overcome the major limitations of traditional cancer treatment. Although CDT remains a cornerstone in oncology, its efficacy is often limited by drug resistance, off-target toxicity, and suboptimal tumor selectivity. Therapeutic gases (CO, NO, and H<sub>2</sub>S) can modulate the TME, enhance drug sensitivity, and induce complementary cytotoxic effects. Recently, Ji *et al.* reported a chemiexcitation-activated polyprodrug system (FT1@P1/P2, Fig. 2a) for the tumor-specific co-delivery of CO and combretastatin A-4 (CA-4).<sup>93</sup> In response to elevated H<sub>2</sub>O<sub>2</sub> levels in the TME, both CO and CA-4 were released simultaneously, achieving potent tumor suppression (Fig. 2b). Notably, CO amplified the anticancer effects of CA-4 through a synergistic mechanism, marking the first reported combination of CO with a microtubule polymerization inhibitor. This approach not only improves the local drug efficacy, but also introduces transition-metal-free gas-chemotherapy co-delivery systems in cancer treatment.

To overcome drug resistance in prostate cancer, Pang *et al.* designed a nanoplatfrom (TK-Fe/LAE NPs) integrating GT, ferroptosis, and chemotherapy (Fig. 2c).<sup>94</sup> Upon activation by elevated intracellular ROS, the system disassembles to release NO, which downregulates P-glycoprotein expression, disrupts mitochondrial function and reverses multidrug resistance (MDR). Concurrently, ferrocene-mediated Fenton reactions induce ferroptosis and amplify oxidative stress, while controlled paclitaxel release ensures targeted chemotherapy. The study

highlights NO's potential to overcoming drug resistance and improving therapeutic outcomes.

H<sub>2</sub>S-releasing hybrid drugs offer a promising approach to enhance therapeutic efficacy while minimizing adverse effects. For instance, NSAID-H<sub>2</sub>S conjugates exhibit synergistic pharmacological benefits by improving anti-inflammatory potency and alleviating the gastrointestinal toxicity associated with conventional NSAIDs.<sup>95</sup> Moreover, H<sub>2</sub>S has been reported to enhance the anti-tumor effects of chemo drugs in melanoma cells.<sup>96</sup> Matson *et al.* reported a dual-responsive nanoplatfrom (AAN-PTC-Fe<sup>2+</sup>) for glioma treatment, integrating CDT with H<sub>2</sub>S GT (Fig. 3).<sup>97</sup> Triggered by overexpressed legumain in tumor cells, this system selectively releases H<sub>2</sub>S, which inhibits catalase activity and promotes H<sub>2</sub>O<sub>2</sub> accumulation. Meanwhile, Fe<sup>2+</sup> catalyzes the Fenton reaction to convert H<sub>2</sub>O<sub>2</sub> into highly toxic hydroxyl radicals ( $\cdot\text{OH}$ ), amplifying ROS levels and leading to enhanced tumor cell death. The co-delivery system demonstrates superior efficacy compared to the chemotherapy drug temozolomide (TMZ) and exhibits negligible cardiotoxicity, underscoring its safety profile. This strategy highlights the potential of tumor-specific H<sub>2</sub>S delivery to augment CDT and overcome the limitations of conventional chemotherapeutics.

The integration of GT with CDT represents a potent synergistic strategy to enhance the anticancer efficacy. Gas molecules such as CO, NO, and H<sub>2</sub>S not only sensitize tumor cells to chemotherapeutic agents by disrupting mitochondrial function, reversing MDR, or inhibiting detoxifying enzymes, but also contribute to amplified oxidative stress or ferroptosis for tumor



**Fig. 2** Schematic of the design rationale of the chemiexcitation-triggered poly-prodrug for the co-activation of CO and CA-4 for combinational therapy. (a) Chemical structures of the triblock copolymers. (b) Mechanism of the H<sub>2</sub>O<sub>2</sub>-triggered co-activation of CA-4 and CO. Reproduced from ref. 93 with permission from Springer Nature, copyright 2025. (c) Reactive oxygen species (ROS) cascade nanoplatfrom targeting the regulation of P-glycoprotein, and the synergistic induction of ferroptosis to reverse multidrug-resistance in prostate cancer. Schematic of the mechanism of nanoplatfrom TK-Fe/LAE NPs with ROS cascade amplification for gas therapy/ferroptosis/chemotherapy. Reproduced from ref. 94 with permission from Wiley-VCH, copyright 2024.

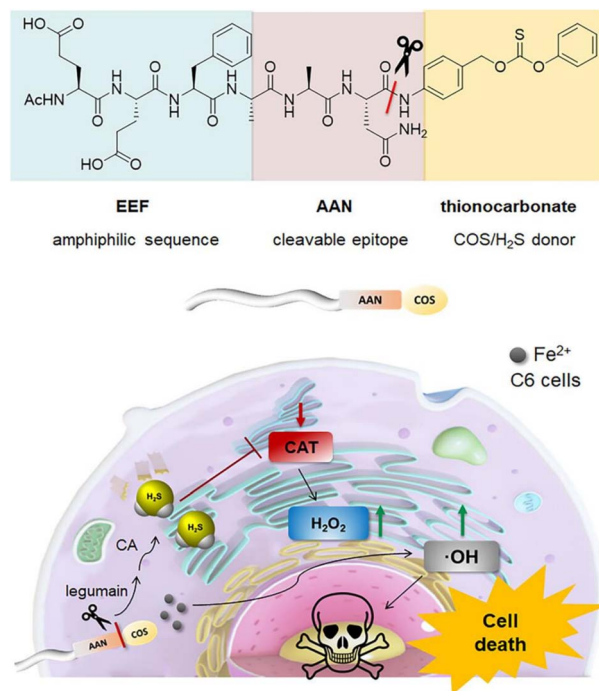


Fig. 3 Schematic of the PHDC-Fe<sup>2+</sup> complex chemical structure and therapeutic mechanism in the C6 glioma cell line. Reproduced from ref. 97 with permission from Wiley-VCH, copyright 2023.

eradication. These hybrid platforms enable tumor-specific, stimulus-responsive drug release, thereby minimizing systemic toxicity while improving therapeutic precision.

### Gas-enhanced phototherapy

Phototherapy mainly includes PDT and PTT, both of which rely on photosensitizers absorbing photon energy. Upon excitation,

an electron transition occurs from the ground state ( $S_0$ ) to an unstable singlet excited state ( $S_n$ ). Electrons in the first singlet state  $S_1$  can relax to  $S_0$  through radiative decay, emitting fluorescence,<sup>98</sup> or through a non-radiative route, generating localized heat for PTT effects. Alternatively, electrons may undergo intersystem crossing (ISC) to the triplet state ( $T_1$ ), whose longer lifetime enables chemical reactions that generate ROS (class I mechanism) or singlet oxygen ( $^1O_2$ ) (class II mechanism), forming the basis of PDT.<sup>99</sup>

Despite advances in photosensitizer (PS) design and light sources, PDT remains limited by hypoxia in late-stage solid tumors.<sup>100,101</sup> Because PDT is oxygen-dependent, low O<sub>2</sub> levels often limit its efficiency, and PDT itself can further exacerbate hypoxia, potentially leading to drug resistance. To address this, the most straightforward strategy is combining PDT with oxygen delivery.<sup>102,103</sup> An alternative strategy involves alleviating hypoxia through modulation of the TME. Abnormal TME not only facilitates tumor proliferation and metastasis, but also establishes physiological barriers that impede effective penetration of therapeutics inside the tumor, posing great challenges for cancer treatment. To tackle this, Min *et al.* developed a hierarchical nanoplatform (denoted as T-PFRT) that can adapt to the TME *via* size transformation (Fig. 4a). In response to matrix metalloproteinase 2 (MMP2), T-PFRT releases the small PFRT module, which depletes stromal components and enhances O<sub>2</sub> delivery *via* hemoglobin (Hb). These therapeutic effects simultaneously overcome stromal and hypoxic barriers, achieving deep tumor penetration, improved PDT performance, and enhanced overall therapeutic efficacy.<sup>104</sup> This strategy demonstrated excellent therapeutic outcomes in the treatment of both primary and metastatic tumors.

Simultaneous modulation of multiple parameters in the TME represents a promising therapeutic direction. Zhao *et al.*

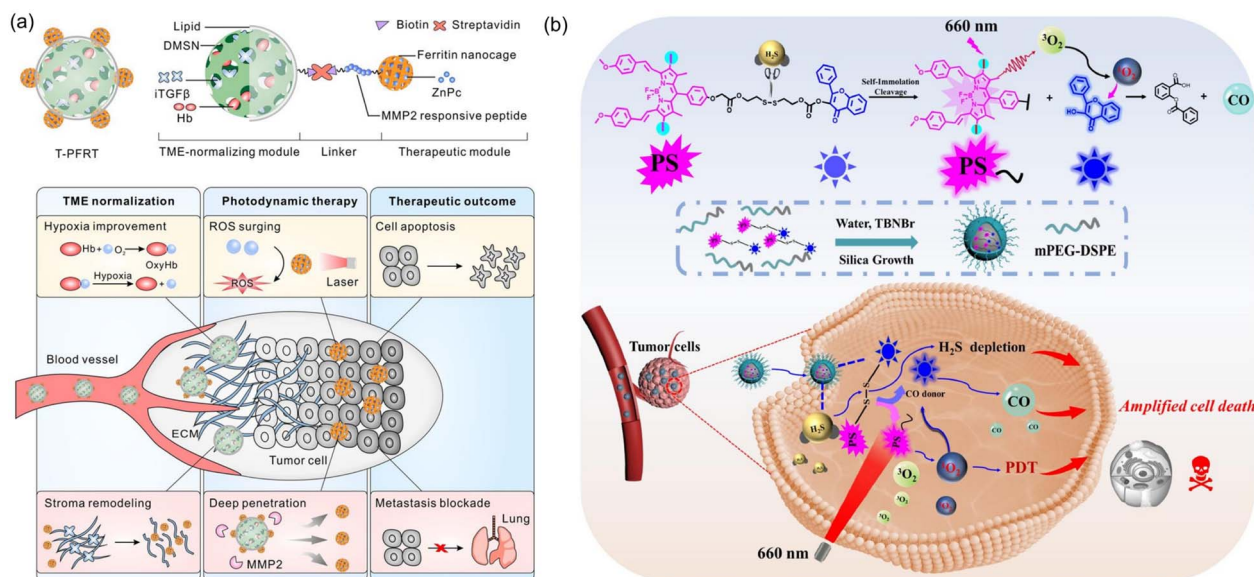


Fig. 4 (a) Structure and composition of T-PFRT; working principles of the therapeutic components in TME normalization and photodynamic therapy for tumor inhibition and metastasis blockade. Reproduced from ref. 104 with permission from Wiley-VCH, copyright 2021. (b) Molecular structure and CO release mechanism of NanoBDP21-S-HF. Reproduced from ref. 105 with permission from Springer Nature, copyright 2024.



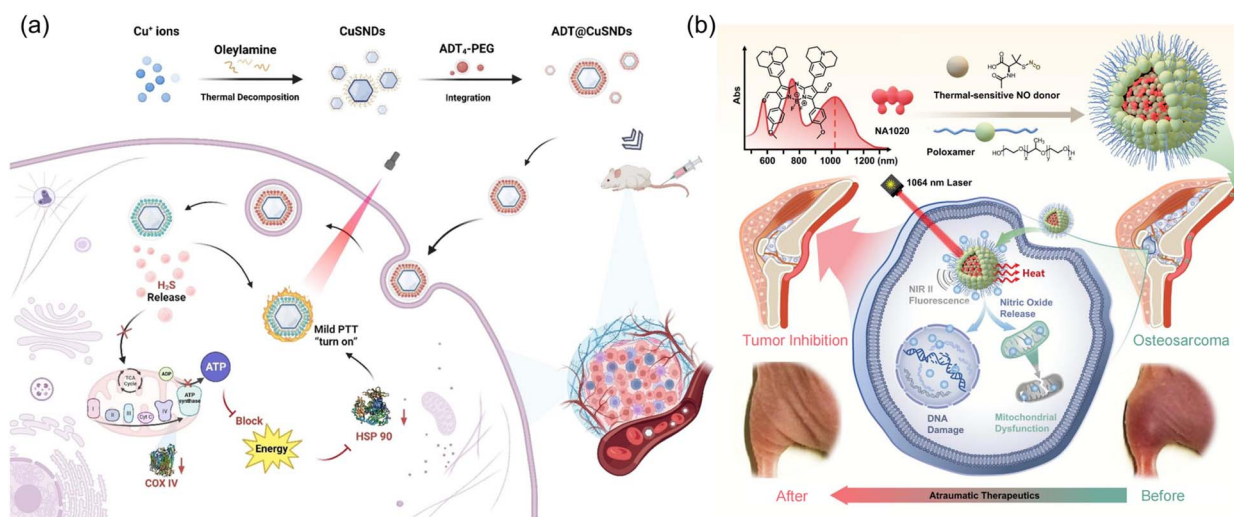
developed a multifunctional nanomedicine, NanoBDP2I-S-HF, which enables precise modulation of multiple gases (CO release and H<sub>2</sub>S depletion), while simultaneously enhancing PDT efficacy (Fig. 4b).<sup>105</sup> This nanomedicine utilizes a disulfide bond to covalently conjugate a PS with the CO donor 3-hydroxyflavone (3-HF), enabling H<sub>2</sub>S-triggered bond cleavage in tumor regions. This process both reduces local H<sub>2</sub>S levels and releases 3-HF for CO-mediated therapy. Upon 660 nm laser irradiation, the PS generates cytotoxic <sup>1</sup>O<sub>2</sub>, which subsequently oxidizes 3-HF to precisely trigger CO release. This H<sub>2</sub>S-light-<sup>1</sup>O<sub>2</sub>-responsive cascade ensures accurate gas delivery and significantly enhances PDT efficacy. Compared to single PDT treatment, NanoBDP2I-S-HF demonstrates superior therapeutic efficacy against HCT116 tumors. This multimodal-activated therapeutic strategy provides an innovative approach for improving both the precision and effectiveness of synergistic cancer treatment.

Compared with PDT, PTT typically requires higher light power due to its lower energy conversion efficiency. However, the use of high-power light sources often causes photodamage to healthy tissue and compromises its clinical feasibility. Effective tumor ablation usually demands localized temperatures exceeding 50 °C, which unavoidably harms surrounding normal tissues through heat diffusion. To address this limitation, the concept of mild PTT was proposed. This strategy focuses on suppressing heat shock protein (HSP) protein expression, which can counteract tumor thermotolerance while reducing PTT-related side effects.<sup>106</sup>

In 2023, Liu *et al.* constructed a co-facilitated gas-photothermal therapy nanoplatform ADT@CuSND (Fig. 5a).<sup>107</sup> This platform enables precise and sustained delivery of H<sub>2</sub>S to

tumor sites. Elevated H<sub>2</sub>S levels effectively inhibit COX IV, thereby disrupting the mitochondrial respiratory chain, inhibiting ADP conversion and downregulating HSP90, which collectively sensitize the tumor to hyperthermia. By reversing tumor thermotolerance, ADT@CuSNDs significantly enhanced mPTT efficacy, achieving effective tumor ablation with a single treatment while simultaneously minimizing damage to healthy tissues. This energy remodeling approach represents a promising paradigm for improving PTT efficacy and holds potential for the future clinical translation of tumor therapy.

NO has also been reported to sensitize tumor cells to PTT by inhibiting protective autophagy, thereby enhancing tumor cell death in combined treatment.<sup>108</sup> Li *et al.* reported a gas/phototheranostic nanocomposite (NA1020-NO@PLX, Fig. 5b), which integrates aza-BODIPY, NA1020 with a thermal-sensitive NO donor. The enhanced ICT process endows the NA1020 with NIR-II-peak absorbance (1020 nm), enabling deep tissue penetration for precise imaging and PTT of deep tissue tumor. Moreover, the NA1020 exhibits a remarkable photothermal conversion efficiency, while NO release upon laser irradiation induces mitochondrial dysfunction and DNA damage, thereby augmenting the efficacy of low-temperature PTT. By combining low temperature PTT with NO delivery, significant tumor eradication in an orthotopic osteosarcoma model was observed without causing undesired tissue damage, thereby significantly minimizing the side effects commonly associated with PTT. In summary, gas/phototheranostic combination strategies have emerged as a research hotspot, underscoring the strengths of enhanced phototherapy in tumor eradication and demonstrating great potential for clinical translation.



**Fig. 5** (a) Schematic of ADT@CuSND application in the mild photothermal therapy of a tumor. After being taken up by the cells, ADT@CuSNDs continuously released H<sub>2</sub>S into the tumor cells, which downregulated COX IV, interfered with the mitochondrial respiratory chain and blocked the energy supply in tumors. The depleted cellular ATP pool reduced the risk of the overexpression of HSP90 in response to heat stress, further reversing the thermotolerance of tumors and allowing ADT@CuSNDs to obtain enhanced mPTT. Reproduced from ref. 107 with permission from Wiley-VCH, copyright 2023. (b) Schematic of the gas/phototheranostic nanocomposite (NA1020-NO@PLX). An enhanced ICT mechanism was introduced to develop the NIR-II-peak absorbing PTA of NA1020, which was combined with thermal-sensitive NO donors to facilitate a combined low temperature PTT with gas therapy. NA1020-NO@PLX emitted the NIR-II fluorescence to guide the heat generation that simultaneously activated NO release using a laser at 1064 nm for atraumatic osteosarcoma therapy. Reproduced from ref. 109 with permission from Wiley-VCH, copyright 2023.



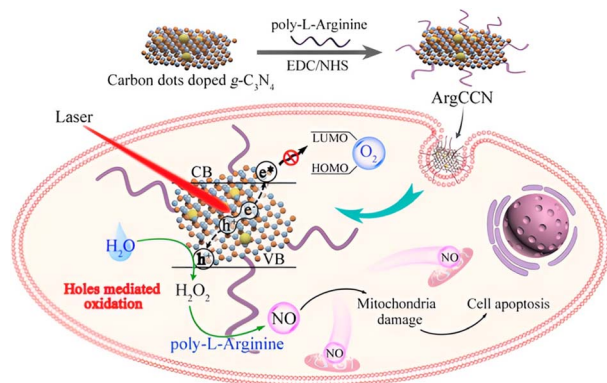


Fig. 6 Schematic of the microenvironment-independent NO-based phototherapeutic nanoplatfrom. Photogenerated hole-mediated oxidation was used to generate NO for hypoxic tumor treatment, which was achieved by poly-L-arginine-modified carbon-dot-doped g-C<sub>3</sub>N<sub>4</sub> (ArgCCN). The holes with oxidizability were generated by laser irradiation of ArgCCN, which oxidized H<sub>2</sub>O to generate H<sub>2</sub>O<sub>2</sub>, and the H<sub>2</sub>O<sub>2</sub> further oxidized the arginine residues to accomplish the NO production that is independent of the tumor microenvironment. Reproduced from ref. 110 with permission from Wiley-VCH, copyright 2021.

In addition to the two classical phototherapeutic modalities, Yang *et al.* reported a NO-based, TME-independent phototherapeutic platform (ArgCCN, Fig. 6).<sup>110</sup> Upon irradiation, the photogenerated holes on ArgCCN converted water into H<sub>2</sub>O<sub>2</sub>, which subsequently oxidized the arginine residues to produce NO. The burst release of NO then induced tumor cell apoptosis. Different from other therapeutic modalities, this approach does not rely on oxygen to produce ROS, nor does it exacerbate tumor hypoxia, thereby effectively overcoming the major limitations of PDT. This distinctive phototherapeutic strategy offers new

perspectives for the advancement of light-based therapeutic modalities.

### Gas enhanced sono-therapy

Phototherapy typically relies on the near-infrared (NIR) or far-infrared (FIR) wavelength light sources to achieve ideal tissue penetration depths. However, the longer wavelengths of these light sources correspond to lower photon energy, which limits the activation efficiency of PS and reduces the overall therapeutic efficacy. To overcome this limitation, SDT, which leverages the deep tissue penetration capacity of ultrasound (more than 10 cm), has emerged as promising alternative therapeutics for the treatment of deep-seated tumors.<sup>111–113</sup> SDT is primarily mediated through three mechanisms: acoustic cavitation, ROS-based mechanism and ROS-independent mechanism.<sup>114</sup> Inspired by PDT, it is well accepted that ROS generation during SDT can precisely kill cancer cells,<sup>98</sup> with the cavitation effect being useful in a wide range of diagnostic and therapeutic applications.<sup>115</sup> Furthermore, SDT can be readily combined with CDT, PTT, GT and other therapeutic modalities to achieve synergistic effects that surpass the efficacy of individual treatments, holding great potential as a next-generation treatment paradigm.

A single dose of SDT is often insufficient for complete tumor eradication, as the persistent hypoxic nature of TME significantly limits its therapeutic efficacy. This highlights the potential of gas delivery to augment the therapeutic efficacy of SDT. Under this premise, Zhao *et al.* designed a pH/ultrasound dual-responsive biomimetic nanoplatfrom for combined GT and SDT, aiming to overcome the limitations of traditional PDT.<sup>116</sup> The nanoplatfrom, consisting of ZIF-8 loaded with chlorin e6 (Ce6) and nitrosoglutathione (GSNO), was coated with homologous tumor cell membranes to enable active tumor

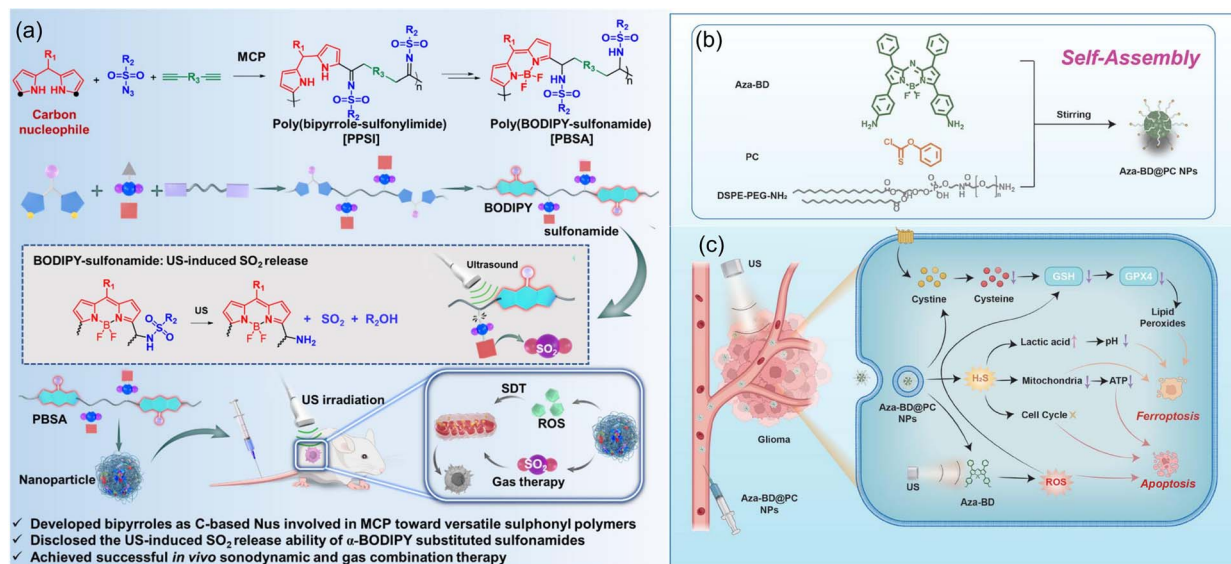


Fig. 7 (a) Schematic of the preparation of PPSIs and PBSAs for the US-driven ROS and SO<sub>2</sub> release to achieve sonodynamic and gas combination therapy. Reproduced from ref. 117 with permission from Wiley-VCH, copyright 2025. (b) Fabrication of Aza-BD@PC NPs. (c) Synergistic GT and SDT effect caused by Aza-BD@PC NPs under US irradiation for enhanced therapeutic efficacy. Reproduced from ref. 118 with permission from Wiley-VCH, copyright 2025.

targeting. In the acidic TME, ultrasound stimulation triggered the controlled release of Ce6 and NO. The released NO not only relieved hypoxia, but also synergized with ultrasound-activated Ce6 to enhance ROS and ONOO<sup>−</sup> production. This gas-sonodynamic combination resulted in effective tumor suppression with demonstrated biocompatibility, reduced phototoxicity, and improved therapeutic precision. The study provides a promising strategy for the design of multifunctional platforms in next-generation cancer therapies.

SO<sub>2</sub> has been demonstrated to induce oxidative stress-mediated damage of biomacromolecules, making it applicable in anti-inflammatory, antibacterial, and anti-cancer therapies. In a recent study, a multicomponent polymerization strategy was developed to synthesize poly(BODIPY-sulfonamide)s (PBSAs) capable of simultaneous ROS and SO<sub>2</sub> generation under US irradiation (Fig. 7a).<sup>117</sup> Among them, a ROS-responsive polymer (PBSA-EG) incorporating thioketal linkers and hydrophilic chains was engineered into nanoparticles for *in vivo* application. Upon US activation, the system effectively released both ROS and SO<sub>2</sub>, achieving enhanced tumor suppression through synergistic sonodynamic-gas therapy. This work highlights the potential of ultrasound-triggered SO<sub>2</sub> delivery as a powerful complement to SDT, overcoming tumor resistance and amplifying therapeutic efficacy.

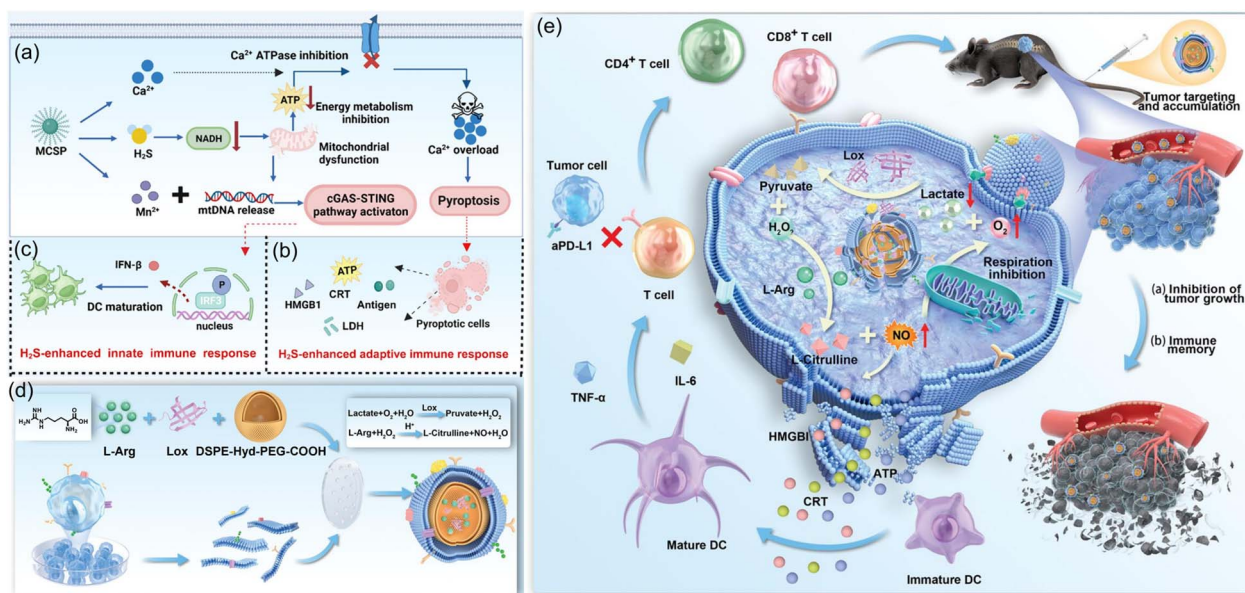
Glioblastoma multiforme (GBM) is the most aggressive and fatal form of glioma, characterized by rapid progression and poor prognosis. To overcome the resistance of GBM to apoptosis, Wu *et al.* developed a nanoplatform (Aza-BD@PC NPs, Fig. 7b), which integrates H<sub>2</sub>S-based GT with ferroptosis-augmented SDT for GBM therapy.<sup>118</sup> Upon internalization, the

nanoplatform consumed intracellular cysteine (Cys), triggering H<sub>2</sub>S release, and disrupting redox balance and metabolism, while also inducing ferroptosis. Concurrently, the released Aza-BD generated abundant <sup>1</sup>O<sub>2</sub> under US irradiation, enabling efficient SDT. The synergistic interplay of H<sub>2</sub>S-mediated ferroptosis and US-triggered ROS production led to significant GBM suppression (Fig. 7c), with *in vivo* inhibition rates up to 97.5%. This strategy offers a promising avenue to enhance SDT efficacy through ferroptosis-enabled GT in treatment-resistant tumors such as GBM.

### Gas-enhanced immunotherapy

The immune system is a highly sophisticated and dynamic physiological network that has emerged as a powerful approach in cancer treatment. However, its efficacy is often limited by the immunosuppressive TME. Notably, specific therapeutic gases can alleviate tumor hypoxia, reduce lactate accumulation, or disrupt mitochondrial function, thereby partially reversing immunosuppression and sensitizing tumors to immune responses.<sup>119</sup>

For instance, Cheng *et al.* developed PEGylated Mn-doped CaS nanoparticles (MCSP) as a TME-responsive platform for gas-amplified metalloimmunotherapy against cervical cancer (Fig. 8a).<sup>120</sup> Upon exposure to the acidic TME, MCSP rapidly releases Ca<sup>2+</sup>, Mn<sup>2+</sup>, and H<sub>2</sub>S. H<sub>2</sub>S disrupts mitochondrial oxidative phosphorylation, leading to calcium overload and pyroptosis, a pro-inflammatory cell death that enhances immunogenicity (Fig. 8b). Simultaneously, H<sub>2</sub>S-induced mitochondrial damage promotes mtDNA leakage, which synergizes with Mn<sup>2+</sup> to robustly activate the cGAS-STING pathway, which



**Fig. 8** (a) Mechanism of pyroptosis and activation of the cGAS-STING pathway induced by MCSP. (b) H<sub>2</sub>S-enhanced adaptive and (c) innate immune response. Reproduced from ref. 120 with permission from the American Chemical Society, copyright 2024. (d) MP@AL manufacturing process. (e) Sketch map showing the double-closed loop of MP@AL-catalyzed metabolite lactate consumption and NO replenishment. The NO produced by the reaction inhibits tumor respiration on the one hand and ensures the continuation of lactic acid depletion response and reverses the TME; on the other hand, it induces the death of tumor immunogenic cells, which synergistically stimulates the immune response and amplifies the efficacy of immunotherapy. Reproduced from ref. 121 with permission from Wiley-VCH, copyright 2025.

triggering dendritic cell maturation (Fig. 8c). This dual mechanism bridges innate and adaptive immunity, reducing the proportion of immunosuppressive  $T_{reg}$  populations and promoting infiltration of  $CD8^+$  T cells and M1 macrophages. Combined with  $\alpha$ PD-1 therapy, MCSP achieves enhanced tumor suppression, demonstrating  $H_2S$ 's pivotal role as a gas mediator to amplify both pyroptosis and STING-driven immune activation.

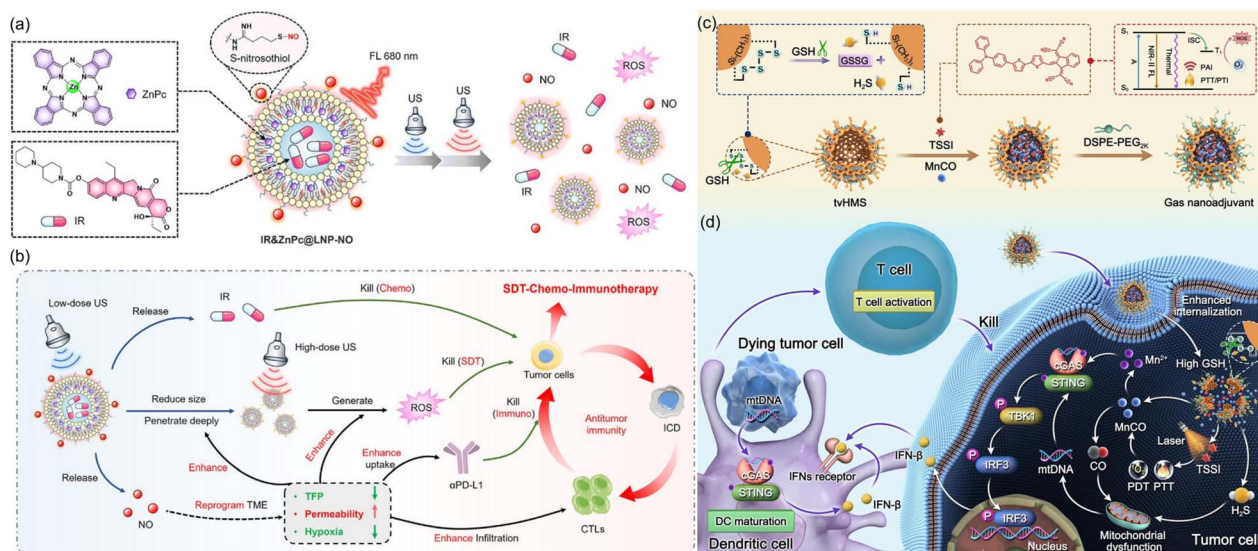
To overcome the limitations of conventional GT in remodeling the immunosuppressive TME, Dong *et al.* developed a biomimetic, pH-responsive nanosystem (MP@AL, Fig. 8d).<sup>121</sup> This system integrates lactate metabolism regulation and NO gas immunotherapy. Lactate oxidase consumes oxygen and decomposes lactate to produce  $H_2O_2$ , which then oxidizes L-arginine to generate NO. NO not only disrupts mitochondrial respiration (reducing tumor oxygen consumption and enhancing lactate clearance) and reshapes the tumor immune microenvironment (TIME), but also induces ICD and activates robust antitumor immune responses. Combined with PD-L1 blockade, this dual closed-loop platform significantly inhibited tumor growth and prevented recurrence (Fig. 8e). This work illustrates that combining GT with immunometabolic modulation synergistically reverses tumor immunosuppression and enhances immunotherapy efficacy.

### Gas-enhanced multi-therapy

The combination of multiple treatment modalities offers distinct advantages in cancer therapy, including enhanced treatment efficacy, complementary strengths, and the ability to overcome individual limitations. To address the dense stroma and immunosuppressive microenvironment of pancreatic cancer, Ye *et al.* presented a US-responsive lipid

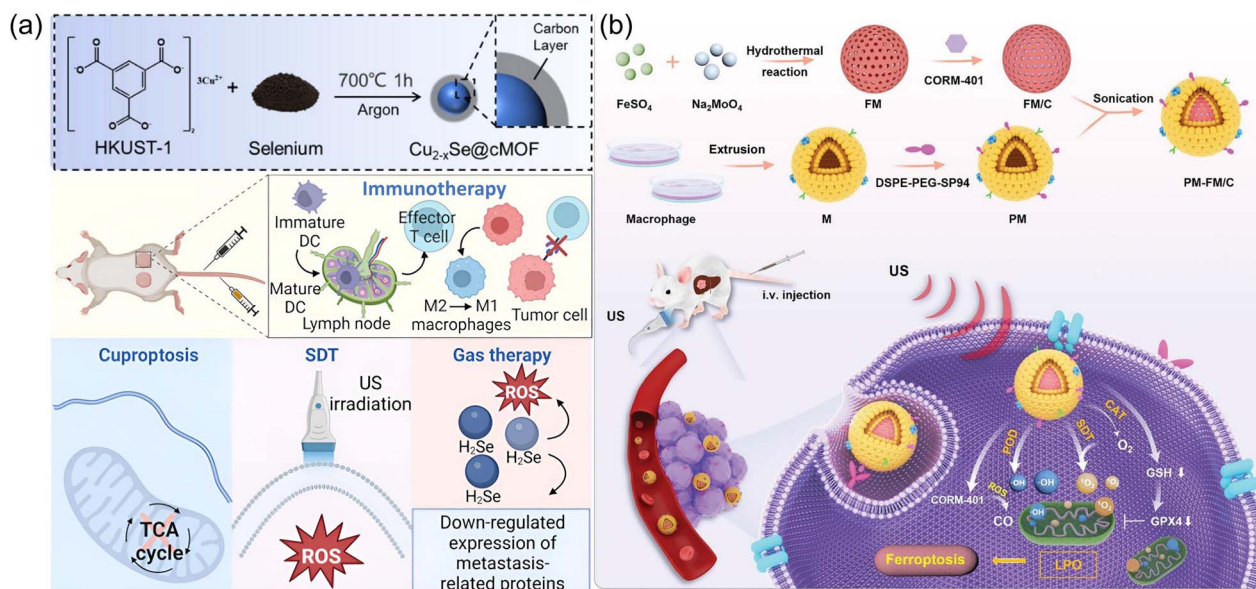
nanosonosensitizer (IR&ZnPc@LNP-NO) combined NO GT with SDT, CDT, and immunotherapy (Fig. 9a).<sup>122</sup> Upon low-dose ultrasound, the nanoplateform underwent size reduction and released NO, which remodelled the TME by normalizing the vasculature and degrading the ECM, improving both drug penetration and immune cell infiltration. In contrast, high-dose ultrasound triggered ROS production and irinotecan (IR) release, inducing ICD and enhancing PD-L1 checkpoint blockade therapy (Fig. 9b). This cascade strategy significantly improved therapeutic efficacy in orthotopic pancreatic tumor models, demonstrating the power of NO-mediated GT in multi-modal cancer treatment.

To overcome the immunosuppressive microenvironment of triple-negative breast cancer (TNBC), Chen *et al.* reported a virus-mimicking gas nanoadjuvant by co-encapsulating an AIE-active photosensitizer and manganese carbonyl (MnCO) into a tetrasulfide-doped hollow mesoporous silica matrix (Fig. 9c).<sup>77</sup> Triggered by tumor-specific GSH, the tetra-sulfide bonds enable selective drug release, enhance PDT, and generate  $H_2S$  for gas-mediated immunomodulation. Upon sequential NIR laser irradiation, the AIEgen-mediated phototherapy triggers the burst of  $CO/Mn^{2+}$ . NO gas molecules disrupt mitochondrial integrity, inducing cytosolic mtDNA leakage and activation of the cGAS-STING pathway.  $Mn^{2+}$  further enhances type I interferon (IFN) production, amplifying immune responses. This gas-augmented nanoplateform significantly boosts AIEgen-mediated PDT and PTT, resulting in effective tumor regression, distant tumor suppression, and prevention of metastasis and recurrence in TNBC models (Fig. 9d). The study highlights gas immunoadjuvants as powerful tools to potentiate photoimmunotherapy in poorly immunogenic tumors.



**Fig. 9** (a) Schematic of IR&ZnPc@LNP-NO, and its response to sequential low-power and high-power US irradiation: size reduction, controlled IR and NO release, and ROS generation. (b) Illustration of the mechanism of IR&ZnPc@LNP-NO synergized with  $\alpha$ PD-L1 for SDT-chemo-immunotherapy of deep-seated pancreatic cancer. Reproduced from ref. 122 with permission from Wiley-VCH, copyright 2025. (c) Schematic illustrating the preparation routes for the gas nanoadjuvant. (d) Schematic of the gas nanoadjuvant-based cGAS-STING pathway-dependent antitumor immune responses. Reproduced from ref. 77 with permission from Springer Nature, copyright 2023.





**Fig. 10** (a) Schematic of trimodal tumor therapy and immunotherapy using  $\text{Cu}_{2-x}\text{Se}@\text{cMOF}$  nanoparticles. Synthesis of  $\text{Cu}_{2-x}\text{Se}@\text{cMOF}$  and proposed dual enhancement of immune function by  $\text{Cu}_{2-x}\text{Se}@\text{cMOF}$  for improved tumoricidal effects. Reproduced from ref. 123 with permission from the American Chemical Society, copyright 2024. (b) Schematic of the dual-targeting biomimetic nanoplatform for integrating CDT/SDT/gas therapy to boost synergistic ferroptosis against orthotopic HCC. The CO-releasing molecule CORM-401 was encapsulated into the bimetallic compound FM to form a multi-modal therapeutic nanoplatform (FM/C), which was further cloaked with a macrophage membrane inserted with the SP94-peptide to endow dual-targeting ability toward HCC. The multi-enzyme activity of FM not only promoted CDT to generate  $\cdot\text{OH}$ , but also improved the SDT performance to produce  $^1\text{O}_2$  by alleviating hypoxia, which in turn activated CO release. As a result, the depletion of GSH and high level of ROS led to the accumulation of lethal lipid peroxidation (LPO) to promote ferroptosis-based tumor death in an orthotopic HCC model. Reproduced from ref. 124 with permission from Wiley-VCH, copyright 2025.

$\text{H}_2\text{Se}$  gas has recently garnered attention within the research community.<sup>59</sup> Although it has not yet been classified as a gaso-transmitter,  $\text{H}_2\text{Se}$  shares many features with  $\text{H}_2\text{S}$  and participates in redox-balance regulation across physiological systems.

Jiang *et al.* constructed a  $\text{Cu}_{2-x}\text{Se}@\text{cMOF}$  nanoplatform for combined sonodynamic/cuproptosis/gas therapy (Fig. 10a).<sup>123</sup> Upon US stimulation, this system generated ROS and released  $\text{H}_2\text{Se}$  gas, which synergistically induced oxidative stress and

**Table 1** Summary of the state-of-the-art gas-mediated synergistic therapeutic modalities for cancer therapy

| Gas                   | Structures                             | Therapeutic model                           | Trigger conditions     | <i>In vivo</i> model          | Ref. |
|-----------------------|----------------------------------------|---------------------------------------------|------------------------|-------------------------------|------|
| CO                    | FT1@P1/P2                              | CO-enhanced CDT                             | $\text{H}_2\text{O}_2$ | 4T1 tumor                     | 93   |
| NO                    | TK-Fc/LAE NPs                          | NO/ferroptosis/CDT                          | GSH                    | DU145 tumor                   | 94   |
| $\text{H}_2\text{S}$  | AAN-PTC- $\text{Fe}^{2+}$              | $\text{H}_2\text{S}$ combination with CDT   | Legumain               | C6 glioma cells               | 97   |
| $\text{O}_2$          | T-PFRT                                 | Oxygen-amplified PDT                        | MMP 2                  | 4T1 tumor                     | 104  |
| CO                    | NanoBDP2I-S-HF                         | CO-amplified PDT                            | $\text{H}_2\text{S}$   | HCT116 tumor                  | 105  |
| $\text{H}_2\text{S}$  | ADT@CuSNDs                             | Gas-mediated sensitizing mild PTT           | Hydrolysis             | 4T1 tumor                     | 107  |
| NO                    | NA1020-NO@PLX                          | NO-mediated low temperature PTT             | Light                  | Orthotopic osteosarcoma model | 109  |
| NO                    | ArgCCN                                 | Photogenerated holes and NO gas therapy     | Light                  | MCF-7 tumor                   | 110  |
| NO                    | GCZ@M                                  | NO GT with SDT                              | pH/US                  | 4T1 tumor                     | 116  |
| $\text{SO}_2$         | PBSA-EG                                | GT and SDT                                  | US                     | H22 tumor-bearing mice        | 117  |
| $\text{H}_2\text{S}$  | Aza-BD@PC NPs                          | GT and SDT                                  | US                     | Glioblastoma multiforme       | 118  |
| $\text{H}_2\text{S}$  | MCSP                                   | $\text{H}_2\text{S}$ gas with immunotherapy | TME                    | U14 tumor                     | 120  |
| NO                    | MP@AL                                  | Gas-immunometabolic therapeutic nanosystem  | pH                     | Hepa1-6 tumor                 | 121  |
| NO                    | IR&ZnPc@LNP-NO                         | Gas-enhanced SDT-chemo-immunotherapy        | US                     | Pancreatic cancer             | 122  |
| $\text{H}_2\text{S}$  | MTHMS                                  | Gas-enhanced PDT/PTT and immunotherapy      | Light                  | 4T1 tumor                     | 77   |
| $\text{H}_2\text{Se}$ | $\text{Cu}_{2-x}\text{Se}@\text{cMOF}$ | GT, cuproptosis and SDT                     | US                     | 4T1 tumor                     | 123  |
| CO/ $\text{O}_2$      | PM-FM/C                                | GT, CDT and SDT                             | US                     | Hepatocellular carcinoma      | 124  |



mitochondrial dysfunction. Concurrently, the copper core promoted cuproptosis by disrupting redox homeostasis and depleting GSH. This multifaceted strategy effectively suppressed tumor growth and metastasis. When combined with the PD-L1 immune checkpoint blockade, the platform further amplified the anti-tumor immunity. This work demonstrated how GT can be exploited to coordinate multiple therapeutic mechanisms, offering a potent strategy against primary and recurrent tumors.

To overcome the therapeutic limitations of hepatocellular carcinoma (HCC), Li *et al.* presented a biomimetic nano-platform by integrating FeMoO<sub>4</sub> and CORM-401, cloaked with a peptide-modified macrophage membrane to synergize SDT, CDT, and GT (Fig. 10b).<sup>124</sup> The multivalent bimetallic FeMoO<sub>4</sub> could decompose H<sub>2</sub>O<sub>2</sub> to O<sub>2</sub>, alleviating tumor hypoxia and enhancing SDT efficiency, while its peroxidase-like activity promoted  $\cdot\text{OH}$  generation *via* Fenton chemistry for CDT. Simultaneously, the excessive ROS triggered intracellular CO release, inducing mitochondrial dysfunction, GSH depletion, GPX4 inhibition, and lethal lipid peroxidation, thereby amplifying ferroptosis. This cascade established a robust ROS–CO–ferroptosis axis, enabling spatially and temporally controllable ferroptosis activation. The biomimetic membrane provided active HCC targeting and immune evasion, facilitating deep tumor penetration. Collectively, this gas-augmented multimodal strategy highlights the therapeutic value of CO gas as both an effector and amplifier of ferroptosis and redox-driven modalities, offering a promising approach for synergistic GT in refractory tumors such as HCC.

## Conclusions and perspective

A single-modality approach to cancer treatment still faces substantial challenges, largely due to tumor heterogeneity, adaptive resistance, and the complexity of the TME. These limitations highlight the necessity of developing combinatorial strategies. Here, we emphasize that combining GT with conventional treatments can substantially improve the therapeutic efficacy. GT offers several inherent advantages that contribute to this enhancement. First, bioactive gases modulate critical signaling pathways in tumor biology, thereby influencing tumor progression and, in certain contexts, directly inducing apoptotic cell death in cancer cells. In addition, gases can act as auxiliary agents by providing essential conditions for certain therapeutic modalities (*e.g.*, O<sub>2</sub>-dependent therapies).

Given these unique features, GT is increasingly being explored in combination with established treatment modalities. A distinct advantage of this strategy is that the treatment platform can be sophisticatedly engineered to meet increasingly complex therapeutic requirements. As highlighted in this perspective, GT could be combined with several mainstream therapeutic modalities (CDT, PDT, PTT, SDT, and immunotherapy) for cancer treatment, as summarized in Table 1. In addition, biotherapeutic gases can substantially enhance therapeutic outcomes, potentially by resolving inflammation, stimulating the immune response, remodeling the tumor

metabolism and bioenergetic processes, and modulating the TME.

However, several key challenges must still be addressed in applying GT to cancer treatment. First, our understanding of the physicochemical and biological properties of these bioactive gases remains limited. Second, compared with conventional non-volatile drugs, gas delivery strategies are still in their infancy, particularly for *in vivo* applications. This creates several specific obstacles. (i) Only a few therapeutic strategies have considered the interactions and cooperative effects among gasotransmitters, even though they often act synergistically rather than independently. (ii) The heterogeneous distribution of gasotransmitters across tissues and cell types makes it difficult to determine optimal therapeutic concentrations. The intrinsic instability and variability of their derivatives further complicate accurate measurement and monitoring. (iii) Current delivery platforms, although sophisticated, raise concerns about biocompatibility. In addition, nanoplateforms that rely on endogenous triggers may lead to premature gas release, while those restricted to a single gas-release profile are often insufficient to meet the increasingly complex therapeutic demands.

To overcome these barriers and advance GT-based synergistic therapies, future research should focus on improving therapeutic efficacy, biocompatibility, and targeting efficiency, while ensuring safe and effective clinical translation. Firstly, a revolution in gas delivery mechanism is needed to diversify the development of small-molecule gas donors and expand their integration into nanoplateforms. For example, enzyme-mediated delivery could mimic endogenous gas-generating pathways, while repurposing clinically approved drugs with controllable gas-donating features or modifying natural biomolecules (1-thio- $\beta$ -D-glucose) could provide safe and flexible delivery options. Secondly, dual gas donors remain rare, yet they are critical for probing gasotransmitters crosstalk, such as the cooperative roles of NO and H<sub>2</sub>S in post-translational modifications, and for designing new therapeutics. Thirdly, more precise synergy modalities are also required. Promising approaches include click-to-release chemistry (*e.g.*, strain-promoted azide–alkyne cycloaddition and SPAAC), antibody–antigen binding for tumor targeting, covalent modification of tumor targeting peptides (*e.g.*, RGD and NGR), and the use of pro-metabolites for metabolic labeling. Additionally, dynamic monitoring should be integrated into gas delivery systems, enabling real-time visualization of metabolic process (*e.g.*, fluorescence-based readouts) when combined with mainstream therapies.

Taken together, gas-based therapies hold considerable promise as combination approaches that diversify treatment strategies, mitigate their side effects, and enhance therapeutic efficacy. The likelihood of clinical translation will increase as these challenges are progressively addressed. Only through a deeper understanding of the complex and sometimes paradoxical roles of gasotransmitters in cancer pathophysiology can truly novel therapeutic paradigms be realized. With continued interdisciplinary research and technological advances, GT is poised to emerge as a transformative force in next-generation cancer treatment.



## Author contributions

All authors contributed to the writing and revision of the manuscript and have approved the final version of the perspective.

## Conflicts of interest

There are no conflicts to declare.

## Data availability

No primary research results, software or code have been included, and no new data were generated or analysed as part of this review.

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