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Review Article

Hydrogen sulfide responsive nanoplatforms: Novel gas responsive drug delivery carriers for biomedical applications

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ABSTRACT

Hydrogen sulfide (H_2S) is a toxic, essential gas used in various biological and physical processes and has been the subject of many targeted studies on its role as a new gas transmitter. These studies have mainly focused on the production and pharmacological side effects caused by H_2S. Therefore, effective strategies to remove H_2S has become a key research topic. Furthermore, the development of novel nanoplatforms has provided new tools for the targeted removal of H_2S. This paper was performed to review the association between H_2S and disease, related H_2S inhibitory drugs, as well as H_2S responsive nanoplatforms (HRNs). This review first analyzed the role of H_2S in multiple tissues and conditions. Second, common drugs used to eliminate H_2S, as well as their potential for combination with anticancer agents, were summarized. Not only the existing studies on HRNs, but also the inhibition H_2S combined with different therapeutic methods were both sorted out in this review. Furthermore, this review provided in-depth analysis of the potential of HRNs about treatment or detection in detail. Finally, potential challenges of HRNs were proposed. This study demonstrates the excellent potential of HRNs for biomedical applications.

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1. Introduction

Recently, drug-delivery systems, that are sensitive to the internal or external stimulus (e.g., temperature, ultrasound, gas, pH, light, oxidation, or reduction), have attracted significant attention in the field of nanomedicine [1]. Among them, gas sensitive nanoparticles, which effectively remove endogenous harmful gasses, are receiving more attention [2]. Currently, many studies have achieved an accurate release of nanoparticles gas-sensitive nanoparticles in response to excess nitric oxide at an inflammatory site [3]. However, the exploration of suitable responsive gasses is a primary concern for these nanoplatforms.

In recent years, hydrogen sulfide (H_2S), which is generated in mammalian tissues, has been explored widely as a stimulus-responsive gas [4]. H_2S, produced *via* the enzymes cysteine γ-lyase (CSE) and cysteine β-synthetase (CBS), is overexpressed in colonic and other cell types [4]. In addition, H_2S has been shown to have certain advantages at relatively lower concentrations [5,6]. However, the "burst" production of H_2S can cause noticeable tissue toxicity to the heart, liver, and many other organs [7–10]. Through many occupational and toxicological studies of H_2S, both sublethal and lethal effects of H_2S on mammals have been elucidated and can be ignored no further [6]. Therefore, nanoplatforms, with the capability to deplete H_2S, will have the enormous potential for clinical therapeutics.

Not only designed H_2S responsive nanoplatforms (HRNs) can consume overproduced H_2S in pathological conditions, but also resist the side effects caused *via* the high H_2S concentration [11]. Furthermore, HRNs, which have a variety of H_2S response units, can achieve accurate release of pathological sites due to H_2S expression under pathological conditions [11–16]. Moreover, HRNs can combine with a suite of therapeutic strategies (such as chemical therapy [11], chemodynamic therapy (CDT) [12], photodynamic therapy (PDT) [13,14], and photothermal therapy (PPT) [15]) to achieve optimal treatment outcomes and avoid toxic side effects. In addition, the combination of H_2S inhibitors with clinical drugs can achieve the pharmacology notion of "1 + 1>2", thereby suggesting great potential for clinical application of HRNs [16].

Although HRNs have the potential for both clinical application and combination, it is important to first measure H_2S levels. Over the years, much attention has been focused on probing the physiological role of H_2S to determine the signaling role of H_2S during pathological conditions [17]. Furthermore, HRNs, with the short development history, have been classified into two categories according to the function. One class consists of smart nanoplatforms to deplete H_2S and record responses to determine therapeutic efficacy. The second category is a nanoplatform probe for the real-time detection of H_2S levels. Although HRNs are mostly used for the treatment of the cancer, they have also received some attention in other disease areas due to the scavenging ability of H_2S [5]. However, HRNs currently lack the systematic introduction, thus hindering their clinical potential development.

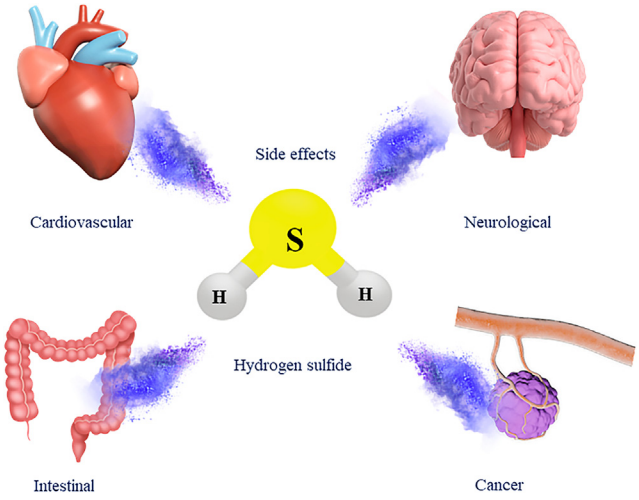

Fig. 1 – Association of different tissues induced *via* H_2S.

Here, we provide a brief review of H_2S relevance of H_2S in diseases and investigate how HRNs can be used for the treatment or detection. Furthermore, HRNs response units have been summarized in this article for reference. We discuss the current challenges and requirements of HRNs for clinical application and expansion of HRNs use.

2. H_2S and diseases

As an endogenous signaling molecule, H_2S has specific physiological functions that aid in the maintenance of cellular health in the circulatory system [18], the nervous system, as well as many other organ systems [19–22]. These functions are attributed to the formation of protein persulfides through the conversion of cysteine residues [23]. A quick glance shows that many studies have been published about the following keywords: "hydrogen sulfide" and "H_2S" [24,25]. Interestingly, different manifestations of H_2S with regards to pathways regulation have also been reported [26]. While it is worth considering that H_2S can induce side effects at high concentrations in multiple tissues types (such as the cardiovascular disease, the brain disease, the intestinal disease, and the cancer, Fig. 1). The potential damage induced *via* overproduction of H_2S is mainly due to inhibition of cytochrome oxidase activation, which inhibits adenosine triphosphate (ATP) synthesis by the mitochondria and causes a pro-inflammatory reaction of H_2S [6]. This process increases cardiovascular diseases burden, brain diseases, intestinal diseases and cancer [6]. Notably, each of these diseases has a specific association with H_2S. Therefore, we have provided a thorough discussion of the association between H_2S and diseases.

2.1. *H_2S and cardiovascular diseases*

Some preclinical trials focusing on cardiovascular diseases have shown that H_2S can regulate blood pressure, protect

blood vessels, and reduce myocardial injury at a low concentration [27]. H_2S can hyperpolarize endothelium-derived factors to dilate blood vessels and ATP-sensitive potassium (K_{ATP}) channels for changing vascular-relaxation activity after showing activity in the circulatory system [28]. Studies have demonstrated that H_2S might act as the inhibitor of cytochrome oxidase, which could reduce ATP levels and activate K_{ATP} channels [29].

However, H_2S is a primary chemical hazard [30]. The degree of H_2S toxicity, with clinical manifestations of pulseless electrical activity and respiratory depression, is associated with the rapid development of cardiac arrest [31]. These symptoms occur when the concentration of H_2S in blood exceeds 2–5 μM [32,33]. Several main potential effects and interactions between H_2S and related molecules involved in cardiomyocytes hampers determination of the mechanism of the action about H_2S upon the cardiotoxicity, including: (i) activation of L-type calcium ion (Ca^{2+}) channels; (ii) activation of K_{ATP} channels [32,34]; (iii) reconfiguration of proteins with cysteine residues [35]; (iv) inhibition of ATP to affect actin–myosin interactions [29]; (v) influence of reactive oxygen species (ROS) accumulation in mitochondria, and then affecting various key ion channels [36]; (vi) interaction between H_2S and nitric oxide to increase production of cyclic guanosine phosphate [37], as well as depression of the cyclic adenosine monophosphate pathway [38], both of which can lead to the cardiac depression. In summary, the interaction between H_2S and the cardiac disease can cause cardiotoxic effects and sequelae in direct or indirect ways.

2.2. H_2S and brain diseases

H_2S in brain tissue is the critical gas regulator in brain-related diseases [39]. H_2S can positively govern pH homeostasis and Ca^{2+} release in microglial cells, neurons, and astrocytes [40–43]. In addition, H_2S takes part in the development of various neurological diseases, including Alzheimer's disease [44], Parkinson's disease [45], cognitive deficits, or epilepsy [46,47]. The influence of H_2S at a low concentration on neurological disorders may depend on anti-apoptotic [48], antioxidant [49], anti-inflammatory, and calcium overload effect [50,51].

The low concentration of H_2S is physiologically beneficial for keeping the homeostasis of the brain [47]. The high H_2S level may cause damage [52], leading to neurodegeneration, neurological sequelae, or death [53], and affecting the pathophysiology of the brain [52,54]. Simultaneously, the lung can become edematous after acute exposure to high levels of H_2S, resulting in reduced oxygen uptake [52,54]. Hypoxia induced *via* H_2S also affects the cardiovascular system [55,56], inducing the vasodilatation that leads to the hypotension and the exacerbates hypoxia [57,58]. The above effects also lead to cerebral ischemia and hypoxia (Fig. 2). Furthermore, H_2S inhibits the cytochrome oxidase in mitochondrial electron transport chain, which reduces ATP production [59,60]. Collectively, these pathological and physiological interactions between H_2S and the brain, causing acute neurotoxic effects and subsequent long-term neurological sequelae [54,61].

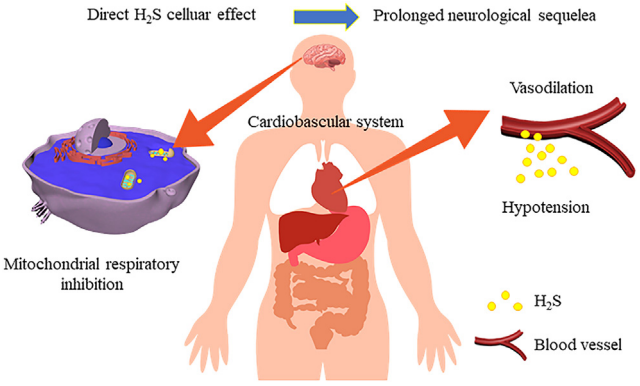

Fig. 2 – Pathophysiology of H_2S induced the neurotoxicity and the cardiotoxicity.

2.3. H_2S and intestinal diseases

The mucus consists of a highly glycosylated polymeric network of mucins linked by disulfide bonds [62], and goblet cells primarily produce mucin proteins in the intestinal epithelium [63]. Mucin (MUC)-2 polymerizes *via* C-terminal dimerization and N-terminal trimerization into large sheets [64–66]. Numerous studies have shown that defects in the mucus layer contribute to the inflammatory bowel disease (IBD) [67,68], which correlates with the rate of H_2S production [69]. H_2S produced by specific intestinal bacteria can break the disulfide bonds in mucus. Thus, solubilizing the polymerized MUC-2 network is one of the main mechanisms of destroying the mucus layer [70]. The human colon has been reported to have the highest luminal concentration of H_2S in the body (1.0–3.4 mM) [71,72]. The production rate of H_2S increases with IBD severity. In the IBD patients, with an increasing number of sulfate-reducing bacteria, the H_2S concentration is 2–3-times higher than healthy people [64,73,74].

Degeneration of the inner and outer mucus layers caused by H_2S can open-up mucus network, allowing bacteria to penetrate and contact with the host epithelium [75]. Under inflammatory conditions, H_2S can reduce the disulfide bond in MUC-2, enabling the formation of trisulfide bonds [74]. In addition, the destructed mucous layer increases interactions between H_2S, bacteria, and epithelial cells [72]. Under pathological conditions, the increasing in sulfate-reducing bacteria in intestinal lumina increases concentration of H_2S in lumen and leads to the instability of the mucosal layer of colonic cells, which also causes H_2S spread to the colonic epithelium, increasing the intracellular H_2S concentration [76].

Ishigami et al. found that low levels of H_2S, absorbed for storaging in cells, interact immediately with cells [77,78], and it can permeate freely through cell membranes [72,73]. The ability of colonic cells to process H_2S is reduced when H_2S concentration in colonic cells is high. The interaction of H_2S with colonic epithelial cells also increases interleukin-6 expression and inducible nitric oxide synthase [76], which aggravates colonic inflammation (Fig. 3).

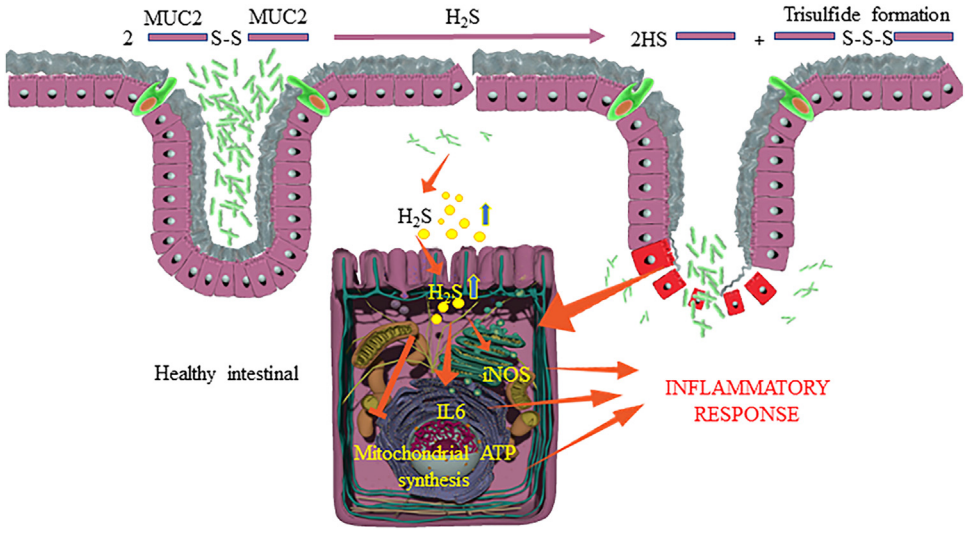

Fig. 3 – Schematic representation of the effect of excess H_2S on mucin-2 and inflammation in colon cells.

Table 1 – Changes in H_2S-producing enzymes in tumor types.

Cancer type	Cell line	H_2S producting enzyme		Ref.
		CBS	CES	
Colon	HT29	↑	↑	[85]
Gastric	SGC-7901	↑	↑	[86]
Prostate	PC3	↑	↑	[87]
Breast	MCF-7	↑	↑	[88]
Liver	HepG2	↑	↑	[89]
Mouth	OSCC	↑	↑	[90]
Melanoma	A375	N/A	↑	[91]
Leukemia	HL-60	↑	N/A	[92]
Ovarian	OV202	↑	N/A	[93]
Gliomas	C6	N/A	N/A	[94]

N/A: Not test; ↑: upregulation; CSE: cysteine γ-lyase; CBS: cysteine β-synthetase.

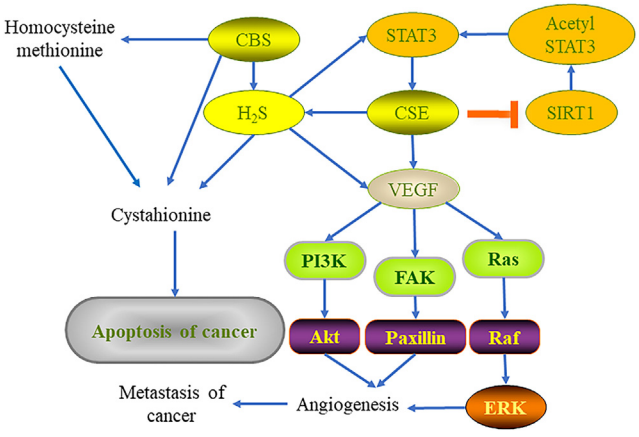

Fig. 4 – Oncogenic signaling pathway regulated by H_2S.

2.4. *H_2S and cancer*

H_2S plays a vital part in the proliferation and metastasis of tumor cells, and it becomes a new target for cancer therapy [79]. Studies have shown that the upregulation of H_2S-producing enzymes in tumor tissues leads to significant increasing in concentration of H_2S [80]. However, endogenous H_2S shows high expression only in some tumor cells, and its concentration can reach 3.4 mM [81]. Some scholars have revealed changes in the expression and role of the enzymes (CSE and CBS) that help to produce H_2S during a development of cancer [82], such as colon [83], gastric [84], prostate [85], breast [86], liver [87], and mouth [88], as summarized in Table 1. The cancer can generate H_2S only through CES [89], or CBS [90,91]. Anyway, there are some cancers without causing changes in CSE and CBS [92].

Studies have demonstrated that H_2S can promote tumor proliferation *via* four main pathways: (i) providing energy for tumor growth *via* mitochondrial respiration and glycolysis [93]; (ii) activating K_{ATP} channels upon vasodilation and then inducing expression of hypoxia-inducible factor-1α [94]; (iii) activating anti-apoptotic pathways [91]; (iv) accelerating the cell cycle and promoting the proliferation of tumor cells [94]. H_2S also has the central role in modulation of oncogenic signaling pathways, such as vascular endothelial growth factor, phosphatidylinositol 3-kinase/protein kinase B [95], Janus kinase/signal transducer and activator of transcription (JAK/STAT) [96,97], and Ras/Raf/extracellular-signal-regulated kinase signaling cascades [95,98], as shown in Fig. 4. In addition, STAT3 can promote expression of CSE and H_2S by activating a CSE promoter. In this way, CSE regulates STAT3 expression *via* the sirtuin-1/acetyl STAT3 pathway, increasing the efficiency of STAT3 [99]. Simultaneously, H_2S can restrict the immunogenicity of tumor cells, thereby reducing its concentration and inducing and improving infiltration of immune cells into the tumor [100,101]. Interestingly, excessive H_2S can also increase the ROS level in normal cells or around

tumor *via* the overexpressed enzyme catalase [102]. However, the comprehensive study of pharmacological properties and mechanisms of these molecules is needed to advance H_2S inhibition research in clinical trials.

3. Inhibition of H_2S production

Pharmacological inhibition or blockade of H_2S expression has been shown to reduce H_2S pathology in some diseases [102]. Novel inhibitors have been synthesized to suppress H_2S production and promote H_2S depletion in the clinic [97].

Three drugs have been shown to help remove H_2S and include: L-aspartic acid (L-Asp), DL-propargylglycine (PAG), and aminooxy acetic acid (AOAA) [103]. The mechanism of action of L-Asp ($C_4H_{14}NO_4$) can scavenge H_2S by blocking the active site of CSE. Wang et al. indicated the suppression of endogenous H_2S generation, caused by L-Asp, could dramatically inhibit the nasopharyngeal carcinoma growth *via* the ROS/mitogen-activated protein kinase pathway [104]. Khan et al. also indicated L-Asp could decrease the endogenous H_2S production to inhibit the growth of human breast cancer [88].

PAG ($C_5H_7NO_2$) is similar to L-Asp. However, the solubility of PAG is much higher than that of L-Asp. Thus, the effect of PAG has been shown to be stronger than L-Asp. Bhatia et al. indicated that PAG could decrease the formation of H_2S on pancreatic to counter role of H_2S in acute pancreatitis and lung injury therapeutic effects [105]. Based on the above results, Ji et al. also indicated that an active suppression of H_2S, caused by PAG, could restore over-activated autophagy, which might be a promising therapeutic approach against acute pancreatitis related injuries. [106]. By the way, PAG can effectively blocked H_2S production in the colon at 2 mM, and inhibitor also can increase spontaneous colonic motility [107]. Although PAG has a great H_2S removal capacity, the removal efficiency about inhibition of H_2S still has a great improvement.

Meanwhile, AOAA has been reported to deplete H_2S *via* inhibiting CBS and CSE [108,109]. AOAA can regulate cell activity by reducing ATP levels and the rate of glycolysis and is highly soluble in water and phosphate-buffered saline (PBS), so it has been applied extensively [107–109]. AOAA has been shown to induce E-cadherin and zonula occludens-1 expression, as well as downregulate fibronectin expression [110]. An analog of AOAA known as 5-aminosalicylic acid has been shown to have a therapeutic effect against IBD and ulcerative colitis by reducing H_2S concentration levels [74].

To some extent, inhibiting H_2S production can reduce or slow-down the growth of a tumor. A study by Yue et al. showed that H_2S inhibitor resistant colon cancer can be prevented [16]. In their study, AOAA and oxaliplatin combination therapy, was used and was successful in reducing H_2S synthesis [16]. Furthermore, AOAA was shown to enhance the effect of oxaliplatin with regards to apoptosis of colon cancer cells as well as the sensitization of colon cancer cells. However, Yue et al. indicated that both potency and specificity of H_2S inhibitors needed to be increased in future studies. Unfortunately, CBS inhibitors affect multiple signaling pathways and cannot accurately mimic the inflammatory effects of H_2S during treatment. H_2S-producing enzymes are present on many biological substrates, therefore inhibitors of H_2S-producing enzymes can cause unwanted side-effects.

In short, H_2S-scavengers allow targeted clearance of H_2S, but their targeted features are limited [111]. Over the last two decades, enormous progress has been made in the development of nanoplatforms, and their targeting properties can be found in many therapeutic approaches [112]. Thus, targeted elimination of H_2S through nanoplatforms may have great potential for using in biomedical applications.

4. Nanoplatforms for H_2S response and inhibition

HRNs, received attention on the cancer therapy, have been constructed and shown great potential in the diagnosis and treatment of diseases [113]. The HRNs enhance therapeutic effects specifically *via* integrating existing therapies. According to their functions, HRNs can be divided into five main categories [114,115] (Fig. 5, Table 2). HRNs can be combined with: (i) chemical therapy; (ii) CDT; (iii) PDT; (iv) photothermic therapy (PTT); (v) multiple therapies. However, the therapeutic actions of HRNs *in vivo* are uneven [116]. In addition, HRNs, the diagnostic strategy, has begun to appear in field of cardiovascular diseases, cancer, hepatitis and other diseases due to association between H_2S and diseases [117,118]. Therefore, analyzing existing nanoplatforms for H_2S response is important.

4.1. *HRNs combined with chemical therapy*

Chemical therapy drugs are the primary means for the clinical treatment. However, the above drugs are limited by poor solubility, low bioavailability and systemic toxicity

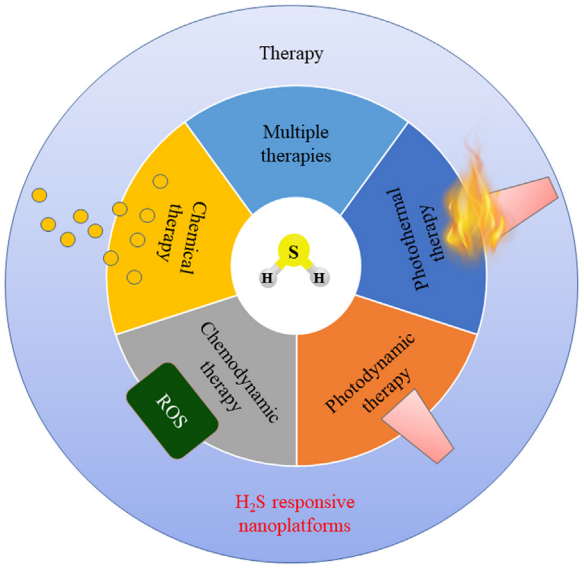

Fig. 5 – Schematic illustration of *in situ* H_2S responsive nanoplatforms and their applications in the disease therapy.

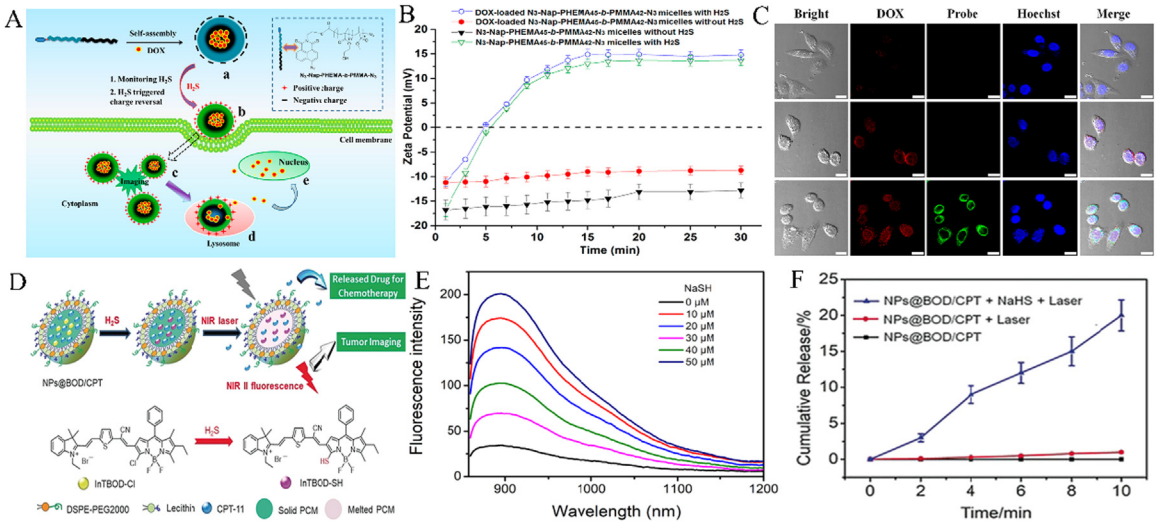

Fig. 6 – Possible mechanism of cellular uptake for N_3_Nap-PHEMA$_{45}$-b-PMMA$_{42}$_N_3 micelles (A) H_2S-triggered charge reversal (B) and positive charge-mediated targeting properties (C) for N_3_Nap-PHEMA$_{45}$-b-PMMA$_{42}$_N_3 micelles. Copyright 2022 Nature [119]. Use of NPs@BOD/CPT for cancer imaging (D) H_2S-triggered NIR photothermal ability (E) and photo-controlled on-demand drug release (F) for NPs@BOD/CPT. Copyright 2019 Wiley Online Library [11].

Table 2 – H_2S responsive nanoplatforms and their applications in the therapy.

Therapeutic type	Therapeutic strategy	H_2S responsive unit	Ref
Chemical Therapy	N3-Nap-PHEMA-b-PMMA-N3	Azide	[119]
	NPs@BOD/CPT	BOD-Cl	[11]
	PALA@CIP	PALA	[120]
Chemodynamic therapy	VZnO	Zn	[12]
	FeOOH NSs	Fe	[2]
Photodynamic therapy	Cu_2(ZnTcpp)·H_2O	Cu	[13]
	ZNNPs@FA	ZM1068-NB	[121]
Photothermal therapy	HKUST-1	Cu	[122]
	NP-Cu	Cu	[123]
Multiple Therapies	5-Fu/Cur-P@HMPB	HMPB	[124]
	Cu_2O@$CaCO_3$@HA	Cu_2O	[14]

[125]. Therefore, most studies have focused on controlling the release of "precision drugs" on-demand by small molecules in pathological region to overcome side-effects of chemical therapy.

H_2S-mediated reduction of azides, which are reduced to positively charged amines *via* H_2S, has become the most common strategy for H_2S detection [119]. Azide-based H_2S responsive material can also be used to control the surface charge of nano-drug carriers. Zhang et al. prepared H_2S-triggered charge-reversal micelles based on azide-based H_2S responsive material (N-(2-hydroxyethyl)-4-azide-1,8-naphthalimide ended amphiphilic diblock copolymer poly (2-hydroxyethyl methacrylate)-block-poly (methyl methacrylate, N_3-Nap-PHEMA$_{45}$-b-PMMA$_{42}$-N_3) to achieve cancer detection and targeted delivery of drugs [119] (Fig. 6A). The surface charge-induced enhanced cellular uptake was reversed *via* N_3-Nap-PHEMA$_{45}$-b-PMMA$_{42}$-N_3 micelles with positive charge-mediated targeting properties (Fig. 6B and 6C). Hence, N_3-Nap-PHEMA$_{45}$-b-PMMA$_{42}$-N_3 micelles can recognize H_2S in cancer cells and deliver doxorubicin to cancer cells for efficacious chemical therapy.

In addition to azide-based H_2S responsive nanoplatforms, the boron-dipyrromethene nanoplatforms have been explored for targeted drug delivery in cancer treatment. Shi et al. prepared HRNs with generation of near infrared (NIR)-triggered hyperthermia for photo-controlled drug release in cancer cells to improve the specific targeting of tumor cells and anticancer performance [11] (Fig. 6D). These HRNs (Boron dipyrromethene/camptothecin nanoparticles, NPs@BOD/CPT) worked as well as NIR photothermal agent (Fig. 6E). Also, the drug, camptothecin-11, was encapsulated into the nanoplatform. In the absence of H_2S, NPs@BOD/CPT without exhibiting the significant hyperthermia effect under NIR laser. Conversely, the NPs@BOD/CPT caused a conversion from solid to liquid, which led to the release of a hydrophilic drug and increased chemotherapeutic effect of camptothecin-11 (Fig. 6F).

Notably, HRNs also have been utilized for the responsive drug delivery systems targeting specific infections. Lu et al. prepared HRNs, which release ciprofloxacin (CIP) for responding to H_2S produced by *Salmonella* spp. in the intestine *via* oral administration [120]. The response mechanism of HRNs is destroying disulfide bond-containing poly (α-lipoic acid) (PALA), and disulfide bonds are reduced to sulfhydryl groups *via* H_2S. The results show that PALA nanoparticles, loaded with CLP (PALA@CIP), can recognize the infection about *Salmonella*, eradicating the bacteria. Therefore, the response of H_2S in the nanoplatform could be an auspicious way to combine chemical therapy.

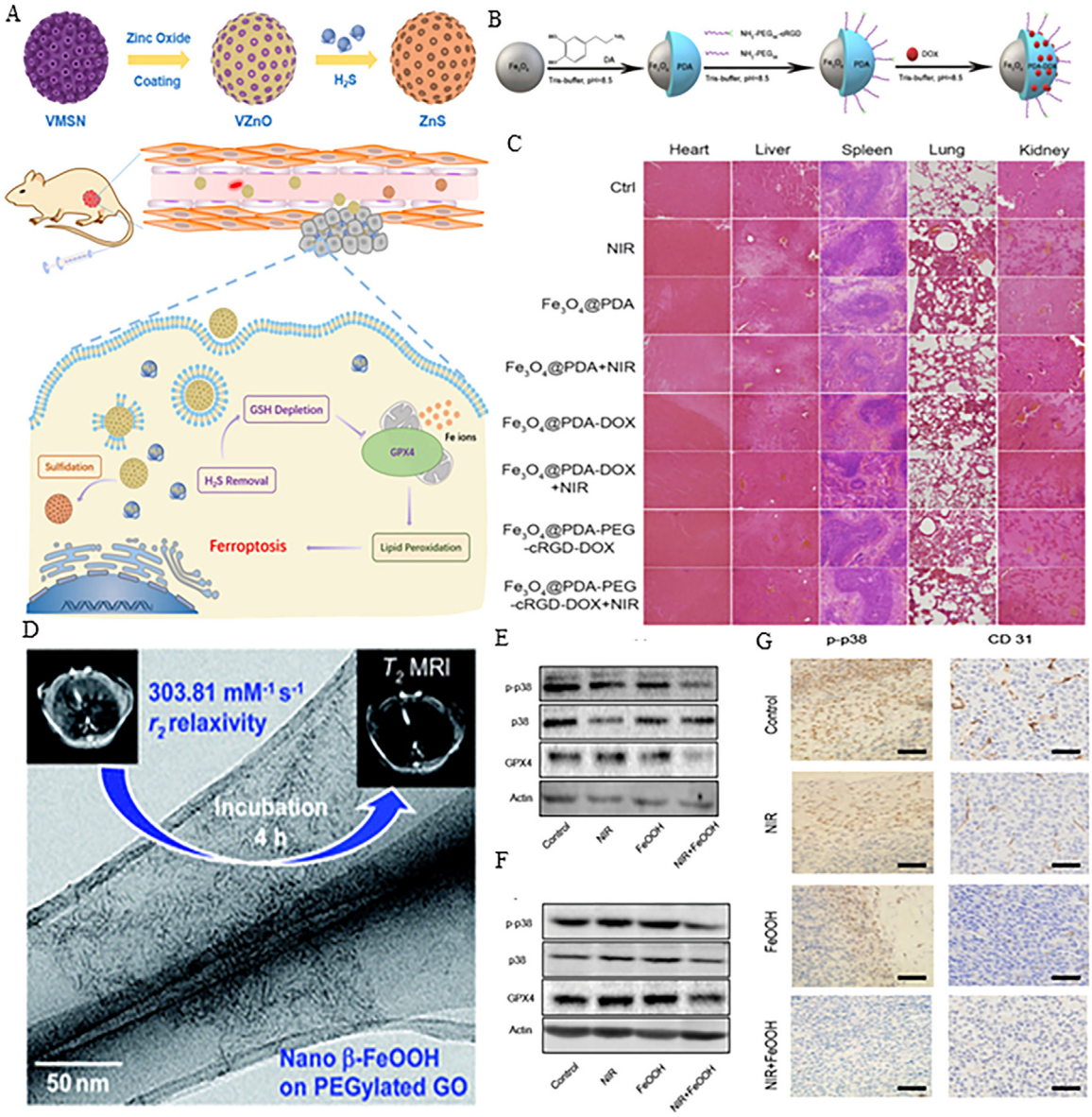

Fig. 7 – Synthetic route to VZnO and H_2S removal for the colorectal cancer therapy (A) Copyright 2021 Springer Nature [12]. Synthetic route to Fe_3O_4@PDA-PEG-cRGD-DOX NPs (B) The hearts, livers, spleens, lungs and kidneys of the treatment group after treatment (C) Copyright 2019 Dove Medical Press [128]. MRI capability of GO-PEG-β-FeOOH (D) Copyright 2013 Springer [129]. Western blots of p-p38 and p38 expression level in CT26 cells after different treatments (E) Western blots of the expression of p-p38, p38, and GPX4 within tumor tissue after various treatments (F) p-p38 and CD31 immunostaining of CT26 tumor sections after a series of treatments (Scale bar = 100 μm) (G) Copyright 2020 Wiley Online Library [2].

4.2. *HRNs combined with CDT*

CDT has been employed to convert hydrogen peroxide (H_2O_2) to the toxic hydroxyl radical (•OH) in tumor tissues, causing damage to tumor cells [126]. Furthermore, CDT combined with removing H_2S gas into a single nanoplatform enhance anticancer effect [127]. Zinc oxide has the great safety profile, which has prompted more attention in the medical research compared with other metal-oxide nanoparticles. Pan et al. reported HRNs based on zinc oxide-coated silica (VZnO) nanoparticles for treatment of colorectal cancer (Fig. 7A). The reduction of H_2S *via* VZnO resulted in an indispensability reduction in cellular levels, which was combined with CDT [12].

Nanoparticles designed with fixed elements (e.g., iron (Fe)) can have therapeutic functions [2,130]. Our research group prepared multifunctional targeting Fe_3O_4 nanoparticles based on modification of polyethylene glycol (Cyclo (Arg-Gly-Asp-D-Phe-Cys) conjugated doxorubicin-loaded Fe_3O_4@polydopamine nanoparticles, Fe_3O_4@PDA-PEG-cRGD-DOX NPs) to integrate the diagnosis and treatment of tumors. These nanoparticles had excellent safety and anti-tumor

effects [128] (Fig. 7B and 7C). At the same time, the H_2S response properties of Fe are also used in cancer treatment. The paramagnetic ferric-hydroxide (FeOOH) nanospindles (NSs), constructed *via* Chen et al., have been used as a magnetic resonance imaging (MRI) contrast agent for the diagnosis and the treatment of the cancer [129] (Fig. 7D). FeOOH NSs not only consume H_2S in tumor environments, but also show the high reactivity and adsorption of H_2S at the room temperature in typical environments. In response to the excellent performance of FeOOH NSs in cancer treatment, Li et al. constructed biocompatible nanosystem for FeOOH NSs to combine colon-cancer treatment with enhanced MR and CDT [2]. The reduced level of phosphorylated-p38 (increased levels of p-38) and glutathione peroxidase 4 (GPX4) promotes therapeutic effects of FeOOH NSs against cancer *via* CDT (Fig. 7E and 7F). In addition, *in vivo* experiments reveal that the group without undergoing laser irradiation show the substantial anti-tumor effect, suggesting that H_2S clearance cause the tumor-killing effect to a certain extent with an excellent synergistic effect on CDT (Fig. 7G). Those results also indicate that HRNs combined with laser irradiation might lead to the extraordinary result.

4.3. *HRNs combined with PDT*

Under action at a specific wavelength (e.g., NIR light), photosensitive materials/genes can kill tumor cells, which is called PDT [131–133]. Compared with conventional therapies such as the chemical therapy, PDT is an ideal strategy for treating cancer (tumor cell apoptosis and necrosis through the activation of ROS) [134]. However, due to unique physicochemical properties (e.g., instability of photosensitive materials/genes), most strategies have led to poor targeting of tumor cells and poor specificity of distribution. Designing and synthesizing a drug for accurate delivery to a tumor site has become an important research direction. Our research team designed a “light-switch” transgene system to regulate (spatially and temporally) the gene expression of the diphtheria toxin under the blue-light irradiation to kill tumor cells selectively [135] (Fig. 8A). This light-switch transgene system improved the targeting and the activation of ROS. Simultaneously, we have explored the potential of this nano-delivery system against melanoma cells [136] (Fig. 8B and 8C).

Studies have shown that some specially treated nanomaterials can implement this strategy effectively [137,138]. For example, Ma et al. developed an “intelligent” H_2S-activated metal-organic framework (MOF) nanosensor that became the photosensitizer upon H_2S action [13] (Fig. 8D). This novel MOF (Copper and zinc metalated 5,10,15,20-tetrakis (4-methoxycarbonylphenyl) porphyrin monohydrate nanoparticles, Cu_2 (ZnTcpp)·H_2O, NP-1) was synthesized using a reversed-phase microemulsion method. NP-1 and H_2S can rapidly complete the reaction within 1 min, and the red fluorescence is restored. ZnTcpp achieve the certain degree of the tumor shrinkage after irradiation, but the effect is less than the NP-1 group. The expression of H_2S in HCT-116 cells confirmed a role of H_2S in radiation-induced injury.

H_2S-activated nanocomposites offer unprecedented strategies for precisely targeted the cancer therapy in form of responsive therapeutic tools. The intelligent and H_2S-activated nanoplatform for scavenging of H_2S and biomedical applications has been reported. The responsive unit of H_2S has been encapsulated *via* biocompatible and amphiphilic mPEG5000-PCL3000 and mPEG5000-PCL3000-Folic acid (FA) polymers to afford the stability and the targeting of the nanoparticle in the biological medium. The nanoparticle (H_2S responsive and depleting nanoplatform, ZNNPs@FA) can undergo the nucleophilic substitution reaction with H_2S to generate NIR conversion and ratiometric photoacoustic signals. Therefore, ZNNPs@FA decrease mitochondrial H_2S levels in cancer cells while activating PDT effects, leading to the significant glycolysis reduction and severe mitochondrial damages [121] (Fig. 8E). This intelligent nanoplatform NP-1 has shown excellent potential as the H_2S-selective photosensitizer for PDT. In addition, the modification with PEG is strongly recommended to enhance systemic circulation and increase the accumulation at tumor sites.

4.4. *HRNs combined with PTT*

As the companion therapy to PDT, our research team demonstrated that PTT kills cancer cells based mainly on the thermal energy *via* laser irradiation [128]. However, laser irradiation also damages surrounding normal tissue, due to the uneven distribution of photothermal agents. Therefore, there is an urgent need for designing the novel PTT agent that can exert PTT mainly at the tumor site while causing less damage to normal tissues.

Li et al. designed the H_2S-activated nanomaterial, Cu-MOF (also known as HKUST-1), to treat the colon cancer [122] (Fig. 9A). Under the action of a high concentration of H_2S in colon cancer, HKUST-1 decompose to form large lamellar copper sulfide (CuS) (Fig. 9B). According to the temperature curve, HKUST-1 absorption increase significantly at 808 nm after reacting with sodium hydrosulfide (NaHS), which demonstrate CuS is the great photothermal material and exhibited concentration-dependent increase in temperature (Fig. 9C). *In vivo* animal experiments showed that the temperature increased at the tumor site about 13 °C after the particular duration of laser irradiation at 808 nm (Fig. 9D). Contrary to expectations, the increasing in the concentration of H_2S without increasing the total amount of CuS, accelerated only the rate of the generation of H_2S. The bodyweight of each group without changing significantly during treatment. Those data suggest that PTT is safe, and the *in situ*-activated HKUST-1 nano-preparation is the excellent drug for PTT [122].

Based on the excellent PTT features of CuS, some scholars develop the nanoplatform (Copper nanoparticle, Cu-NP) frame *via* assembling chlorin e6 (Ce6), hypoxia-responsive prodrug (mitoxantrone) with clickable dibenzocyclooctyne, and copper-ion complex (Fig. 9E). Subsequently, CuS is generated *via* the reaction of H_2S with Cu^{2+} to aid PTT [123] (Fig. 9F).

4.5. *HRNs combined with multiple therapies*

Whether PDT or PTT, single treatment often fails to achieve the desired antitumor effect, leading to tumor recurrence and distant metastasis [139]. Immunotherapy using programmed

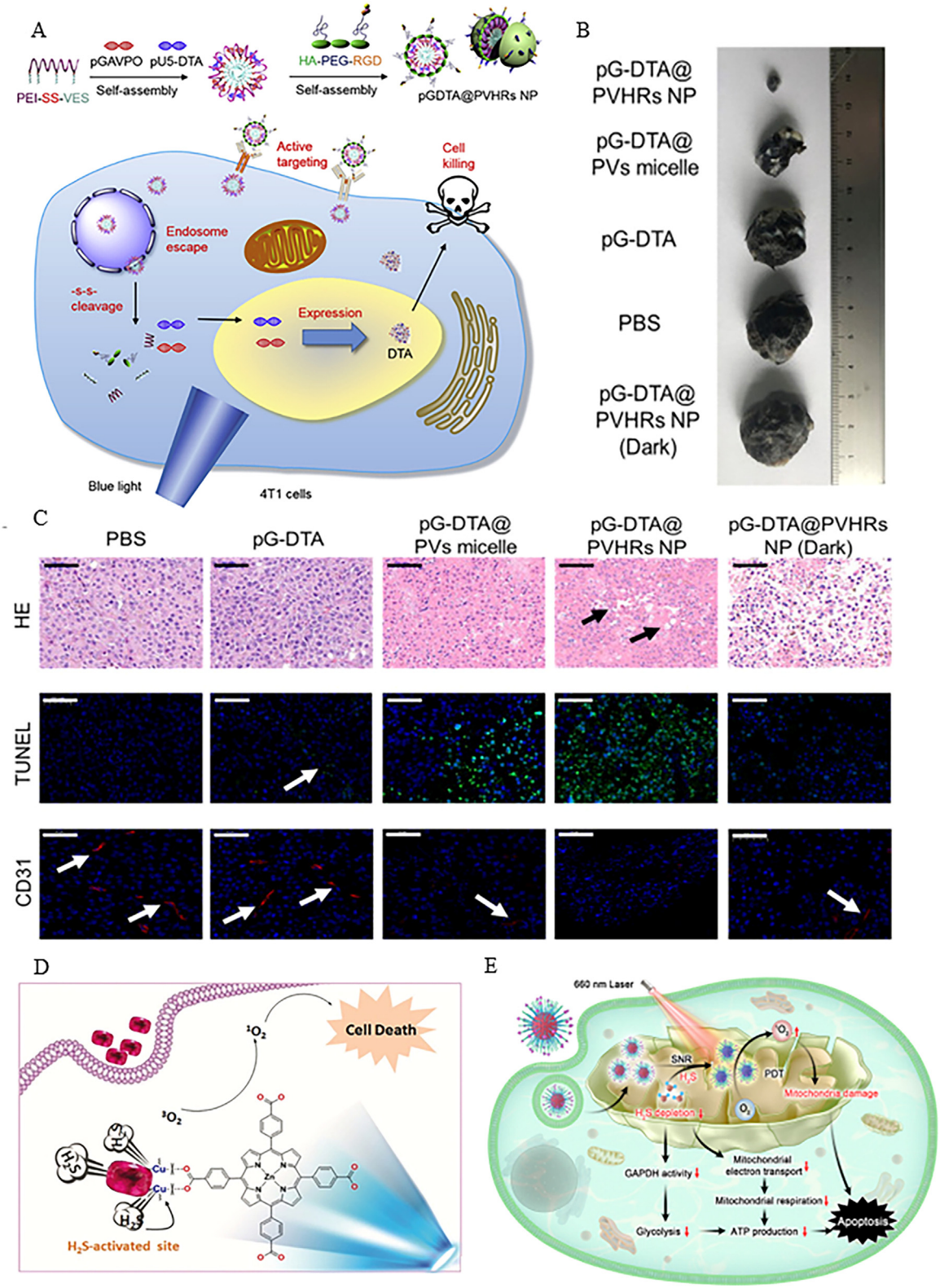

Fig. 8 – (A) Scheme of DTA based nanodrug delivery system combined with LightOn gene expression system for PDT of breast cancer. Copyright 2020 ScienceDirect [135]. (B) The tumor was collected at the end of treatment *via* LightOn gene expression system, and (C) Immunofluorescence staining of CD31 and TUNEL for tumor tissue sections and H&E-stained tumors after treatment with LightOn gene expression system. Copyright 2020 ScienceDirect [136]. (D) Simple structural fragment of MOF NP-1 and the proposed strategy for $^1O_2$ generation in cancer therapy. Copyright 2017 Wiley Online Library [13]. (E) The activation of PDT by ZNNPs@FA and the inhibition of ATP synthesis *via* depletion of H_2S in CRC. Copyright 2020 American Chemical Society [121].

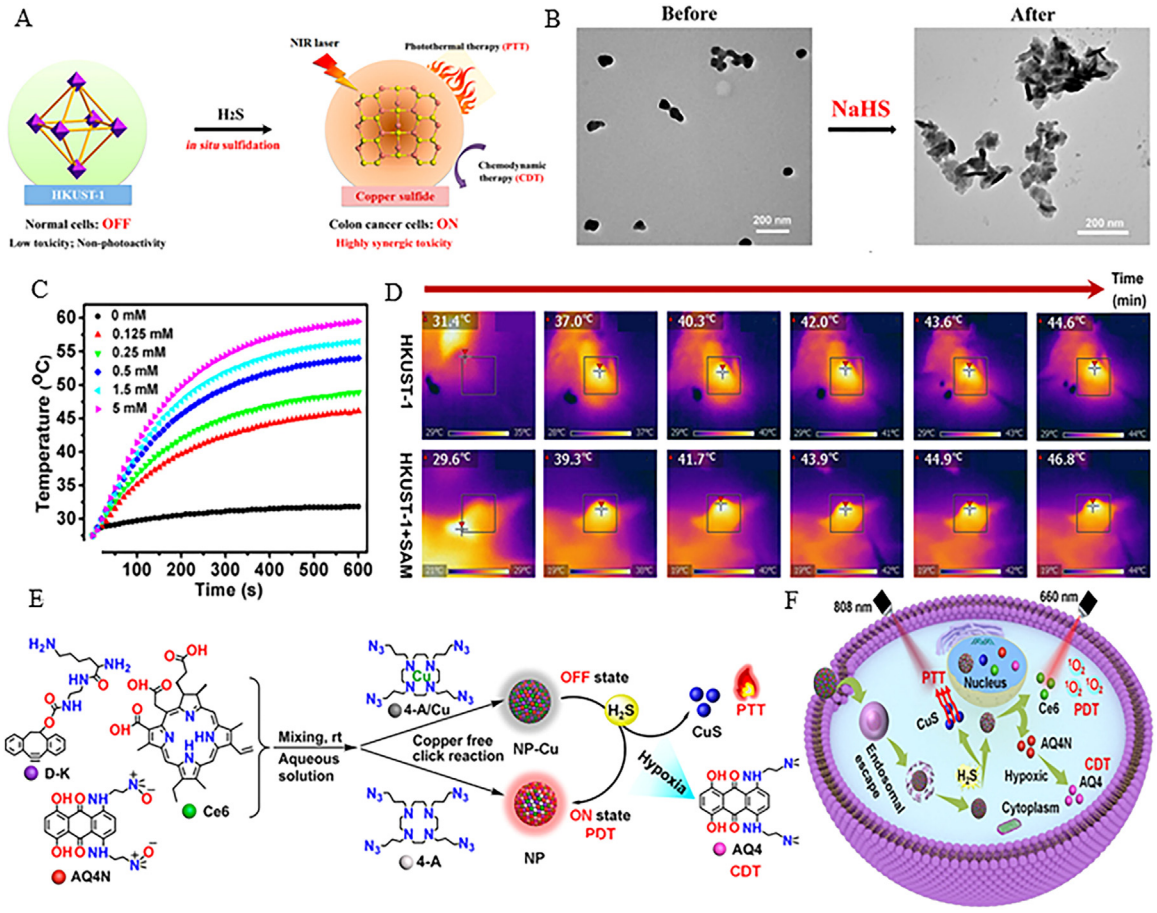

Fig. 9 – (A) Schematic diagram of the PTT of colon cancer by HKUST-1 nanoenzyme in response to H_2S. (B) Transmission electron micrograph of HKUST-1 nanoparticles with H_2S. (C) Temperature curves of aqueous NaHS solutions (5 mM) in the presence of HKUST-1 nanoparticles (0–5 mM) under the laser irradiation for 10 min. (D) Heatmap of the same concentration of HKUST-1 after 10 min laser irradiation at NaHS concentration of 5 mM. Copyright 2022 American Chemical Society [122]. (E) NP-Cu nanocomplex constructed using a simple clickable self-assembly strategy. (F) Simple strategy of endogenous H_2S-triggered of PTT. Copyright 2022 American Chemical Society [123].

cell death protein-1 has achieved excellent clinical results, but it is suitable only for specific populations [139]. A single nanotherapeutic agent can be combined with other types of treatment [140–144]. Subsequently, the combination therapy often failure of specificity to the tumor site, inducing in superfluous damage to serviceable tissues [145–147].

Colleagues developed the nanomedicine (5-Fu/Cur-P@HMPB) *via* encapsulation of natural anticancer drug curcumin (Cur) and chemotherapeutic drug 5-fluorouracil (5-Fu) into a hollow mesoporous Prussian Blue (HMPB) [124] (Fig. 10A). The task of the iron (II) ion (Fe^{2+}) detection is realized mainly *via* 1,10-phenanthroline. The iron (III) ion (Fe^{3+}) is reduced to Fe^{2+} *via* a reaction with H_2S, and this process is detected in the presence of NaHS at 511 nm (Fig. 10B). HMPB with the low fenton catalytic activity can be converted to the prussian white with the high fenton catalytic activity based on the combined action of HMPB and H_2S for activating CDT and the chemical therapy (Fig. 10C).

Considering the potential of combining multiple therapies in HRNs, PTT, PDT, and CDT is combined in a HRNs. Chang et al. constructed core-shell nanostructures (Cu_2O@$CaCO_3$@HA, CCH) by targeting the high concentration of H_2S and acidic microenvironment in the colon cancer [14]. The calcium carbonate ($CaCO_3$) shell of Cu (I) oxide (Cu_2O) decomposes under acidic conditions. Hence, the core of Cu_2O generates djurleite ($Cu_{31}S_{16}$) with PTT, PDT, and CDT under the action of H_2S (Fig. 10D). Moreover, the high temperature and oxidative stress generate by CCH can reprogram macrophages of the M2 (tumor-promoting) phenotype to the M1 (tumor-suppressive) phenotype and initiate vaccine-like immune effects to inhibit distant metastasis and the recurrence of colon cancer (Fig. 10E). Given the potential of HRNs in the combination with multiple therapies, many related studies are ongoing.

4.6. *HRNs combined with diagnosis*

Based on the association of H_2S with various diseases, H_2S detection techniques have been developed [124]. For instances, Zhang et al. indicated the plasma level of H_2S had both high sensitivity and specificity rates to predict

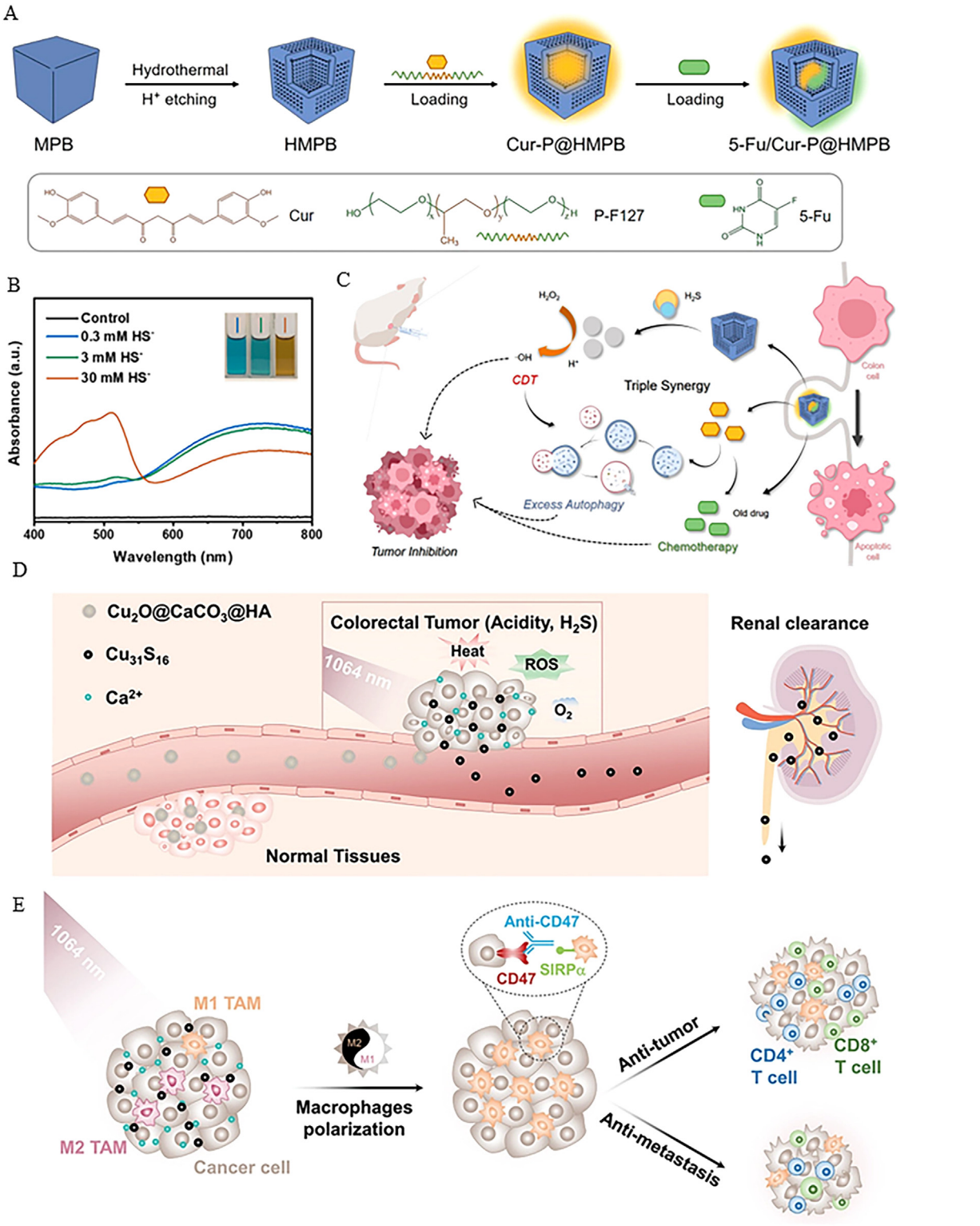

Fig. 10 – (A) Schematic Illustration of Cur-P@HMPB NPs and 5-Fu/Cur-P@HMPB NPs preparation. (B) UV–vis spectral changes induced *via* the mutual action of HMPB and different concentration of NaHS by 1, 10-phenanthrolineis. (C) Summary figure of 5-Fu/Cur-P@HMPB activating CDT and chemical therapy against colon cancer. Copyright 2021 Wiley Online Library [124]. (D) Mechanistic diagram of the antitumor effects, degradation and renal clearance of the tumor microenvironment triggered nanoparticles. (E) Mechanism diagram of the anti-tumor immune response triggered *via* the regulation of the tumor microenvironment from CCH. Copyright 2020 Wiley Online Library [14].

postural orthostatic tachycardia syndrome [148]. However, most methods are not suitable for *in vivo* monitoring of H_2S in the disease states [149]. Therefore, HRNs, with H_2S response and focal targeting characteristics [150], have been widely concerned in the detection of H_2S field about cardiovascular diseases, brain diseases, cancer and other diseases. In short, HRNs can offer the better cell-compatibility and higher spatiotemporal resolution than previously employed techniques.

4.6.1. *HRNs combined with diagnosis in cardiovascular diseases*

According to the importance of H_2S in cardiovascular disease, Jing et al. developed HRNs composed of nitrogen-doped Cdots (N-Cdots)/TiO_2 nanowire (N-Cdot-TiO_2 NW), which allowed real-time detection of H_2S produced *via* myocardial myoblasts [118]. N-Cdot-TiO_2 NW is set to the off state *via* soaking into Cu^{2+} solution as HRNs. The high concentration of H_2S can combine with Cu^{2+} on the surface of N-Cdot-TiO_2 NWs to gradually restore the photocurrent, calling "on" state, to realize the detection of H_2S in cardiomyocytes. Although there without more research about the detection and treatment of HRNs in field of the heart, above studies have produced significant implications for the treatment of HRNs in cardiovascular diseases.

4.6.2. *HRNs combined with diagnosis in brain diseases*

The accurately detecting H_2S levels in the brain remains a huge challenge. With the development of synthetic technology, a series of materials that respond to H_2S in the brain have emerged in recent years [151,152]. However, the above materials are mostly injected into the brain, which is harmful to the brain. The above mentioned ZNNPs@FA, which have the ability to treat colon cancer, can detect trace amounts of H_2S in the damaged brains *via* the targeting characteristics of HRNs [121]. Therefore, we speculate that HRNs has great potential in the detection of H_2S about brain diseases in the future.

4.6.3. *HRNs combined with diagnosis in cancer*

Given the highly expressed H_2S in some cancer sites, HRNs, based on BOD or Ag_2S nanoparticles, have been designed for H_2S-related bioimaging in the cancer [153,154]. For example, Deng et al. developed an endogenous H_2S-activated NIR-II emitting optical probe (Ag-CEW) for diagnosis of colorectal cancer. Ag_2S, which formed from H_2S reactions with Ag-CEW, emitted a strong NIR-II fluorescence signal at approximately 1090 nm, enabling ultrasensitive detection ability of H_2S from HRNs [154]. In addition to colon cancer, HRNs can also be used to detect H_2S in other cancer sites. Zheng et al. synthesized the HRNs (AB-DS@BSA-N_3 NYs) by conjugating 3-azidopropylamine (–N_3(–)) with Bi_2S_3-Ag_2S-DATS@BSA nanoparticles (AB-DS@BSA). Under the action of H_2S, –N_3 (–) of AB-DS@BSA-N_3 NYs could be reduced to –NH_3 (+) by H_2S for the treatment and diagnosis of liver cancer [155]. Furthermore, Ma et al. presented a Cu (II)-metalated 3D porous nanoscale metal–organic framework (nano-MOF) and successfully employ this nano-MOF as a novel heterogeneous fluorescence probe for H_2S detection in HepG-2 [156], indicating the application prospect of HRNs in the diagnosis of liver cancer. To note, HRNs, containing Mn, can also be used for the MRI of breast cancer to achieve diagnosis and treatment [127]. These related studies demonstrate the importance of HRNs in cancer diagnosis.

4.6.4. *HRNs combined with diagnosis in other diseases*

In order to achieve H_2S detection in the inflammation of liver and lung, Zhou et al. developed the lanthanide-doped upconversion nanoparticles (UCNPs) to monitor H_2S in the lipopolysaccharide induced mouse [157]. By the way, HRN can also be used for the separate detection of H_2S in the hepatic diseases. Qin et al. developed HRNs for sensing of H_2S *via* the absorption competition induced effect *via* H_2S responsive chromophores and lanthanide-based NIR-II luminescence nanoparticles to image lipopolysaccharide induced hepatic inflammation. The absorption of chromophores at 808 nm, and the NIR-II emission of nanoparticles recovers after the hepatitis environment leads to high H_2S expression [117]. The above HRNs can detect the ability of CSE inhibitors to remove H_2S from the liver, and results indicate that decrease of inflammatory cell infiltration is accompanied *via* removal of H_2S, as well as recovery of liver function. The result also suggested that HRNs may have some therapeutic potentials in hepatitis. In addition, HRNs also can detect H_2S in other inflammatory sites. Based on the trap volatile H_2S in a solid form by using radioactive copper, Swarbhanu et al. detected H_2S in the inflamed paw accurately on the basis of the high sensitivity of the radioisotopes from ^{64}Cu–cyclen [158]. Compared with other signal molecular response nanoplatforms, there are few studies on the therapeutic and diagnostic capabilities of HRNs. With the growing understanding of H_2S and nanoplatforms, the treatment and detection from HRNs in more disease areas can be encountered.

5. Conclusions

Over the past decade, the exploration of the correlation between H_2S and diseases for biomedical application has led to use H_2S being used in the clinic. Changes in H_2S concentration can lead to cardiovascular diseases, neurodegenerative diseases, intestinal diseases, and cancer. In this study, we described the potential link between H_2S and these diseases and summarized the therapeutic potential of combination with drugs.

Nevertheless, there needs to be a more thorough investigation of the link between H2S and diseases in future studies. This paper presented problems facing H_2S research as well as the advantages of combining H_2S with nanotechnology. The potential employment of existing nanoplatforms for modulation of H_2S in various therapeutic strategies, including chemical therapy, CDT, PDT and PTT, was described in detail. Furthermore, the relationship between photothermal conversion and H_2S responsive nanoplatforms cannot be ignored. Although HRNs have potential for the clinical detection and treatment of diseases, challenges cannot be ignored. Based on our understanding of HRNs, these challenges can be summarized below.

The first challenge involves finding ways to selectively regulate H_2S concentration in tissues and cells. Due to the high tissue specificity of H_2S, increasing the H_2S concentration may be favorable to one tissue or cell type and harmful to others. Using HRNs to design tissue- or cellular-targeted strategies that alter local H_2S concentrations is a rational approach. The challenge involves developing and improving the detection of H_2S. Detection is the most common challenge for the gas-responsive nanoplatforms. Solving this problem will assist in establishing the major role of H_2S amongst different nanosystems and under different conditions. The third problem involves development of oral HRNs. Currently, HRNs are administered intravenously and have unwanted side-effects and suffer from poor patient compliance. These problems affect the potential for clinical application. Therefore, developing HRNs that can be administered orally will broaden the clinical prospects of HRNs. The fourth problem involves the development of HRNs and gene therapy. Gene therapy (i.e., changing the genetic information of diseased cells) has gradually become a mainstream method used in multiple biomedical applications [159]. More than 1000 gene therapy clinical trials have been completed in the past decade. However, most of them have stability problems. HRNs have great stability and can help realize gene-based drugs loadings while simultaneously consuming H_2S, which provides new applications for future gene therapies. The fifth problem involves the development of HRNs, such as the one that regulates the intestinal microenvironment and prevents intestinal diseases such as IBD. To date, there have been few studies on the regulation of HRNs in the intestinal microenvironment. Developing nanoplatforms that can effectively regulate H_2S concentration in intestinal lesions could revolutionize clinical treatment of intestinal diseases. Finally, the therapeutic effects of low H_2S concentrations deserve attention [27]. In future studies, the regulation of optimal response concentrations and the response termination of HRNs need many studies to fully deduce. In summary, HRNs, a novel therapeutic strategy, present significant potential for the clinical treatment with some challenges.

Conflicts of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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REFERENCES

[1] Demirel GB, Bayrak S. Ultrasound redox pH-responsive hybrid nanoparticles for triple-triggered drug delivery. J Drug Delive Sci Tec 2022;71:103267–76.
[2] Li Y, Chen W, Qi Y, Wang S, Li L, Li W, et al. H_2S-scavenged and activated iron oxide-hydroxide nanospindles for MRI-guided photothermal therapy and ferroptosis in colon cancer. Small 2020;16(37):2001356–69.
[3] Kim T, Suh J, Kim WJ. Polymeric aggregate-embodied hybrid nitric-oxide-scavenging and sequential drug-releasing hydrogel for combinatorial Treatment of rheumatoid arthritis. Adv Mater 2021;33(34):2008793.
[4] Sunzini F, De Stefano S, Chimenti MS, Melino S. Hydrogen sulfide as a potential regulatory gasotransmitter in arthritic diseases. Int J Mol Sci 2020;21(4):1180–205.
[5] Feng L, Zhao Y. Research progress in endogenous H_2S-activatable nanoplatforms for cancer theranostics. View 2020;1(2):15–38.
[6] Wang R. Physiological implications of hydrogen sulfide: a whiff exploration that blossomed. Physiol Rev 2012;92(2):791–896.
[7] Rowan FE, Docherty NG, Coffey JC, Connell PR. Sulphate-reducing bacteria and hydrogen sulphide in the aetiology of ulcerative colitis. Brit J Surg 2009;96(2):151–8.
[8] Yao CK, Sarbagili SC. Gaseous metabolites as therapeutic targets in ulcerative colitis. World J Gastroenterol 2023;29(4):682–91.
[9] Kushkevych I, Dordevic D, Vitezova M. Toxicity of hydrogen sulfide toward sulfate-reducing bacteria desulfovibrio piger Vib-7. Arch Microbiol 2019;201(3):389–97.
[10] Kushkevych I, Dordevic D, Kollar P. Analysis of physiological parameters of desulfovibrio strains from individuals with colitis. Open Life Sci 2018;13:481–8.
[11] Shi B, Ren N, Gu L, Xu G, Wang R, Zhu T, et al. Theranostic nanoplatform with hydrogen sulfide activatable NIR responsiveness for imaging-guided on-demand drug release. Angew Chem Int Edit 2019;58(47):16826–30.
[12] Pan X, Qi Y, Du Z, He J, Yao S, Lu W, et al. Zinc oxide nanosphere for hydrogen sulfide scavenging and ferroptosis of colorectal cancer. J Nanobiotechnol 2021;19(1):392.
[13] Ma Y, Li X, Li A, Yang P, Zhang C, Tang B. H_2S-activable MOF nanoparticle photosensitizer for effective photodynamic therapy against cancer with controllable singlet-oxygen release. Angew Chem Int Edit 2017;56(44):13752–6.
[14] Chang M, Hou Z, Jin D, Zhou J, Wang M, Wang M, et al. Colorectal tumor microenvironment-activated bio-decomposable and metabolizable $Cu_2O@CaCO_3$ nanocomposites for synergistic oncotherapy. Adv Mater 2020;32(43):2004647–58.
[15] Tao C, An L, Lin J, Tian Q, Yang S. Surface plasmon resonance-enhanced photoacoustic imaging and photothermal therapy of endogenous H_2S-triggered $Au@Cu_2O$. Small 2019;15(44):1903473–84.
[16] Yue T, Zuo S, Bu D, Zhu J, Chen S, Ma Y, et al. Aminooxyacetic acid (AOAA) sensitizes colon cancer cells to oxaliplatin via exaggerating apoptosis induced by ROS. J Cancer 2020;11(7):1828–38.
[17] Dillon KM, Carrazzone RJ, Matson JB, Kashfi K. The evolving landscape for cellular nitric oxide and hydrogen sulfide delivery systems: a new era of customized medications. Biochem Pharmacol 2020;176:113931.

[18] Olas B. Hydrogen sulfide in signaling pathways. Clin Chim Acta 2015;439:212–18.
[19] Cirino G, Szabo C, Papapetropoulos A. Physiological roles of hydrogen sulfide in mammalian cells, tissues, and organs. Physiol Rev 2023;103(1):31–276.
[20] Bełtowski J, Kowalczyk-Bołtuc J. Hydrogen sulfide in the experimental models of arterial hypertension. Biochem Pharmacol 2023;208:115381–94.
[21] Panthi S, Manandhar S, Gautam K. Hydrogen sulfide, nitric oxide, and neurodegenerative disorders. Transl Neurodegener 2018;7:3–11.
[22] Sun WH, Liu F, Chen Y, Zhu YC. Hydrogen sulfide decreases the levels of ROS by inhibiting mitochondrial complex IV and increasing SOD activities in cardiomyocytes under ischemia/reperfusion. Biochem Bioph Res Co 2012;421(2):164–9.
[23] Benchoam D, Cuevasanta E, Moller MN, Alvarez B. Persulfides, at the crossroads between hydrogen sulfide and thiols. Essays Biochem 2020;64(1):155–68.
[24] Huang YQ, Jin HF, Zhang H, Tang CS, Du JB, et al. Interaction among hydrogen sulfide and other gasotransmitters in mammalian physiology and pathophysiology. Adv Exp Med Biol 2021;1315:205–36.
[25] Xu S, Liu Z, Liu P. Targeting hydrogen sulfide as a promising therapeutic strategy for atherosclerosis. Int J Cardiol 2014;172(2):313–17.
[26] Collin M, Thiemermann C. Hydrogen sulfide and sulfite: novel mediators in the pathophysiology of shock and inflammation. Shock 2005;24(6):595–6.
[27] Polhemus DJ, Lefer DJ. Emergence of hydrogen sulfide as an endogenous gaseous signaling molecule in cardiovascular disease. Circ Res 2014;114(4):730–7.
[28] Gade AR, Kang M, Akbarali HI. Hydrogen sulfide as an allosteric modulator of ATP sensitive potassium channels in experimental colitis. Mol Pharmacol 2013;83(1):294–306.
[29] Cooper CE, Brown GC. The inhibition of mitochondrial cytochrome oxidase by the gases carbon monoxide, nitric oxide, hydrogen cyanide and hydrogen sulfide: chemical mechanism and physiological significance. J Bioenerg Biomembr 2008;40(5):533–9.
[30] Nikkanen HE, Burns MM. Severe hydrogen sulfide exposure in a working adolescent. Pediatrics 2004;113(4):927–9.
[31] Judenherc HA, Zhang XQ, Sonobe T, Song J, Rannals MD, Wang J, et al. Methylene blue counteracts H_2S toxicity-induced cardiac depression by restoring L-type Ca channel activity. Am J Physiol-Reg I 2016;310(11):1030–44.
[32] Geng B, Yang JH, Qi YF, Zhao J, Pang YZ, Du JB, et al. H_2S generated by heart in rat and its effects on cardiac function. Biochem Bioph Res Co 2004;313(2):362–8.
[33] Ginimuge PR, Jyothi SD. Methylene blue: revisited. J Anaesth Clin Pharm 2010;26(4):517–20.
[34] Sun YG, Cao YX, Wang WW, Ma SF, Yao T, Zhu YC. Hydrogen sulphide is an inhibitor of L-type calcium channels and mechanical contraction in rat cardiomyocytes. Cardiovasc Res 2008;79(4):632–41.
[35] Zhang R, Sun Y, Tsai H, Tang C, Jin H, Du J. Hydrogen sulfide inhibits L-type calcium currents depending upon the protein sulfhydryl state in rat cardiomyocytes. PLoS One 2012;7(5):37073–106.
[36] Gong CM, Shi C, Ding XT, Liu CX, Li JS, et al. Hydrogen sulfide induces Ca^{2+} signal in guard cells by regulating reactive oxygen species accumulation. Plant Signal Behav 2020;15(11):1805228–31.
[37] Altaany Z, Yang G, Wang R. Crosstalk between hydrogen sulfide and nitric oxide in endothelial cells. J Cell Mol Med 2013;17(7):879–88.
[38] Yong QC, Pan TT, Hu LF, Bian JS. Negative regulation of beta-adrenergic function by hydrogen sulphide in the rat hearts. J Mol Cell Cardiol 2008;44(4):701–10.
[39] Tan BH, Wong PT, Bian JS. Hydrogen sulfide: a novel signaling molecule in the central nervous system. Neurochem Int 2010;56(1):3–10.
[40] Zhang JF, Wu HB, Zhao YF, Zu HB. Therapeutic effects of hydrogen sulfide in treating delayed encephalopathy after acute carbon monoxide poisoning. Am J Ther 2016;23(6):1709–14.
[41] Pascual R, Baraibar AM, Mendez LI, Perez CM, Polo VI, Gandía L, et al. Hydrogen sulphide facilitates exocytosis by regulating the handling of intracellular calcium by chromaffin cells. Pflugers Arch 2018;470(8):1255–70.
[42] Kimura Y, Mikami Y, Osumi K, Tsugane M, Ji Oka, Kimura H. Polysulfides are possible H_2S-derived signaling molecules in rat brain. Nitric Oxide 2014;39(6):2451–7.
[43] Lu M, Choo CH, Hu LF, Tan BH, Hu G, Bian JS. Hydrogen sulfide regulates intracellular pH in rat primary cultured glia cells. Neurosci Res 2010;66(1):92–8.
[44] Giovinazzo D, Bursac B, Sbodio JI, Nalluru S, Vignane T, Snowman AM, et al. Hydrogen sulfide is neuroprotective in Alzheimer's disease by sulfhydrating GSK3 beta and inhibiting Tau hyperphosphorylation. Proc Natl Acad Sci USA 2021;118(4):2017225118–47.
[45] Murros KE. Hydrogen sulfide produced by gut bacteria may induce Parkinson's disease. Cells 2022;11(6):978–90.
[46] Cho C, Zeigler M, Mizuno S, Morrison RS, Totah RA, Barker-Haliski M. Reductions in hydrogen sulfide and changes in mitochondrial quality control proteins are evident in the early phases of the corneally kindled mouse model of epilepsy. Int J Mol Sci 2022;23(3):1434–54.
[47] He JT, Li H, Yang L, Mao CY. Role of hydrogen sulfide in cognitive deficits: evidences and mechanisms. Eur J Pharmacol 2019;849:146–53.
[48] Zhu S, Li X, Dang B, Wu F, Gou K, Wang C, et al. Hydrogen sulfide protects retina from blue light-induced photodamage and degeneration via inhibiting ROS-mediated ER stress-CHOP apoptosis signal. Redox Rep 2022;27(1): 100–110.
[49] Wang L, Chen S, Shao J, Zhang C, Mei L, Wang K, et al. Hydrogen sulfide alleviates chilling injury in peach fruit by maintaining cell structure integrity via regulating endogenous H_2S, antioxidant and cell wall metabolisms. Food Chem 2022;391:283–94.
[50] Kimura H. Physiological role of hydrogen sulfide and polysulfide in the central nervous system. Neurochem Int 2013;63(5):492–7.
[51] Kimura H. Signaling by hydrogen sulfide (H_2S) and polysulfides (H_2S_n) in the central nervous system. Neurochem Int 2019;126:118–25.
[52] Ji Y, Li Y, Zhao Z, Li P, Xie Y. Hydrogen sulfide overproduction is involved in acute ischemic cerebral injury under hyperhomocysteinemia. Front Neuroenergetics 2020;14:582851–65.
[53] Nogue S, Pou R, Fernandez J, Sanz-Gallen P. Fatal hydrogen sulphide poisoning in unconfined spaces. Occup Med 2011;61(3):212–14.
[54] Rumbeiha W, Whitley E, Anantharam P, Kim DS, Kanthasamy A. Acute hydrogen sulfide-induced neuropathology and neurological sequelae: challenges for translational neuroprotective research. Ann N Y Acad Sci 2016;1378(1):5–16.
[55] Sabino JP, Ariza Traslavina GA, Branco LG. Role of central hydrogen sulfide on ventilatory and cardiovascular responses to hypoxia in spontaneous hypertensive rats. Respir Physiol Neurobiol 2016;231:21–7.
[56] Donatti AF, Soriano RN, Sabino JP, Branco LGS. Endogenous hydrogen sulfide in the rostral ventrolateral medulla/Botzinger complex downregulates ventilatory responses to hypoxia. Respir Physiol Neurobiol 2014;200:97–104.

[57] Zhang Y, Gong W, Xu M, Zhang S, Shen J, Zhu M, et al. Necroptosis inhibition by hydrogen sulfide alleviated hypoxia-induced cardiac fibroblasts proliferation via sirtuin 3. Int J Mol Sci 2021;22(21):893–910.
[58] Li H, Chen L, Hou X, Zhou H, Zheng Y. Hydrogen sulfide attenuates hypoxia-induced respiratory suppression in anesthetized adult rats. Respir Physiol Neurobiol 2016;220:1–9.
[59] Yang X, Wang CD, Zhang XD, Chen SQ, Chen LP, Lu SS, et al. Redox regulation in hydrogen sulfide action: from neurotoxicity to neuroprotection. Neurochem Int 2019;128:58–69.
[60] Nii T, Eguchi R, Yamaguchi S, Otsuguro K. Hydrogen sulfide induces Ca^{2+} release from the endoplasmic reticulum and suppresses ATP-induced Ca^{2+} signaling in rat spinal cord astrocytes. Eur J Pharmacol 2021;891:684–94.
[61] Anantharam P, Whitley EM, Mahama B, Kim DS, Imerman PM, Shao D, et al. Characterizing a mouse model for evaluation of countermeasures against hydrogen sulfide-induced neurotoxicity and neurological sequelae. Ann N Y Acad Sci 2017;1400(1):46–64.
[62] Herath M, Hosie S, Bornstein JC, Franks AE, Hill-Yardin EL. The role of the gastrointestinal mucus system in intestinal homeostasis: implications for neurological disorders. Front Cell Infect Microbiol 2020;10:248–62.
[63] Maares M, Keil C, Straubing S, Robbe MC, Haase H. Zinc deficiency disturbs mucin expression, O-glycosylation and secretion by intestinal goblet cells. Int J Mol Sci 2020;21(17):6149–65.
[64] Kushkevych I, Dordevic D, Vitezova M. Possible synergy effect of hydrogen sulfide and acetate produced by sulfate-reducing bacteria on inflammatory bowel disease development. J Adv Res 2020;27:71–8.
[65] Johansson ME, Thomsson KA, Hansson GC. Proteomic analyses of the two mucus layers of the colon barrier reveal that their main component, the muc2 mucin, is strongly bound to the Fcgbp protein. J Proteome Res 2009;8(7):3549–57.
[66] Javitt G, Calvo MLG, Albert L, Reznik N, Ilani T, Diskin R, et al. Intestinal gel-forming mucins polymerize by disulfide-mediated dimerization of D3 domains. J Mol Biol 2019;431(19):3740–52.
[67] Fernandez TS, Moreno LO, Chaparro M, Gisbert JP. Gut microbiota and dietary factors as modulators of the mucus layer in inflammatory bowel disease. Int J Mol Sc 2021;22(19):10224–48.
[68] Stiegeler S, Mercurio K, Iancu MA, Corr SC. The Impact of microRNAs during inflammatory bowel disease: effects on the mucus layer and intercellular junctions for gut permeability. Cells 2021;10(12):3358–86.
[69] Ijssennagger N, Belzer C, Hooiveld GJ, Dekker J, van Mil SWC, Muller M, et al. Gut microbiota facilitates dietary heme-induced epithelial hyperproliferation by opening the mucus barrier in colon. Proc Natl Acad Sci USA 2015;112(32):10038–43.
[70] Ijssennagger N, Van DM, Van MS. Sulfide as a mucus barrier-breaker in inflammatory bowel disease. Trends Mol Med 2016;22(3):190–9.
[71] Libiad M, Vitvitsky V, Bostelaar T, Bak DW, Lee HJ, Sakamoto NY, et al. Hydrogen sulfide perturbs mitochondrial bioenergetics and triggers metabolic reprogramming in colon cells. J Biol Chem 2019;294(32):12077–90.
[72] Blachier F, Beaumont M, Kim E. Cysteine-derived hydrogen sulfide and gut health: a matter of endogenous or bacterial origin. Curr Opin Clin Nutr 2019;22(1):68–75.
[73] Dordevic D, Jancikova S, Vitezova M, Kushkevych I. Hydrogen sulfide toxicity in the gut environment: meta-analysis of sulfate-reducing and lactic acid bacteria in inflammatory processes. J Adv Res 2021;27:55–69.
[74] Pitcher MCL, Beatty ER, Cummings JH. The contribution of sulphate reducing bacteria and 5-aminosalicylic acid to faecal sulphide in patients with ulcerative colitis. Gut 2000;46(1):64–72.
[75] Guo FF, Yu TC, Hong J, Fang JY. Emerging roles of hydrogen sulfide in inflammatory and neoplastic colonic diseases. Front Physiol 2016;7:156–88.
[76] Blachier F, Andriamihaja M, Larraufie P, Ahn E, Lan A, Kim E. Production of hydrogen sulfide by the intestinal microbiota and epithelial cells and consequences for the colonic and rectal mucosa. Am J Physiol-Gastrl 2021;320(2):125–35.
[77] Kumar M, Sandhir R. Hydrogen sulfide in physiological and pathological mechanisms in brain. Cns Neurol Disord-Dr 2018;17(9):654–70.
[78] Ishigami M, Hiraki K, Umemura K, Ogasawara Y, Ishii K, Kimura H. A source of hydrogen sulfide and a mechanism of its release in the brain. Antioxid Redox Sign 2009;11(2):205–14.
[79] Wu D, Si W, Wang M, Lv S, Ji A, Li Y. Hydrogen sulfide in cancer: friend or foe? Nitric Oxide-Biol Ch 2015;50:38–45.
[80] Filipovic MR, Zivanovic J, Alvarez B, Banerjee R. Chemical biology of H_2S signaling through persulfidation. Chem Rev 2018;118(3):377–461.
[81] Bhattacharyya S, Saha S, Giri K, Lanza IR, Nair KS, Jennings NB, et al. Cystathionine beta-synthase (CBS) contributes to advanced ovarian cancer progression and drug resistance. Plos One 2013;8(11):79167–205.
[82] Khattak S, Rauf MA, Khan NH, Zhang QQ, Chen HJ, Muhammad P, et al. Hydrogen sulfide biology and its role in cancer. Molecules 2022;27(11):3389–533.
[83] Wang G, Cen D, Ren Z, Wang Y, Cai X, Chen X, et al. Zinc sulfide nanoparticle-decorated fibre mesh to enable localized H_2S-amplified chemotherapy. Chem Commun 2020;56(31):4304–7.
[84] Murphy B, Bhattacharya R, Mukherjee P. Hydrogen sulfide signaling in mitochondria and disease. Cfaseb J 2019;33(12):13098–125.
[85] Kodela R, Nath N, Chattopadhyay M, Nesbitt DE, Velazquez-Martinez CA, Kashfi K. Hydrogen sulfide-releasing naproxen suppresses colon cancer cell growth and inhibits NF-kappa B signaling. Drug Des Dev Ther 2015;9:4873–82.
[86] Ye F, Li X, Sun K, Xu W, Shi H, Bian J, et al. Inhibition of endogenous hydrogen sulfide biosynthesis enhances the anti-cancer effect of 3,3'-diindolylmethane in human gastric cancer cells. Life Sci 2020;261:118348–66.
[87] Wang YH, Huang JT, Chen WL, Wang RH, Kao MC, Pan YR, et al. Dysregulation of cystathionine gamma-lyase promotes prostate cancer progression and metastasis. Embo Rep 2019;20(10):45986–6032.
[88] Khan NH, Wang D, Wang W, Shahid M, Khattak S, Ngowi EE, et al. Pharmacological inhibition of endogenous hydrogen sulfide attenuates breast cancer progression. Molecules 2022;27(13):4049–94.
[89] Huang Y, Ning K, Li WW, Lin G, Hou CL, Wang MJ, et al. Hydrogen sulfide accumulates LDL receptor precursor via downregulating PCSK9 in HepG2 cells. Am J Physiol Cell Ph 2020;319(6):1082–96.
[90] Meram AT, Chen J, Patel S, Kim DD, Shirley B, Covello P, et al. Hydrogen sulfide is increased in oral squamous cell carcinoma compared to adjacent benign oral mucosae. Anticancer Res 2018;38(7):3843–52.
[91] Xiao Q, Ying J, Qiao Z, Yang Y, Dai X, Xu Z, et al. Exogenous hydrogen sulfide inhibits human melanoma cell development via suppression of the PI3K/AKT/mTOR pathway. J Dermatol Sci 2020;98(1):26–34.

[92] Zhen Y, Zhang W, Liu C, He J, Lu Y, Guo R, et al. Exogenous hydrogen sulfide promotes C6 glioma cell growth through activation of the p38 MAPK/ERK1/2-COX-2 pathways. Oncol Rep 2015;34(5):2413–22.
[93] Rahman MA, Cumming BM, Addicott KW, Pacl HT, Russell SL, Nargan K, et al. Hydrogen sulfide dysregulates the immune response by suppressing central carbon metabolism to promote tuberculosis. P Natl Acad Sci USA 2020;117(12):6663–74.
[94] Li H, Mu J, Sun J, Xu S, Liu W, Xu F, et al. Hydrogen sulfide releasing oridonin derivatives induce apoptosis through extrinsic and intrinsic pathways. Eur J Med Chem 2020;187:111978–94.
[95] Cao X, Ding L, Xie ZZ, Yang Y, Whiteman M, Moore PK, et al. A review of hydrogen sulfide synthesis, metabolism, and measurement: is modulation of hydrogen sulfide a novel therapeutic for cancer? Antioxid Redox Sign 2019;31(1):1–38.
[96] Chen S, Yue T, Huang Z, Zhu J, Bu D, Wang X, et al. Inhibition of hydrogen sulfide synthesis reverses acquired resistance to 5-FU through miR-215-5p-EREG/TYMS axis in colon cancer cells. Cancer Lett 2019;466:49–60.
[97] Dong Q, Yang B, Han JG, Zhang MM, Liu W, Zhang X, et al. A novel hydrogen sulfide-releasing donor, HA-ADT, suppresses the growth of human breast cancer cells through inhibiting the PI3K/AKT/mTOR and Ras/Raf/MEK/ERK signaling pathways. Cancer Lett 2019;455:60–72.
[98] Wang L, Shi H, Zhang X, Zhang X, Liu Y, Kang W, et al. I157172, a novel inhibitor of cystathionine -lyase, inhibits growth and migration of breast cancer cells via SIRT1-mediated deacetylation of STAT3. Oncol Rep 2019;41(1):427–36.
[99] You J, Shi X, Liang H, Ye J, Wang L, Han H, et al. Cystathionine-gamma-lyase promotes process of breast cancer in association with STAT3 signaling pathway. Oncotarget 2017;8(39):65677–86.
[100] Youness RA, Assal RA, Motaal AA, Gad MZ. A novel role of sone/nos3/no signaling cascade in mediating hydrogen sulphide bilateral effects on triple negative breast cancer progression. Nitric Oxide-Biol Ch 2018;80:12–23.
[101] Youness RA, Gad AZ, Sanber K, Ahn YJ, Lee GJ, Khallaf E, et al. Targeting hydrogen sulphide signaling in breast cancer. J Adv Res 2021;27:177–90.
[102] Untereiner AA, Pavlidou A, Druzhyna N, Papapetropoulos A, Hellmich MR, Szabo C. Drug resistance induces the upregulation of H_2S-producing enzymes in HCT116 colon cancer cells. Biochem Pharmacol 2018;149:174–85.
[103] Whiteman M, Winyard PG. Hydrogen sulfide and inflammation: the good, the bad, the ugly and the promising. Expert Rev Clin Phar 2011;4(1):13–32.
[104] Wang DY, Zhang J, Li HX, Zhang YX, Jing MR, Cai CB, et al. Inhibition of endogenous hydrogen sulfide production suppresses the growth of nasopharyngeal carcinoma cells. Mol Carcinog 2023;62(5):652–64.
[105] Bhatia M, Wong FL, Fu D, Lau HY, Moochhala SM, Moore PK. Role of hydrogen sulfide in acute pancreatitis and associated lung injury. FASEB J 2005;19(6):623–5.
[106] Ji L, Li L, Qu F, Zhang G, Wang Y, Bai X, et al. Hydrogen sulphide exacerbates acute pancreatitis by over-activating autophagy via AMPK/mTOR pathway. J Cell Mol Med 2016;20(12):2349–61.
[107] Gil V, Gallego D, Jimenez M. Effects of inhibitors of hydrogen sulphide synthesis on rat colonic motility. Br J Pharmacol 2011;164(2):485–98.
[108] Asimakopoulou A, Panopoulos P, Chasapis CT, Coletta C, Zhou Z, Cirino G, et al. Selectivity of commonly used pharmacological inhibitors for cystathionine synthase (CBS) and cystathionine lyase (CSE). Brit J Pharmacol 2013;169(4):922–32.
[109] Hellmich MR, Chao C, Modis K, Ding Y, Zatarain JR, Thanki K, et al. Efficacy of novel aminooxyacetic acid prodrugs in colon cancer models: towards clinical translation of the cystathionine beta-Synthase inhibition concept. Biomolecules 2021;11(8):1073–112.
[110] Ascencao K, Dilek N, Augsburger F, Panagaki T, Zuhra K, Szabo C. Pharmacological induction of mesenchymal-epithelial transition via inhibition of H_2S biosynthesis and consequent suppression of ACLY activity in colon cancer cells. Pharmacol Res 2021;165:105393–105410.
[111] Wang Y, Ni X, Chadha R, McCartney C, Lam Y, Brummett B, et al. Methods for suppressing hydrogen sulfide in biological systems. Antioxid Redox Signal 2022;36(4–6):294–308.
[112] Majernik M, Jendzelovsky R, Vargova J, Jendzelovska Z, Fedorocko P. Multifunctional nanoplatforms as a novel effective approach in photodynamic therapy and chemotherapy, to overcome multidrug resistance in cancer. Pharmaceutics 2022;14(5):1075–97.
[113] Jose DA, Sharma N, Sakla R, Kaushik R, Gadiyaram S. Fluorescent nanoprobes for the sensing of gasotransmitters hydrogen sulfide (H_2S), nitric oxide (NO) and carbon monoxide (CO). Methods 2019;168:62–75.
[114] Fan W, Yung B, Huang P, Chen X. Nanotechnology for multimodal synergistic cancer therapy. Chem Rev 2017;117(22):13566–638.
[115] Xiao Q, Zheng X, Bu W, Ge W, Zhang S, Chen F, et al. A core/satellite multifunctional nanotheranostic for *in vivo* imaging and tumor eradication by radiation/photothermal synergistic therapy. J Am Chem Soc 2013;135(35):13041–8.
[116] Youness RA, Gad AZ, Sanber K, Ahn YJ, Lee GJ, Khallaf E, et al. Targeting hydrogen sulphide signaling in breast cancer. J Adv Res 2021;27:177–90.
[117] Liu Q, Zhong Y, Su Y, Zhao L, Peng J. Real-time imaging of hepatic inflammation using hydrogen sulfide-activatable second near-infrared luminescent nanoprobes. Nano Lett 2021;21(11):4606–14.
[118] Tang J, Zhang Y, Kong B, Wang Y, Da P, Li J, et al. Solar-driven photoelectrochemical probing of nanodot/nanowire/cell interface. Nano Lett 2014;14(5):2702–8.
[119] Zhang H, Kong X, Tang Y, Lin W. Hydrogen sulfide triggered charge-reversal micelles for cancer-targeted drug delivery and imaging. Acs Appl Mater Inter 2016;8(25):16227–39.
[120] Han L, Liu XW, Zang T, Ren H, Liang DS, Bai SC, et al. H_2S responsive PEGylated poly (lipoic acid) with ciprofloxacin for targeted therapy of Salmonella. J Control Release 2022;351:896–906.
[121] Zhang Y, Fang J, Ye S, Zhao Y, Wang A, Mao Q, et al. A hydrogen sulphide-responsive and depleting nanoplatform for cancer photodynamic therapy. Nat Commun 2022;13(1):1685–701.
[122] Li Y, Zhou J, Wang L, Xie Z. Endogenous Hydrogen sulfide-triggered MOF-based nanoenzyme for synergic cancer therapy. Acs Appl Mater Inter 2020;12(27):30213–20.
[123] Yang L, Zhu Y, Liang L, Wang C, Ning X, Feng X. Self-assembly of intelligent nanoplatform for endogenous H_2S-triggered multimodal cascade therapy of colon cancer. Nano Lett 2022;22(10):4207–14.
[124] Chen J, Xue F, Du W, Yu H, Yang Z, Du Q, et al. An endogenous H_2S-activated nanoplatform for triple synergistic therapy of colorectal cancer. Nano Lett 2022;22(15):6156–65.
[125] Maggiore U, Palmisano A, Buti S, Giudice GC, Cattaneo D, Giuliani N, et al. Chemotherapy, targeted therapy and immunotherapy: which drugs can be safely used in the solid organ transplant recipients? Transpl Int 2021;34(12):2442–58.
[126] Yang Y, Zuo S, Li L, Kuang X, Li J, Sun B, et al. Iron-doxorubicin prodrug loaded liposome nanogenerator programs multimodal ferroptosis for efficient cancer therapy. Asian J Pharm Sci 2021;16(6):784–93.
[127] He T, Qin XL, Jiang C, Jiang DW, Lei S, Lin J, et al. Tumor pH-responsive metastable-phase manganese sulfide

nanotheranostics for traceable hydrogen sulfide gas therapy primed chemodynamic therapy. Theranostics 2020;10(6):2453–62.
[128] Fan X, Yuan Z, Shou C, Fan G, Wang H, Gao F, et al. cRGD-conjugated Fe_3O_4@PDA-DOX multifunctional nanocomposites for MRI and antitumor chemo-photothermal therapy. Int J Nanomed 2019;14: 9631–9645.
[129] Chen ML, Shen LM, Chen S, Wang H, Chen XW, Wang JH. *In situ* growth of beta-FeOOH nanorods on graphene oxide with ultra-high relaxivity for *in vivo* magnetic resonance imaging and cancer therapy. J Mater Chem 2013;1(20):2582–9.
[130] Zhang L, Forgham H, Shen A, Qiao RR, Guo B. Recent advances in single Fe-based nanoagents for photothermal-chemodynamic cancer therapy. Biosensors 2022;12(2):86–106.
[131] Wang Q, Sun M, Li C, Li D, Yang Z, Jiang Q, et al. A computer-aided chem-photodynamic drugs self-delivery system for synergistically enhanced cancer therapy. Asian J Pharm Sci 2021;16(2):203–12.
[132] Tao WH, He ZG. ROS-responsive drug delivery systems for biomedical applications. Asian J Pharm Sci 2018;13(2):101–12.
[133] Zhou Z, Song J, Nie L, Chen X. Reactive oxygen species generating systems meeting challenges of photodynamic cancer therapy. Chem Soc Rev 2016;45(23):6597–626.
[134] Rossi F, Khoo EH, Su X, Thanh N. Study of the effect of anisotropic gold nanoparticles on plasmonic coupling with a photosensitizer for antimicrobial film. ACS Appl Bio Mater 2020;3(1):315–26.
[135] Hou X, Shou C, He M, Xu J, Cheng Y, Yuan Z, et al. A combination of LightOn gene expression system and tumor microenvironment-responsive nanoparticle delivery system for targeted breast cancer therapy. Acta Pharm Sin B 2020;10(9):1741–53.
[136] He MY, Wang Y, Chen X, Zhao Y, Lou K, Wang Y, et al. Spatiotemporally controllable diphtheria toxin expression using a light-switchable transgene system combining multifunctional nanoparticle delivery system for targeted melanoma therapy. J Control Release 2020;319:1–14.
[137] Lim CK, Heo J, Shin S, Jeong K, Seo YH, Jang W-D, et al. Nanophotosensitizers toward advanced photodynamic therapy of Cancer. Cancer Lett 2013;334(2):176–87.
[138] Rui Q, Yin ZZ, Cai WR. Hyaluronic acid encapsulated aminated mesoporous silica nanoparticles for pH-responsive delivery of methotrexate and release kinetics. B Korean Chem Soc 2022;43(5):43–51.
[139] Diaz LA Jr, Le DT. PD-1 blockade in tumors with mismatch-repair deficiency reply. New Engl J Med 2015;373(26):2509–20.
[140] Yan S, Zeng X, Tang Ya, Liu BF, Wang Y, Liu X. Activating antitumor immunity and antimetastatic effect through polydopamine-encapsulated core-shell upconversion nanoparticles. Adv Mater 2019;31(46):1905825–32.
[141] Fu LH, Qi C, Hu YR, Lin J, Huang P. Glucose oxidase-instructed multimodal synergistic cancer therapy. Adv Mater 2019;31(21):1808325–39.
[142] Yu Z, Zhou P, Pan W, Li N, Tang B. A biomimetic nanoreactor for synergistic chemiexcited photodynamic therapy and starvation therapy against tumor metastasis. Nat Commun 2018;9(1):5044–53.
[143] Wang M, Chang M, Chen Q, Wang D, Li C, Hou Z, et al. Au_2Pt-PEG-Ce_6 nanoformulation with dual nanozyme activities for synergistic chemodynamic therapy/phototherapy. Biomaterials 2020;252:120093–105 .
[144] Chang M, Hou Z, Wang M, Wang M, Dang P, Liu J, et al. Cu_2MoS_4/Au heterostructures with enhanced catalase-like activity and photoconversion efficiency for primary/metastatic tumors eradication by phototherapy-induced immunotherapy. Small 2020;16(14):1907146–60.
[145] Yang Y, Zhu W, Cheng L, Cai R, Yi X, He J, et al. Tumor microenvironment (TME)-activatable circular aptamer-PEG as an effective hierarchical-targeting molecular medicine for photodynamic therapy. Biomaterials 2020;246:119971–81.
[146] Wang L, Huo M, Chen Y, Shi J. Tumor microenvironment-enabled nanotherapy. Adv Healthc Mater 2018;7(8):1701156–79.
[147] Wu W, Yu L, Pu Y, Yao H, Chen Y, Shi J. Copper-enriched Prussian blue nanomedicine for *in situ* disulfiram toxification and photothermal antitumor amplification. Adv Mater 2020;32(17):2000542–54.
[148] Zhang F, Li X, Stella C, Chen L, Liao Y, Tang C, et al. Plasma hydrogen sulfide in differential diagnosis between vasovagal syncope and postural orthostatic tachycardia syndrome in children. J Pediatr 2012;160(2):227–31.
[149] Deng M, Zhang M, Sun F, Ma J, Hu L, Yang X, et al. A gas chromatography-mass spectrometry based study on urine metabolomics in rats chronically poisoned with hydrogen sulfide. BioMed Res Int 2015;2015:295241.
[150] Ding H, Chang J, He F, et al. Hydrogen Sulfide: an emerging precision strategy for gas therapy. Adv Healthc Mater 2022;11:2101984–2016.
[151] Dong H, Zhou Q, Zhang L, Tian Y. Rational design of specific recognition molecules for simultaneously monitoring of endogenous polysulfide and hydrogen sulfide in the mouse brain. Angew Chem Int Ed Engl 2019;58(39):13948–53.
[152] Qian Y, Zhang L, Tian Y. Highly Stable Electrochemical probe with bidentate thiols for ratiometric monitoring of endogenous polysulfide in living mouse brains. Anal Chem 2022;94(2):1447–55.
[153] Shi B, Yan Q, Tang J, Xin K, Zhang J, Zhu Y, et al. Hydrogen sulfide-activatable second near-infrared fluorescent nanoassemblies for targeted photothermal cancer therapy. Nano Lett 2018;18(10):6411–16.
[154] Deng Z, Jiang M, Li Y, Liu H, Zeng S, Hao J. Endogenous H_2S-triggered *in situ* synthesis of NIR-II-emitting nanoprobe for *in vivo* intelligently lighting up colorectal cancer. iScience 2019;17:217224.
[155] Zheng Z, Chen Q, Dai R, Jia Z, Yang C, Peng X, et al. A continuous stimuli-responsive system for NIR-II fluorescence/photoacoustic imaging guided photothermal/gas synergistic therapy. Nanoscale 2020;12(21):11562–72.
[156] Liu Y, Yang F, Yuan C, Li M, Wang T, Chen B, et al. Magnetic nanoliposomes as *in situ* microbubble bombers for multimodality image-guided cancer theranostics. ACS Nano 2017;11(2):1509–19.
[157] Zhou Y, Chen W, Zhu J, Pei W, Wang C, Huang L, et al. Inorganic-organic hybrid nanoprobe for NIR-excited imaging of hydrogen sulfide in cell cultures and inflammation in a mouse model. Small 2014;10(23):4874–85.
[158] Sarkar S, Ha YS, Soni N, et al. Immobilization of the gas signaling molecule H_2S by radioisotopes: detection, quantification, and *in vivo* imaging. Angew Chem Int Ed Engl 2016;55(32):9365–70.
[159] Chen W, Hu Y, Ju DW. Gene therapy for neurodegenerative disorders: advances, insights and prospects. Acta Pharm Sin B 2020;10(8):1347–59.