Review article

Intelligent polymeric hydrogen sulfide delivery systems for therapeutic applications

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Hydrogen sulfide (H\textsubscript{2}S) plays an important role in regulating various pathological processes such as protecting mammalian cell from harmful injuries, promoting tissue regeneration, and regulating the process of various diseases caused by physiological disorders. Studies have revealed that the physiological effects of H\textsubscript{2}S are highly associated with its concentrations. At relatively low concentration, H\textsubscript{2}S shows beneficial functions. However, long-time and high-dose donation of H\textsubscript{2}S would inhibit regular biological process, resulting in cell dysfunction and apoptosis. To regulate the dosage of H\textsubscript{2}S delivery for precision medicine, H\textsubscript{2}S delivery systems with intelligent characteristics were developed and a variety of biocompatibility polymers have been utilized to establish intelligent polymeric H\textsubscript{2}S delivery systems, with the abilities to specifically target the lesions, smartly respond to pathological microenvironments, as well as real-timely monitor H\textsubscript{2}S delivery and lesion conditions by incorporating imaging-capable moieties. In this review, we focus on the design, preparation, and therapeutic applications of intelligent polymeric H\textsubscript{2}S delivery systems in cardiovascular therapy, inflammatory therapy, tissue regenerative therapy, cancer therapy and bacteria-associated therapy. Strategies for precise H\textsubscript{2}S therapies especially imaging-guided H\textsubscript{2}S theranostics are highlighted. Since H\textsubscript{2}S donors with stimuli-responsive characters are vital components for establishing intelligent H\textsubscript{2}S delivery systems, the development of H\textsubscript{2}S donors is also briefly introduced.

1. Introduction

Hydrogen sulfide (H\textsubscript{2}S) is well known as a toxic gas and an air pollution with the characteristic smell of rotten eggs. However, research in the past two decades have shown that H\textsubscript{2}S could be endogenously generated and is extensive distributed in human bodies, playing an important role in regulating several physiological and pathological processes by participating cellular signaling pathways including activation of adenosine triphosphate-sensitive potassium (K\textsubscript{ATP}) channels [1], suppression of nuclear factor \( \kappa \)B (NF-\( \kappa \)B) signaling [2] and regulation of cellular redox [3]. Thus, H\textsubscript{2}S was identified as one of the endogenous gaseous signaling molecules (generally called “gaso-transmitter”) like nitric oxide (NO) and carbon monoxide (CO) [1,4]. Notably, H\textsubscript{2}S is a weak acid and there is a dynamic equilibrium among H\textsubscript{2}S, hydrosulfide ion (HS\textsuperscript{-}) and sulfide ion (S\textsuperscript{2-}) under physiological conditions [5] (in which S\textsuperscript{2-} is unlikely to be involved in the biological regulating effects as recent study suggested that S\textsuperscript{2-} may be not a relevant species in water [6]). It’s still unclear whether H\textsubscript{2}S or the HS\textsuperscript{-} or both contribute to the observed bioactivities [7]. In this review, the term “H\textsubscript{2}S” will refer to the equilibrium mixture of these total reactive sulfur species (RSSs).

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Generally, H\textsubscript{2}S is endogenously synthesized by a number of enzymes responsible for \( \gamma \)-cysteine (L-Cys) metabolism, including cystathionine-\( \gamma \)-lyase (CSE), cystathionine-\( \beta \)-synthase (CBS), 3-mercaptoppyruvate sulfurtransferase (3-MST), and could also be produced through some non-catalytic routes \[8\]. Owing to its high lipophilicity, H\textsubscript{2}S could freely penetrate biological membranes without any specific receptor mediation \[4,9\]. H\textsubscript{2}S is also involved in several intracellular chemical reactions, which are important basis of its biological effects \[8\]. For example, H\textsubscript{2}S could chelate with metalloproteins or induce \( S \)-persulfidation of cysteine residues, which in turn modulates protein activities \[10,11\]. In addition, H\textsubscript{2}S participates in many intracellular redox reactions including the reduction of disulfide bonds and acts as anti-oxidant to scavenge free radicals \[8\]. Physiological concentration of H\textsubscript{2}S usually shows a typical “protective” effect that could protect cells and tissues from harmful oxidative injuries, through a combination of anti-oxidant and antiapoptotic signals \[12\]. In cardiovascular system, H\textsubscript{2}S dilates blood vessels \[13\] and is of importance in cytoprotection during the evolution of myocardial ischemia-reperfusion (MI-R) injury \[14\]. In the nervous system, H\textsubscript{2}S serves as synaptic modulator and neuroprotectant \[12\]. H\textsubscript{2}S also promotes endothelial cell proliferation and angiogenesis \[15,16\], thus enhancing tissue regeneration. In addition, H\textsubscript{2}S shows complex effects in inflammation \[17\] and cancers \[2\], and

**Abbreviations**

- 3-MST: 3-Mercaptoppyruvate sulfurtransferase
- ACS14: 2-Acetylxybenzoic acid 4-(3-thiooxo-3H-1,2-dithiol-5-yl) phenyl ester
- ADSC: Adipose-derived stem cell
- ADT: Anetholedithiolethione
- ALG-CHO: Partially oxidized alginate
- AML: Anetholedithiolethione-loaded H\textsubscript{2}S delivery magnetic nanoliposome
- APTC: 2-Aminopyridyline-5-thiocarboxamid
- BSA: Bovine serum albumin
- BSA@MnS: Bovine serum albumin modified \( \gamma \)-phase MnS nanotheranostic
- CA: Cardiac arrest
- CAP-w-FC: Diallyl trisulfide loaded gelatin capsules with foaming ability
- CBS: Cystathionine-\( \beta \)-synthase
- CD44: Cyclic-diguanylate-guanosine monophosphate
- CFE: Oxime-containing phenylalanine-glutamic acid amphiphilic dipeptides
- CLSM: Confocal laser scanning microscopy
- CO: Carbon monoxide
- COS: Carbonyl sulfide
- CP-PEG: Polyethylene glycol-grafted conjugated polymer
- CPR: Cardiopulmonary resuscitation
- CSE: Cystathionine-\( \gamma \)-lyase
- CY: Cyanine
- DAI: Disease activity index
- DATS: Diallyl trisulfide
- DATS@MION-PEG-LF: Diallyl trisulfide loaded polyethylene glycol and lactoferrin modified mesoporous iron oxide nanoparticle
- DTPA: Diethylene trimine pentaacetic acid
- DTT: Dithiothreitol
- E. coli: Escherichia coli
- EPR: Enhanced permeability and retention
- ESIPIT: Excited-state intramolecular proton transfer
- GSH: Glutathione
- GYY4137: Morpholin-4-ium-4-methoxyphenyl(morpholino) phosphinodithioate
- H\textsubscript{2}S: Hydrogen sulfide
- HA: Hyaluronic acid
- hMSC: Human bone marrow stromal cell
- HS\textsuperscript{-}: Hydroxysulfide ion
- HUVEC: Human umbilical vein endothelial cell
- IBD: Inflammatory bowel disease
- IDD: Intervertebral disc degeneration
- IL-10: Interleukin-10
- IL-6: Interleukin-6
- IVIS: In vivo imaging system
- K\textsubscript{ATP} channel: Adenosine triphosphate-sensitive potassium channel
- LBL: Layer-by-layer
- L-Cys: \( \gamma \)-cysteine
- LF: Lactoferrin
- LPS: Lipopolysaccharide
- LV: Left ventricle
- MI-R: Myocardial ischemia-reperfusion
- MION: Mesoporous iron oxide nanoparticle
- MRI: Magnetic resonance imaging
- MS: Microsphere
- NF-\( \kappa \)B: Nuclear factor \( \kappa \)B
- NHEK: Normal human epidermal keratinocytes
- NIR: Near infrared
- NO: Nitric oxide
- NSAID: Non-steroidal anti-inflammatory drug
- NTA: N-thiocarboxyanhydride
- P(Lys-stat-SATO): Poly[lysine-stat-(S-aroylthiooxime)]
- PA: Photocoustic
- PAH: Pulmonary arterial hypertension
- PCL: Polycaprolactone
- PEG: Polyethylene glycol
- PLA: Poly(lactic acid)
- PLGA: Poly(lactic-co-glycolic acid)
- Pry-Ps: 2,2’-Dipyridyl tetrasulfide
- PSD: Polysulfide H\textsubscript{2}S donor
- PTT: Photothermal therapy
- RA: Rheumatoid arthritis
- ROS: Reactive oxygen specie
- RSS: Reactive sulfur specie
- S. aureus: Staphylococcus aureus
- S\textsuperscript{2-}: Sulfide ion
- SA: Sodium alginate
- SATO: S-aroylthiooxime
- SBC: Sodium bicarbonate
- SDS: Sodium dodecyl sulfate
- SF: Silk fiber
- S-FE: S-aroylthiooxime-functionalized phenylalanine-glutamic acid amphiphilic dipeptides
- SPRC: S-propargyl-cysteine
- SPRC@PLA: S-propargyl-cysteine loaded poly(lactic acid) microsphere
- TA: Tetraaniline
- TME: Tumor microenvironment
- TNBC: Triple-negative breast cancer
- TNF-\( \alpha \): Tumor necrosis factor alpha
- UC: Ulcerative colitis
- US: Ultrasound
- UV: Ultraviolet
- VEGF: Vascular endothelial growth factor
- \( \alpha \)-CHCA: \( \alpha \)-Cyano-4-hydroxycinnamic acid
involves in some diseases such as Alzheimer’s disease [18], Parkinson’s disease [19] and glycometabolic disorders [20]. It should be noted that H$_2$S follows dose-dependent biological effects. Physiological low concentration of H$_2$S has beneficial and cytoprotective effects. When the biosynthesis of H$_2$S was inhibited, or the administration of H$_2$S is too excessive, the equilibrium of physiological RSSs would be changed drastically, and the stimulatory effect of H$_2$S would be superseded by an inhibitory effect [21].

The widespread discovery of the physiological effects of H$_2$S has led to the development of H$_2$S therapies. Inhalation therapy is the most conspicuous method for delivering exogenous H$_2$S and has shown protective effect against ventilator-induced lung injury [22]. However, the delivery rate and dosage of gaseous H$_2$S need to be strictly controlled, and the short half-life of H$_2$S limits the therapeutic delivery to deep lesions [23]. Compounds that could release H$_2$S (also known as H$_2$S donors) have become useful chemical tools for studying of H$_2$S therapies. Inorganic sulfide salts are the simplest H$_2$S donors and the most frequently used alternatives to gaseous H$_2$S during research, but they release H$_2$S immediately once in aqueous solution, which is difficult to mimic endogenous H$_2$S. To achieve controlled H$_2$S delivery, a series of H$_2$S donors activated by varying endogenous stimuli including hydrolysis, thiol containing compounds, enzyme, and exogenous stimuli like light have been developed in recent years [24,25]. These H$_2$S donors have prolonged release kinetics compared with sulfide salts, and most of these molecules have shown significant therapeutic potentials in a variety of biological processes [26].

Though lots of small molecular H$_2$S donors have been developed, they usually unable to meet the requirements of in vivo applications, since the stability, water solubility, stimuli-responsive property, and toxicity of donors themselves or their byproducts are difficult to regulate at the small molecule level [27]. With the purpose to overcome these limits, various biocompatible polymers are utilized to establish H$_2$S delivery systems, mainly by physically encapsulating or chemically conjugating H$_2$S donors with polymeric carriers such as micelles [28,29], liposomes [30], nanoparticles [31], nanofibers [32], or hydrogels [33]. The main advantage of these polymeric H$_2$S delivery systems is that the H$_2$S releasing behaviors including releasing dosage, releasing kinetics, as well as releasing locations are effectively regulated and the biocompatibility is significantly improved without drastically changing the chemical properties of the loaded H$_2$S donors.

More recently, against the dose-dependent therapeutic effects of H$_2$S, researchers have dedicated themselves to the development of H$_2$S delivery systems with intelligent characteristics, which integrate specific targeting, stimuli responsive and imaging guided capabilities to minimize side effects and maximize therapeutic efficacy, facilitating the precise treatment of various diseases. Through the rational design of macromolecular architectures and the utilization of suitable H$_2$S donors, the abilities to specifically target and selectively accumulate in lesions, as well as smartly respond to pathological microenvironments (pH [34], thiol containing compounds [35], enzyme [36], etc.) and exogenous stimuli (light [37], ultrasound [38], etc.) to release H$_2$S in a controlled manner could be endowed. The strategy to induce multistage in vivo reaction is promising for achieving precise and efficient H$_2$S therapy. Moreover, the utilization of materials with imaging capability (e.g., conjugated polymer) make it possible for imaging guided H$_2$S theranostics, to real-time monitor H$_2$S release and lesion condition.

In this review, we overview the recent advances of intelligent polymers H$_2$S delivery systems for biomedical applications (summarized on Table 1), focusing on the design principles and intelligent characters of materials, as well as the physiological and pathological functions mediated by H$_2$S.

2. H$_2$S donors categorized by different activation mechanisms

H$_2$S donor has become a useful tool for studying therapeutic effects of H$_2$S and an important basis for constructing intelligent polymeric H$_2$S delivery systems. Thus, we discuss the classification of H$_2$S donors first, mainly focusing on the stimuli-responsive mechanisms and the application scopes of different donors (Fig. 1). In addition, polymeric H$_2$S donors have been actively explored for controlled H$_2$S delivery, showing enhanced stability and bioavailability over their small molecular counterparts [74–76]. In this part, the methods for incorporating H$_2$S donors with polymeric carriers would also be discussed.

2.1. Sulfide salts as direct sources of H$_2$S

Sulfide salts, such as Na$_2$S and NaHS, are the simplest H$_2$S donors and currently the most used alternatives to evaluate the therapeutic potential of exogenous H$_2$S. Though generally classified as H$_2$S donors, these sulfides salts are direct sources of H$_2$S [24]. Once dissolved in water, they would hydrolyze and generate an equilibrium between H$_2$S, HS$^{-}$ and S$^{2-}$ immediately, and afterward a rapid volatilization of H$_2$S would occur. Since high-dose administration of sulfide salts is usually required for studying the biological effects of H$_2$S, it would cause the initial concentration of H$_2$S higher than physiological level and then decrease rapidly [24]. This is contradictory to the strictly modulated production of endogenous H$_2$S, usually cannot sustain therapeutic effects and may induce side effects. In order to achieve controlled H$_2$S delivery, polymeric carriers could be employed to encapsulate these sulfide salts [57,77]. Unlike Na$_2$S and NaHS, some other sulfide salts (MnS$_2$, Fe$_2$S, ZnS, etc.) have poor water solubility, but could hydrolyze slowly to generate H$_2$S and metal ions under acid pH [63]. For biomedical applications, these sulfide salts could be prepared as nanoparticles and modified with biocompatible polymers [63,78,79]. The released metal ions may also show therapeutic functions in synergistic with H$_2$S.

2.2. Hydrolysis-activated H$_2$S donors

Hydrolysis-activated H$_2$S donors are able to release H$_2$S spontaneously in aqueous solution. Lawesson’s reagent and its derivatives are phosphorodithioiate containing H$_2$S donors with slow releasing property. Among them, the most well-known is morpholin-4-ium-4-methoxyphenyl(morpholino)phosphorodithioate (GY4137), which has been utilized in many studies about the physiological effects of H$_2$S [80]. Another type of phosphorodithioate containing H$_2$S donor is JK donors possessing a unique acidic pH accelerated H$_2$S releasing behavior [81]. To further regulate H$_2$S delivery, phosphorodithioate containing H$_2$S donors were generally incorporate with polymeric systems through physical encapsulation [32,47,55]. Dithiocarbamates could also be activated by acidic pH to release H$_2$S, which have been incorporated with polymeric carriers for therapeutic application [34]. These acidic pH-responsive H$_2$S donors are more suitable for the pathological conditions associated with acidic microenvironments, such as the sites of tumor, inflammation, and ischemic injury.

2.3. Thiols-activated H$_2$S donors

Many H$_2$S donors could be reduced by thiol containing bioactive compounds such as cysteine (Cys) and glutathione (GSH) to release H$_2$S. These donors are particularly suitable for controlled delivery of H$_2$S to the pathologically redox microenvironments. N-(benzoyl)benzamides developed by Yuan et al. [82] undergo a thioester exchange reaction to form N-SH intermediates, which further react with these compounds to produce H$_2$S. S-aryloylthiooximes (SATOs) developed by Matson et al. [83] could react with Cys-containing compounds to form thiooxime intermediates that further react with these compounds to generate H$_2$S. The H$_2$S releasing profiles of the above two donors could be regulated by tuning the concentrations of donor aromatic rings. Furthermore, thiooxime formation reaction could be conducted at mild condition with high efficiency, thus SATOs have been utilized to establish polymeric H$_2$S donors through postpolymerization approaches [28,73]. Naturally occurring polysulfides, represented by diallyl trisulfide
form hydrosulfide intermediates, which further react with thiol compounds [DATS], undergo a thiol-promoted cleavage of polysulfide bond and release hydrogen sulfide. The mechanism of these reductions may be enzymatic hydrolysis [36]. The ester-protected structure of liver microsomes and reduced nicotinamide adenine dinucleotide 

| Table 1 | Summary of intelligent polymeric H$_2$S delivery systems. |
|---------|----------------------------------------------------------|
| Polymeric carriers | H$_2$S donors | Intelligent abilities | Therapeutic potentials | References |
| Large porous microspheres | ACS14 | Lung accumulation | Relief of pulmonary arterial hypertension | [30] |
| Peptide hydrogels | SATO | Cys responsive | Limiting the development of intimal hyperplasia in human vein segments | [40] |
| Hyaluronic acid and chitosan self-assembled films | ACS14 | pH responsive | Regulating vascular remodeling | [41] |
| Conductive hydrogel | 2-Aminopyridine-5-thiocarboxamide | Thiol responsive | Myocardial infarction treatment | [42] |
| Polymeric micelles | ADT | N/A | Protecting cardiomyocytes from ischemic cell death | [43] |
| PEG and lactoferrin modified mesoporous iron oxide nanoparticles | DATS | Magnetic guided, blood-brain barrier targeting, brain-targeting, MRI cardiac arrest | Cerebral and myocardial protection after cardiac arrest | [44] |
| Polymeric hydrogel | α-Thiobenzoate | UV responsive | Antithrombosis | [45] |
| SDS and SBC loaded gelatin capsule | DATS | ln situ self-spray, thiol-responsive | Inflammatory bowel disease treatment | [46] |
| Collagen hydrogel | JK1 | pH and enzyme dual-responsive | Disc degeneration treatment | [47] |
| Poly(lactic acid) microspheres | SPBC | N/A | Rheumatoid arthritis alleviation | [48] |
| PEG-ADT conjugate | ADT | N/A | Promoting inflammation | [49] |
| Polymeric micelles | ADT | N/A | Promoting inflammation | [50] |
| Polymeric nanoparticles | Arythioamide | Thiol responsive | Angiogenesis | [51] |
| Polymeric micelles | ADT | N/A | Angiogenesis | [52] |
| Polycaprolactone nanofibers | JK1 | pH responsive | Wound healing | [53] |
| Hyaluronic acid hydrogel | JK1 | pH responsive | Wound healing | [53] |
| Sodium alginate sponge | JK1 | pH responsive | Wound healing | [54] |
| Silk fibroin porous scaffolds | GY4137 | N/A | Bone tissue engineering | [55, 56] |
| Phase-change material-loaded wound dressing | Na2S | Thermal responsive | Diabetic wound healing | [57] |
| Enzyme-functionalized albumin | Thiosulfate cyanide sulphurtransferase | In situ enzyme generation | Cardiac tissue repair | [58] |
| PEG-cholesterol conjugate | Trisulfide | Thiol reactive | Anticancer effects | [59] |
| Polymeric micelles | SATO | Cys responsive | Anticancer effects | [28] |
| Magnetic nanoliposomes | ADT | Magnetic guided, US and MRI dual model imaging | Anticancer effects | [50, 61] |
| BSA modified MnS nanoparticles | Metastable-phase MnS | pH responsive, MRI imaging | Anticancer effects | [62] |
| Fe$_3$O$_4$ embedded BSA nanoassemblies | Fe$_3$O$_4$ | pH responsive, MRI imaging | Anticancer effects | [63] |
| FL27 nanoparticles | Polysulfide | GSH responsive, ratiometric PA imaging | Triple-negative breast cancer treatment | [35] |
| PEG-modified conjugated polymer nanoparticles | Polysulfide | GSH responsive, NIR Fluorescence imaging | Cancer treatment, wound healing | [64] |
| Hyaluronated liposomes | Phenyl substituent ADT-doxorubicin conjugate | Tumor-targeted | Cancer treatment | [30] |
| Zwitterionic nanoparticles | L-Cys | GSH responsive | Cancer treatment | [65] |
| Polymersomes | SATO | Bacteria-targeted, Cys responsive | Healing of infectious diabetic wound | [66] |
| Peptide hydrogels | DATS | Cys responsive | Disrupting S. aureus biofilms | [67] |
| Polymeric microspheres | DATS | Thiol-responsive | Limb ischemia treatment | [68] |
| PEG-coated upconversion nanoparticles | Geminal-dithiol | NIR responsive, bioimaging | N/A | [37] |
| PEG brush polymers | Trisulfide | Thiol reactive | Ameliorating cellular oxidative stress | [69] |
| Aggregates of mPEG and cholesterol conjugates | Trisulfide | Thiol reactive | Mitigating ROS generation | [70] |
| Crescent-shaped peptide assemblies | SATO | Cys responsive, enhanced cell internalization | Reducing ROS levels in macrophages | [71] |
| Polymeric hydrogels | SATO | Elastase-degradable, Cys responsive | Reducing toxicity of doxorubicin | [33] |
| Polyacrylamide microspheres | N-(benzoylthio)benzamide | Thiol responsive | Protecting cell from oxidative damage, cells proliferation | [72] |
| Polymeric micelles | Arythioamide | Thiol responsive | Spatiotemporally confined cell signaling | [29] |
| Polymeric nanoparticles | SATO | Cys responsive, bioimaging | N/A | [75] |

(DATS), undergo a thiol-promoted cleavage of polysulfide bond and form hydrosulfide intermediates, which further react with thiol containing compounds to produce H$_2$S [84]. Polysulfide linkers have been introduced to the backbones or side chains of polymers to enable controlled H$_2$S delivery for various biological applications [59, 69, 70, 85]. Synthetic acyl perthiols are also S-S bond containing H$_2$S donors [24] and have been modified on the end group of polymers [86]. In addition, arythioamides could release H$_2$S in response to both thiol containing compounds and hydrolysis, although its chemical mechanism is unclear [87]. Dithiobenzoate end group of polymers synthesized through reversible addition fragmentation chain transfer polymerization may themselves be H$_2$S donors upon exposure to thiol containing compounds [88]. In comparison with these thiol containing compounds specific H$_2$S donors, dinuclear persulfide-bridged ruthenium complex could be activated by a variety of reducing agents including HSO$_3^-$, Cys, GSH and ascorbate to release H$_2$S, showing unique advantage in hypoxia conditions [89].

2.4. Enzyme-activated H$_2$S donors

Utilizing enzyme-activated H$_2$S donors has many advantages for targeted H$_2$S delivery to enzyme-overexpressed microenvironments of lesions. Trimethyl lock group containing H$_2$S donors possess typical esterase-activated characteristics [36]. The ester-protected structure could be enzymatic hydrolyzed by esterase to produce nucleophilic hydroxy group, which further attack the carbonyl group and undergo a lactonization reaction to produce H$_2$S. In addition, the bis (4-nitrobenzyl)sulfanes could be reduced by nitroreductase and produce hydroxylamino- or amino-aryl derivatives to generate geminal diithiols through self-immolation, which could be further hydrolyzed to generate H$_2$S [90]. Dithiothiones (DTTs), represented by anetholidithiothiolethione (ADT), were generally considered as hydrolysis-activated H$_2$S donors [91]. However, recent studies have revealed that H$_2$S release of ADT could occur through an enzymatic process in the presence of liver microsomes and reduced nicotinamide adenine dinucleotide (NADH).
phosphate [92]. ADT could be conjugated with polymers to overcome the poor solubility and possible side effects [49]. Naturally occurring glucosinolates could be hydrolyzed under the catalysis of myrosinase [93]. One of the possible products depending on glucosinolate side chains and reaction conditions, isothiocyanate, could act as H$_2$S donors [94]. A more recent study demonstrated that 1-thio-β-D-glucose could act as a H$_2$S/H$_2$O$_2$ dual donor catalyzed by glucose oxidase, which could cause efficient protein S-persulfidation synergistically, since thiol groups of proteins could be oxidate by H$_2$O$_2$ to generate sulfenic acids (RSOH) that could react with H$_2$S for persulfidation more efficiently [95].

2.5. Light-activated H$_2$S donors

In recent years, strategies using exogenous stimuli as triggers to regulate H$_2$S delivery are being actively developed. Among these exogenous stimuli, light could trigger the H$_2$S release without perturbing native biochemical process, minimize off-target effects though direct spatiotemporal control, showing great advantages in the tissue-specific delivery of H$_2$S [24]. Light-activated H$_2$S donors usually contain photoremovable protecting groups, which could be deprotected under light irradiation at appropriate wavelength to release H$_2$S. α-Nitrobenzyl caged geminal dithiols [96] and ketoprofenate caged H$_2$S donors [97] are reported to release H$_2$S under ultraviolet (UV) light. In addition, α-thioetherketones are UV light-activated prodrugs of thioaldehydes, which could further release H$_2$S in the presence of amines [45].
p-Hydroxyphenacyl photocaged H$_2$S donors could respond to visible light to release H$_2$S [98]. Meanwhile, the light-induced deprotection activates the excited-state intramolecular proton transfer (ESIPT) process, which leads to a distinct fluorescent emission color change (green to blue) for real-time monitoring. However, currently developed H$_2$S donors are mostly activated by UV or visible light with short wave-length, showing poor tissue penetration ability and potential injury to normal tissues. Thus, H$_2$S donors triggered by physiological-friendly and tissue-penetrable visible or near infrared (NIR) light need to be further developed.

2.6. Carbonyl sulfide (COS) precursors as H$_2$S donors

COS could be quickly hydrolyzed to H$_2$S by carbonic anhydrase that is ubiquitously distributed in human tissues. The connection between COS and H$_2$S has led to the study on COS generating compounds as H$_2$S donors for biological applications. Matson et al. reported that N-thio-carboxyanhydrate (NTA) could generate COS upon ring-opening by a biological nucleophile [99]. In addition, the strategies utilizing S-alkyl or O-alkyl thiocarbamate or thiocarbonate based self-immolative linkers, initially proposed by Pluth et al. [100], have been employed for customizing COS donors, since COS release is the result of the self-immolative reactions, and the activation mechanism could be tuned by altering the protecting groups. Specifically, aryl boronate ester linked thiocarbonate/thiocarbonate could respond to reactive oxygen species (ROSs) to activate self-immolative process to generate H$_2$S via COS [101, 102]. When protected by imine, acidic pH activated COS release could be achieved upon imine cleavage [103]. When para-pivaloyl group or pivaloxyloxyethyl group are linked, the donors could be activated by esterases [104,105]. When photoactivated groups such as o-nitrobenzyl [106] or boron dipyrromethene chromophores with different substituents [107,108] were linked, UV to NIR light activated H$_2$S release could be achieved. In addition, through the linkage of appropriate fluorophores, self-reporting release of COS could also be achieved for real-time monitoring [109–112]. Furthermore, an oligo(thiourethane) containing S-alkyl thiocarbamate linkers was synthesized through the polyaddition of 4-isothiocyanatobenzyl alcohol and end-capped with aryl azide, which could undergo self-abstracted depolymerization to release multiple equivalents COS in response to per equivalent of H$_2$S [113].

3. Therapeutic applications of intelligent polymeric H$_2$S delivery systems

3.1. Cardiovascular therapy

H$_2$S has demonstrated critical effects on cardiovascular system [114]. Study on isolated blood vessels exhibited that H$_2$S could increase the K$_{ATP}$ channel currents of smooth muscle cells and hyperpolarize the membrane, thus relaxing smooth muscles, dilating blood vessels and reducing blood pressure [13]. Additionally, H$_2$S was reported to exhibit significant cardioprotective ability by attenuating MI-R injury [14]. The process of reperfusion after myocardial ischemia could cause severe oxidative damage to myocardial cells due to the generation of ROS [115]. Under the oxidative stress during MI-R, H$_2$S could act as a potent antioxidant, and up-regulate the GSH production to protect myocardial cells from oxidative damage together [12]. In addition, H$_2$S could inhibit leukocyte adherence to reduce myocardial inflammation, regulate mitochondrial respiration to preserve mitochondrial function, and inhibit the apoptosis of cardiomyocytes during MI-R injury [14].

Several research teams have started the exploration of exogenous H$_2$S delivery for treating cardiovascular diseases. Xian et al. developed a series of controllable H$_2$S donors and evaluated the cardioprotective effects against MI-R injury [81,116,117]. Compared with small molecular H$_2$S donors, nanosized polymeric H$_2$S delivery systems exhibit more excellent cardioprotective properties. Matson et al. reported that SATO-bearing peptide assemblies could rescue H9C2 cardiomyocytes from doxorubicin-induced cytotoxicity [118]. Hasegawa et al. showed that ADT-containing polymeric micelle could release H$_2$S intracellurally and prevent cardiomyocyte apoptosis in an in vitro ischemia model, more effective than NaHS and ADT-OH [43]. Sun et al. loaded the polysulphide H$_2$S donor DATS on the polyethylene glycol (PEG) and lactoferrin (LF) modified mesoporous iron oxide nanoparticles (MIONs) to form DATS@MION-PEG-LF [44]. PEG was used to acquire the prolonged circulation time, and LF could help nanoparticles to across the blood brain barrier and gain brain-targeting effects. The DATS@MION-PEG-LF showed prominent protective effects against cerebral and cardiac ischemic injury after cardiac arrest (CA), which was proved by in vitro hypoxia/reoxygenation models and in vivo CA/cardio pulmonary resuscitation (CPR) models. The treatment process could also be non-invasively traced through magnetic resonance imaging (MRI).

M-IR injury usually arises in patients suffering from acute ST-segment elevation myocardial infarction, and limiting the size of myocardial infarction is the main treatment strategy currently [115]. H$_2$S is a potent regularizing factor that could significantly reduce the myocardial infarct size and improve survival rate in acute myocardial infarction [119,120]. Liu et al. reported a stem cell loaded conductive hydrogel with H$_2$S delivery capacity for myocardial infarction treatment (Fig. 2a) [42]. ALG-TA-APTC copolymer was formed by grafting H$_2$S donor 2-aminopyridine-S-thiocarbamidoxime (APTC) and tetraaniline (TA) oligomer onto partially oxidized alginate (ALG-CHO), for endowing H$_2$S delivering capability and reestablishing the electrical impulse signals between myocardial cells in the infarcted area. Hydrogel was fabricated via covalent cross-linking of gelatin, ALG-CHO and ALG-TA-APTC, exhibiting controlled H$_2$S release in vitro (Fig. 2d). This hydrogel showed outstanding bioadhesive property (Fig. 2b), which could ensure a stable anchoring to the wet and beating hearts and enhance the retention of adipose-derived stem cells (ADSCs) in the MI zone (Fig. 2c) to promote the regeneration of myocardium. After hydrogel injection, an elevated H$_2$S concentration in rat myocardium was observed, accompanied by the increase of cardiac-related mRNA and angiogenic factors and the decrease of inflammatory factor, tumor necrosis factor alpha (TNF-α). Furthermore, the reduction in cardiac fibrosis area (Fig. 2e) and the mitigatory of left ventricle (LV) wall thinning (Fig. 2f) demonstrated the therapeutic potential of this H$_2$S delivery hydrogel for reducing infarction size and improving cardiac functions.

Pulmonary arterial hypertension (PAH) is a cardiovascular disease characterized by a persistent elevation in pulmonary vascular pressure and pulmonary vascular remodeling, which may cause right ventricular failure and even death under some circumstances [121]. H$_2$S has been proven to reduce pulmonary vascular remodeling via promoting the apoptosis of pulmonary artery smooth muscle cells and inhibiting collagen deposition [122]. Though gaseous H$_2$S could be delivery to the lung through inhalation, it is difficult to mimic slow and constant H$_2$S release in vivo in this way. To overcome this problem, Zhang et al. developed a H$_2$S delivery poly(lactic-co-glycolic acid) (PLGA)-based large porous microspheres (MSs) for inhaled therapy of PAH [39]. PLGA-based porous MSs was prepared through microfluidic technology, and 2-acetyloxybenzoic acid 4-[(3-thioxi-3H-1,2-dithiol-5-yl) phenyl ester (ACS14), a H$_2$S donor comprising of a dithioleneethione conjugated with aspirin, was loaded to form ACS14 MSs. The high porosity made ACS14 MSs light enough to reach deeply into the lungs via inhalation, and the ~5 μm of mass median aerodynamic diameter was suitable for deposition in alveolar region. The sustained release of ACS14 for up to seven days was observed in simulated lung fluid. Furthermore, H$_2$S was generated slowly and continuously in lung tissues after the inhaled administration of ACS14 MSs, reaching maximum in 24 h and showing negligible effect on the plasma level of H$_2$S. In vivo fluorescence imaging of rats showed that ACS14 MSs had the characteristics of long-term lung retention and passive lung targeting. In a rat model of monocrotaline-induced PAH, the therapeutic effect of ACS14 MSs
through inhalation was significantly higher than the corresponding systemic delivery of free ACS14, equivalent to sildenafil that is conventionally employed in PAH treatment.

Atherosclerotic stenosis could cause various fatal cardiovascular diseases and interventional therapy is the most common treatment method for atherosclerotic stenosis, showing considerable effectiveness in clinic. However, this therapy could damage the health tissues which may cause complications including inflammation, intimal hyperplasia, late thrombosis, and in-stent restenosis. H$_2$S has been found to relief vascular inflammatory response, vascular remodeling, and thrombosis at atherosclerotic sites. On account of the weak acidic microenvironment at the angioplasty site with inflammation, Huang et al. prepared a pH-responsive layer-by-layer (LBL) self-assembled film to coat on the implant surface to achieve controlled delivery of H$_2$S (Fig. 3a) [41]. The LBL coating was fabricated on the surface of dopamine-modified stainless-steel implants, through the sequential immersion in catechol chitosan solution, catechol hyaluronic acid solution and ACS14 solution for several rounds. Under weak acidic microenvironment, the stability of LBL coating was changed, resulting in the enhanced release of ACS14 for over 60 days (Fig. 3b and c). Ex vivo experiments on isolated arteries and veins of rabbits showed that coatings loaded with 10 $\mu$mol/L of ACS14 possessed good blood compatibility, significantly inhibiting red blood cell and platelet adhesion (Fig. 3d), which was also confirmed by reduced blood flow obstruction (Fig. 3e) and thrombus weight (Fig. 3g). To evaluate the in vivo therapeutic effects of the H$_2$S delivery LBL coating, ACS14-loaded LBL-coated filaments were implanted into the abdominal aorta of SD rats. No significant thrombus clogging, and inflammation were observed after 30 days, providing a novel method to solve in-stent restenosis.

3.2. Inflammatory therapy

Inflammation is an adaptive response of innate immune system triggered by noxious stimuli to eliminate tissue injury and initiate tissue repair [123]. Conventionally, inflammation is beneficial for restoring homeostasis, lasting for only a short period of time before the body returns to health. However, when this physiological process persisted abnormally, it could lead to inflammatory diseases such as rheumatoid arthritis (RA). There is increasing evidence that H$_2$S acts as an endogenous modulator for resolution of inflammatory response [124]. Unlike CO that shows definite anti-inflammatory effects [125,126], the role of H$_2$S in inflammation is complex. Studies have shown that H$_2$S exerts anti-inflammatory effects by reducing the expression of many pro-inflammatory cytokines, chemokines and enzymes to inhibit the activation of NF-$\kappa$B pathways, suppressing the leukocyte adhesion and recruitment, driving macrophage differentiation towards the anti-inflammatory M2 phenotype, and inducing apoptosis in neutrophils [124]. H$_2$S could also reduce the formation of edema [127] and relieve pain caused by inflammation [128]. It has been reported that H$_2$S donor-conjugated non-steroidal antiinflammatory drugs (NSAIDs) exhibit improved efficacy and reduced toxicity compared with the parent NSAIDs [129]. However, H$_2$S could also exhibit
pro-inflammation effects on a number of pathological processes [130]. The reduced inflammatory response could be observed after treatment of H$_2$S synthase inhibitors [131]. Hasegawa et al. reported that PEG-ADT conjugate and ADT-containing micelle capable of delivering H$_2$S could enhance the pro-inflammatory cytokine TNF-α [49,50]. The contradictory effects of H$_2$S in inflammation observed during studies probably associate with its dose-dependent activity and varying roles at different stages of inflammation, which still needs to be further elucidated. The anti-inflammatory effect of intelligent polymeric H$_2$S delivery systems is the main focus of current studies, as well as the major content of this section.

RA is a complex autoimmune and inflammatory disease that could cause severe damage to joint tissues, with subsequent high morbidity and mortality. In order to alleviate RA, Zhu et al. developed a poly(lactic acid) (PLA)-based microsphere loaded with S-propargyl-cysteine (SPRC), an endogenous H$_2$S modulator that could stimulate H$_2$S generation in vivo via CSE/H$_2$S signaling pathways, named SPRC@PLA [48]. After subcutaneous injection of SPRC@PLA, a sustained elevation of plasma H$_2$S concentration was observed, different with the rapid production and fast decrease of H$_2$S by injecting free SPRC. Further research showed that SPRC@PLA could increase the expression of CSE to enhance the generation of H$_2$S, and alleviate paw swollen in adjuvant-induced arthritis rat. Intervertebral disc degeneration (IDD) is also highly associated with inflammation. Against the characteristic pathological environment of IDD including overexpressed proteolytic enzymes and acidic pH due to the accumulation of lactic acid as a result of glycolysis, Xiao et al. developed an enzyme and pH dual-responsive H$_2$S delivery hydrogel for IDD treatment [47]. JK1, a H$_2$S donor that could undergo an acidic pH-accelerated hydrolysis to release H$_2$S, was encapsulated in collagen hydrogel to form Col-JK1. Collagen could be gradually degraded by the highly expressed matrix metalloproteinases in IDD to release JK1, and subsequently the acidic pH within the disc could trigger the generation of H$_2$S in situ. Col-JK1 exhibited better therapeutic efficacy to annular puncture-induced IDD in rats than free JK1 as observed through MRI. Further study revealed that Col-JK1 could inhibit the apoptosis of nucleus pulposus cells and attenuate the degradation of the disc extracellular matrix to protect the disc from degeneration. The protective effect of Col-JK1 was attributed to its anti-inflammatory effects through the deactivation of the NF-κB signaling pathway, which could be demonstrated by the decreased expression of inflammatory...
cytokines interleukin-6 (IL-6) and TNF-α, as well as the increased expression of anti-inflammatory cytokines interleukin-10 (IL-10).

Inflammatory bowel diseases (IBDs), represented by ulcerative colitis (UC) and Crohn’s disease, are chronic relapsing disorders of the gastrointestinal tract characterized by overexpression of pro-inflammatory cytokines, as well as adhesion of leukocytes to the vascular endothelium and their migration to the inflamed bowel. The garlic-derived natural H₂S donor, DATS, exhibited anti-inflammatory effects in both in vitro and in vivo studies [132,133]. However, due to its poor water solubility, appropriate administering strategies are still required for improved therapeutic effects. In order to treat IBD using DATS, Sung et al. [46] developed a in situ self-spray coating system based on DATS loaded gelatin capsules with foaming ability (CAP-w-FC), which were composed of a mixture of acid initiator (diethylene triamine pentaacetic acid, DTPA), foaming agent (sodium bicarbonate, SBC), surfactant (sodium dodecyl sulfate, SDS) and DATS.

Fig. 4. Formulation, mechanism of action of in situ self-spray coating system, as well as its anti-inflammation effects in vitro and in vivo. (a) Schematic illustrations of dispersion of a coating of DATS-loaded micellar particles on luminal surface of colon to repair colonic inflamed tissues. (b) Fluorescence images and schematic illustrations of formation of bubble carriers and their transformation to DATS-loaded micellar particles that are stabilized by SDS. (c) CLSM fluorescence images of H₂S production in Caco-2 cells. (d) IVIS images of L-012-derived luminescence signals, showing inflamed sites in colon and their corresponding intensities in IBD rats. (e) Expression levels of TNF-α, MCP-1, and IL-6 in LPS-induced RAW264.7 cells following various treatments (*p < 0.05). (f) DAI scores of IBD rats following various treatments [46]. Copyright 2018, Elsevier Ltd.
decomposition of foaming agent SBC to produce CO$_2$ (Fig. 4a). CAP-w-FC was rectally administered to rats with UC. After the bubble carrier rose to the water/air interface and burst, the atomized DATS-loaded SDS micellar particles were formed and sprayed on the luminal surface of the colorectal tract. This process was proved by fluorescence labeling experiment in simulated intestinal fluid (Fig. 4b). In the simulated in vivo release experiment, the fluorescence signal of H$_2$S fluorescence probe showed that DATS was uniformly internalized by colonic epithelial cells and converted to H$_2$S, as observed through confocal laser scanning microscopy (CLSM) fluorescence images (Fig. 4c). Meanwhile, the pro-inflammatory cytokines, including TNF-a, MCP-1, and IL-6, were decreased and macrophage adhesion was inhibited in lipopolysaccharide (LPS)-induced RAW264.7 cells (Fig. 4e). In vivo experiments were carried out in a rat model of UC, showing that CAP-w-FC reduced the level of ROS in the colon and alleviated the inflammatory response, as observed by in vivo imaging system (IVIS) (Fig. 4d). Significantly reduced disease activity index (DAI) score was also observed after treating by CAP-w-FC (Fig. 4f).

### 3.3. Tissue regenerative therapy

H$_2$S has been reported to promote the proliferation and migration of endothelial cells, as well as activate the vascular endothelial growth factor (VEGF) receptors and the KATP channel, to facilitate angiogenesis, which is vital to the tissue regenerative process [18]. Meanwhile, the inflammation modulating and oxidative stress suppressing abilities of H$_2$S also contribute to its promotor role in tissue regeneration [53, 72]. In recent years, intelligent polymeric H$_2$S delivery systems have started to show their unique benefits in tissue regenerative therapy. Hasegawa et al. studied the pro-angiogenic effects of ADT-containing H$_2$S delivery micelles which were prepared from amphiphilic block copolymers consisting of a hydrophilic poly(N-acryloyl morpholine) block and a hydrophobic block containing ADT groups [52]. The micelles could be internalized by human umbilical vein endothelial cells (HUVECs) and release H$_2$S intracellularly, as observed by CLSM. In the gap closure migration assay on HUVECs, ADT-containing micelles showed significant effects on cell migration, similar with the group treated by the growth factor VEGF$_{121}$ and higher than ADT-treated group. The micelles also showed significant promoting effects on endothelial cell tube formation and vascularization in the in ovo chick chorioallantoic membrane assay. Another gasotransmitter, NO, could also induce angiogenesis, showing a synergistic effect with H$_2$S in cell signaling pathways [134]. Thus, the angiogenesis effect is expected to be amplified by establishing H$_2$S and NO co-delivery systems. Lee et al. reported a H$_2$S and NO co-delivery nanoparticle formed by the self-assembly of thio-benzamide-functionalized methoxy poly(ethylene glycol-b-lactic-co-glycolic-co-hydroxymethyl propionic acid), loading N-diazoniumiodolated diethylenetriamine as NO donor [51]. This co-delivery system showed significantly enhanced in vitro tube formation effect on HUVECs and ex vivo angiogenesis effect on rat aorta, compared with the only NO or H$_2$S delivery groups.

Minor injuries in healthy individuals could generally heal well [135]. However, when it comes to open wounds caused by wars or accidents and chronic wounds such as diabetic foot ulcers, the self-healing processes may not work very well [136]. Polymeric wound dressings based on hydrogels, fibrous membranes, sponges, etc., are able to create a moist environment around the wound, facilitating the regeneration of skin tissues. Wang et al. developed a series of polymeric H$_2$S delivery wound dressing and managed to elucidate the mechanisms in wound healing acceleration [32,53,54,72]. According to the acidic pH at the acute wound tissues, they fabricated a JK1-loaded pH-controllable H$_2$S delivery polycaprolactone (PCL) fibrous material as wound dressing [32]. When lowered the pH from 7.4 to 6.0, the faster H$_2$S release from PCL-JK1 was observed. In the full-thickness cutaneous wound model on mice, the healing rate of the PCL-JK1 treated group was significantly higher than PCL treated group at all time points studied. Histological analysis on day 20 showed that PCL-JK1 treated group have newly regenerated tissues with fully developed granulation and re-epithelialization, as well as more and mature newly formed vascularization toward the wound compared with PCL treated group. In their following study, JK1 was doped in hyaluronic acid (HA) hydrogel to form a wound dressing (HA-JK1) [53]. Since HA is a major constituent of extracellular matrix, this hydrogel highly showed biocompatibility for in vivo wound healing. HA-JK1 significantly accelerated the wound regeneration process through enhanced re-epithelialization, collagen deposition, angiogenesis, and cell proliferation. One important observation is that this H$_2$S delivery hydrogel was able to induce the in situ polarization of macrophages from inflammatory M1 phenotype to pro-healing, anti-inflammatory M2 phenotype, thus reducing inflammation around the wound and improved wound remodeling effects. More recently, towards the wounds with heavy exudate levels, the same research group developed a wound dressing by incorporating JK1 into a sodium alginate (SA) sponge (Fig. 5a) [54]. The SA-based sponge could not only absorb wound exudate effectively to form hydrogel and maintain a moist environment but could also release H$_2$S continuously to the wound bed in response to acidic pH. The SA-based sponge could reach the maximum water uptake in approximately 1 h with high swelling ratios to promote the drainage of exudates. Additionally, the diameters of the SA-based sponge were barely changed after swelling, showing excellent dimension stability to avoid wound laceration. H$_2$S release under acidic pH was accelerated as measured through methylene blue assay (Fig. 5b). Accordingly, in vitro cell scratch assay exhibited improved fibroblast proliferation and migration at pH 6.0 than at pH 7.0. Moreover, the in vivo assay using a full thickness dermal defect model revealed that the sponge could significantly improve wound healing process (Fig. 5c–e).

### 3.4. Cancer therapy

Similar to the physiological roles in inflammatory response, H$_2$S exhibits complex effects on cancer [2]. H$_2$S could act as a bioenergetic stimulator to promote glucose uptake and glycolysis efficiency to provide the energy of cancer cells. Furthermore, H$_2$S is able to promote the angiogenesis, activate the anti-apoptotic pathways and accelerate the cell cycle of cancer cells to facilitate cancer development. The excessive generation of H$_2$S has been demonstrated in numerous types of cancer cells, which has also become potential targets in anticancer therapy to develop H$_2$S-triggered theranostic nanoagents for the diagnosis and treatment of cancer [137–142]. However, this strategy is beyond the scope of our review.

When high-dose and long-term administration of exogenous H$_2$S were performed, anticancer effects are usually observed. The anticancer property of H$_2$S could be partly attribute to the uncontrolled cellular acidification caused by the H$_2$S-mediated glycolysis enhancement [2]. In addition, H$_2$S could suppress the cell signaling pathways that are abnormally activated during cancer development, such as NF-$\kappa$B pathways [143]. H$_2$S could also induce cell cycle arrest in several cancer cell lines and lead to cell apoptosis [144]. Several in vitro studies exhibited that exogenous H$_2$S seems to work specifically on cancer cells, with no obvious impacts on normal cells. In 2017, Matson et al. reported a H$_2$S delivery polymer micelle formed by SATO-containing amphiphilic block copolymers, which could concentration-dependently reduce the survival of HCT116 colon cancer cells, but led to no significant effect on the viability of NIH/3T3 fibroblasts [28].

Notably, conditions of the tumor lesions in the patient’s body differ greatly from that of cancer cells in vitro. Therefore, in order to enhance in vivo anticancer effects, intelligent polymeric H$_2$S delivery systems should be formulated based on the pathological conditions of tumor
lesions. On the one hand, the enhanced permeability and retention (EPR) effect of the abnormal tumor neovasculature and highly expressed targets in cancer cells allow the targeted delivery of polymeric nanocarriers in passive and active manners [145]. Cluster of differentiation (CD) 44, a cell surface protein overexpressing in cancer cells to promote tumor growth and metastatic dissemination, could act as a target of HA [146]. HA-modified liposome encapsulating H2S donor-doxorubicin conjugate developed by Riganiti et al. could effectively induce cell death against doxorubicin-resistant osteosarcoma cells, which was attributed to the alteration of drug delivery to endoplasmic reticulum, sulfhydration and ubiquitination of protein, and activation of endoplasmic reticulum stress pro-apoptotic response [30]. On the other hand, stimuli in characteristic tumor microenvironment (TME) including low pH, altered redox potential, hypoxia, hyperthermia, etc. [147] could be utilized to regulate H2S delivery by modulating macromolecular architectures. A TME responsive zwitterionic H2S delivery system was recently reported by Wan et al., which was formed through the polymerization of zwitterionic sulfobetaine methacrylate monomer using N,N-bis-(acryloyl) cystamine as crosslinker and the subsequent loading of L-cysteine (L-Cys) and α-cyano-4-hydroxycinnamic acid (α-CHCA) [65]. It could be degraded by high concentration of GSH in TME to release L-Cys and α-CHCA. L-Cys could act as a substrate of highly expressed CSE in TME to produce H2S, which subsequently promoted the uptake of glucose to induce tumor cell acidosis. Meanwhile, α-CHCA destroy the lactic acid transmission chain of tumor cells and cause excessive intracellular accumulation of lactic acid, leading to the destruction of tumor metabolism symbiosis and the ultimate cell death. More excessive H2S and α-CHCA were released after incubation with MCF-7 cancer cells than normal endothelial cells HUVECs, demonstrating the good responsiveness to TME. Compared with the steady intracellular pH value of HUVECs (about 7.1), intracellular pH value of MCF-7 cancer cell deceased significantly to 6.1 due to lactic acid accumulation as a product of glycolysis. A significant decrease in ATP production was also observed in the treated cancer cells due to the disorder of cell metabolism. These results demonstrated the selective toxicity of this TME responsive H2S delivery system.

In addition to the targeted and TME responsive polymeric H2S delivery systems, the utilization of external stimuli (light and magnetic field, etc.) to regulate H2S delivery temporally and spatially to the deep regions of tumors has been proven to be of great efficiency, and advanced imaging technologies facilitate the precise and visual cancer diagnosis and treatment. Inorganic iron- or manganese-based contrast agents, have been widely studied in cancer theranostics through MRI, showing enhanced biosafety than conventional gadolinium-based contrast agents. Biocompatible polymers are usually utilized for modification of these contrast agents. For example, Huang et al. developed a bovine serum albumin (BSA) modified γ-phase MnS nanotheranostic (BSA@MnS), which could be dissociated in acidic tumor microenvironment, releasing H2S and Mn2+ ions simultaneously [62]. The released Mn2+ could not only act as contrast agent for MRI, but also catalyze Fenton-like reaction to convert H2O2 into toxic hydroxyl radical at tumor tissues, showing synergistic anticancer effects with H2S. Besides, Gu et al. developed a ADT-loaded H2S delivery magnetic nanoliposome (AML) with MRI and ultrasound (US) dual-model imaging capability for cancer theranostics by loading ADT in the phospholipid membrane and small superparamagnetic nanoparticles in the core of the liposome (Fig. 6a) [60]. AMLs could be ingested by HepG2 cancer cells and generate H2S bubbles intracellularly, behaving like bubble bombers to physically destroy the cells (Fig. 6b). Due to the incorporation of superparamagnetic nanoparticles, the tumor targeting of AMLs could be enhanced under external static magnetic field, and the specific intratumoral distribution of AMLs could be dynamically monitored through MRI (Fig. 6d). In addition, the in situ generated H2S bubbles could sensitize the ultrasound (US) imaging signal, to monitor the dynamic process of intratumoral H2S production (Fig. 6c). Furthermore, therapeutic US intensity could disrupt the H2S bubbles and enhance the physical bombing effect on tumors. The intratumorally generated high concentration of H2S could rapidly travel through deep tumor membrane barrier to enhance antitumor effect. In their following research, the mechanisms of tumor cell death induced by H2S bubbling were elucidated [61]. The gradual generated H2S bubbles opened the calcium channel of cancer cells and enhanced the intracellular calcium concentration, which could interrupt the intracellular ion microenvironment (Fig. 6e). The bubble breakage also induced the generation of hydroxyl...
radicals, significantly influencing the intracellular redox homeostasis in tumor cells. In addition to affecting the tumor cell microenvironment, the intracellular mechanical stress also destroyed the cell cytoskeleton, as observed by transmission electron microscopy (TEM) images of HepG-2 cells (Fig. 6g) and fluorescence images of cytoskeleton actin network (Fig. 6h) after incubation with AMLs, which was attributed to the ultrasound-stimulated intracellular blasting of bubbles. A 2D map of stress was also estimated using a numerical model to determine the force threshold for destroying the cell cytoskeleton (Fig. 6f).

In addition to imaging strategies based on the inorganic components, imaging strategies based on organic compounds or polymer carriers themselves have also been actively explored for the formulation of polymeric H$_2$S delivery systems. Our group proposed a ratiometric photoacoustic (PA) monitored and TME initiated H$_2$S therapy for the detection and treatment of triple-negative breast cancer (TNBC) [35]. Ratiometric PA probe cyanine (CY) and polysulfide H$_2$S donor (PSD) were encapsulated in self-assembled polymeric nanoparticle formed by amphiphatic block polymers (Pluronic F127). The thiol abundant TME triggered PSD to release H$_2$S, which exerted therapeutic effects against cancer and activated the ratiometric PA signal change of CY from 808 nm to 707 nm (Fig. 7a and b), for real-time H$_2$S monitoring and in vivo tumor pinpointing (Fig. 7c). CY-PSD nanoparticles showed excellent anticancer effects both in vitro and in vivo on TNBC cells and tumor-bearing mice. Pharmacological analysis revealed that CY-PSD nanoparticles exerted anticancer effects by inducing mitochondrial dysfunction and down-regulating oxidative stress. Besides utilizing small molecular compounds as imaging agents, polymers with intrinsic imaging property were also applied to establish H$_2$S delivery systems in our following research [64]. A PEG-grafted conjugated polymer (CP-PEG) was synthesized, which was then employed for loading polysulfide H$_2$S donor 2,2′-dipyridyl tetrasulfide (Pry-Ps) to prepare H$_2$S delivery nanoparticles (named as Pry-Ps@CP-PEG) (Fig. 7d). The wide NIR absorption cross-section of CP-PEG endowed highly efficient photothermal performance (Fig. 7e) for cancer cell killing and simultaneous NIR-II fluorescence (Fig. 7f) for tracing the tumor and monitoring the entire therapeutic process (Fig. 7g). More importantly, due to the generation of H$_2$S activated by GSH (Fig. 7f), Pry-Ps@CP-PEG was not only able to induce mitochondrial dysfunction of cancer cells but could also act as a nanoregulator to dramatically downregulate the level of proinflammation cytokines generated during photothermal therapy (PTT) without hindering the immune therapeutic performance of PTT.

Fig. 6. Anticancer effects of AMLs through magnetic targeting, H$_2$S bubbling, as well as MRI and US dual imaging monitoring. (a) Scheme illustrating the composition of AML and its synergetic H$_2$S generation, tumor bombing and MRI/US dual-model imaging theranostic mechanisms. (b) Cellular morphology changes and intracellular bubble generation captured at different time points treated by different samples, in which ALs refers to ADT-loaded liposomes without encapsulating superparamagnetic nanoparticles. In vivo (c) US images and (d) MRI of mouse tumors before and after administration of different samples [60]. Copyright 2017, reproduced with permission from American Chemical Society. (e) Scheme of the equipment for magnetic field and ultrasound dual-manipulated cell membrane mechanosensing, as well as intracellular bubble blasting and intracellular redox disorder induced cell structure destruction. (f) Representative cell stress profiles simulated by 2D deformation fields. (g) TEM images of bubble-induced cell destruction after incubation for 8 h. (h) Fluorescence images of HepG-2 cells after fluorescein isothiocyanate (FITC)-phalloidin staining for F-actin characterization after different incubation times [61]. Copyright 2020, The Royal Society of Chemistry.
3.5. Bacteria-associated therapy

Compared with H\(_2\)S generated by mammals, bacteria derived H\(_2\)S has been identified for centuries, although it was long perceived primarily as a byproduct of bacterial metabolism. For example, sulfate-reducing bacteria utilize a wide range of organic compounds as substrates to reduce sulfate to H\(_2\)S and generate metabolic energy [148, 149]. H\(_2\)S-generating enzymes homologous with mammalian CBS, CSE, or 3-MST, at least in part, were identified in most of nonsulfur bacteria [150], and the probable physiological functions of bacteria-derived H\(_2\)S were observed recently [151]. However, the metabolic and signaling pathways of this gas in bacteria are still far from clear. The other two gasotransmitters, NO and CO, both exert bactericidal effects at relatively high concentrations [152–154] and have been incorporated with polymeric systems for antibacterial applications [155–158]. However, the antibacterial property of H\(_2\)S seems not so definite as NO and CO. Indeed, high concentration of H\(_2\)S (close to millimolar level) is able to induce severe oxidative damage to bacteria [159]. But such high concentration of H\(_2\)S would also induce cytotoxicity and inflammation to mammals [8]. Therefore, H\(_2\)S is generally not considered to be potential antibacterial agent like NO and CO. In contrast, H\(_2\)S could act as cytoprotective agent to protect bacteria from harmful oxidative stress imposed by antibiotics [150]. One major mechanism is H\(_2\)S-mediated sequestration of free iron to prevent the Fenton reaction that generates toxic hydroxyl radicals [160]. Besides, although garlic-derived diallyl polysulfanes, the natural H\(_2\)S donors, are known to exhibit broad spectrum antimicrobial activity [161], there is growing evidence that the property might not derived from the generation of H\(_2\)S, but the hydrogen polysulfanes (e.g., H\(_2\)S\(_2\) and H\(_2\)S\(_3\)) and other RSSs [162,163].

Nevertheless, recent advances about the interaction between H\(_2\)S and bacteria has led to the revaluation of its potential in antibacterial therapy. Though the direct antibacterial effect of H\(_2\)S is limited, H\(_2\)S is able to relieve inflammation induced by acute bacterial infection [164], as well as lipopolysaccharide of gram-negative bacteria [165], which indicates the potential role of H\(_2\)S-releasing agents in the treatment of bacterial infections through anti-inflammatory pathways. In addition,
H₂S could exhibit excellent synergistic therapeutic effects towards hard-to-heal infected wounds. Recently, Du et al. developed a H₂S delivery polymersome, which was utilized in the form of spray for treating bacteria-infected diabetic wounds (Fig. 8a) [66]. The polymersome was prepared through the self-assembly of diblock copolymer containing hydrophobic PCL block to form the membrane and poly[lysine-stat-(S-aryloxythio)) [P(Lys-stat-SATO)] to form the corona. In the presence of cysteine, the polymersome could generate H₂S gradually for up to 12 h (Fig. 8b). Intracellular generation of H₂S in normal human epidermal keratinocytes (NHEK) cells was also observed using a H₂S fluorescent probe (Fig. 8c). Due to the positively charged lysine amino groups in the outer corona of the polymersome, it possessed intrinsic antibacterial property through the electrostatic interaction with negatively charged bacterial membranes, showing potent bactericidal effects on both gram-negative *Escherichia coli* (*E. coli*) and gram-positive *Staphylococcus aureus* (*S. aureus*) in vitro (Fig. 8d), as well as infected diabetic wounds (Fig. 8g). And the slow and sustained release of H₂S could accelerate the healing of diabetic wounds (Fig. 8e and f).

Biofilms are heterogeneous communities of bacteria encapsulated in a self-produced polymer matrix, providing potent defense against the killing effects of antibiotics and host immune systems [166]. Recent studies pointed out that H₂S may act as an important biofilm disruptor at proper concentration. H₂S delivery hydrogel developed by Matson et al. showed biofilm dispersal efficacy on *S. aureus* [67]. This hydrogel was formed through the self-assembly of SATO-functionalized amphiphilic dipeptides (S-FE). The pretreating of S-FE hydrogel before biofilm formation led to 57% reduction of biofilm biomass, more effective than C-FE hydrogel (39% reduction), the control hydrogel bearing oxime group but incapable of H₂S release. S-FE hydrogel treatment on established biofilms also led to 8% reduction in biomass, compared with a 2% decrease for the C-FE. As far as we know, this work provided the first example of the application of H₂S-releasing materials in anti-biofilm research, but the underlying mechanism is still unknown. NO, another gasotransmitter, is able to induce biofilm dispersal by stimulating bacterial phosphodiesterase activity to decrease the intracellular levels of cyclic-diguanylate-guanosine monophosphate (c-di-GMP), the intracellular second messenger of bacteria responsible for regulating the formation of biofilms [167, 168]. In mammalian systems, H₂S is able to enhance the production of NO by inducting the expression of endothelial NO synthase and stimulating its activity [169, 170]. Whether H₂S-induced biofilm dispersal involves the pathway of promoting NO generation in bacterial cells is still unclear, but it deserves further investigation.

Gut microbiota is an important source of H₂S in human body. H₂S in gastrointestinal tract is able to influence many physiological and pathophysiological processes [171]. On the one hand, the bacteria-derived H₂S acts as a metabolic fuel of epithelial cells, and is involved in several aspects of mucosal defense and repair [172]. On the other hand, delivery of H₂S into the colon could influence the state of microbiota and promote harmonious coexistence of the bacteria with the

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Fig. 8. H₂S delivery polymersome for infected diabetic wound healing. (a) Schematic illustration of the formation and mechanism of action of the H₂S delivery polymersome against infected diabetic wound. (b) H₂S releasing profiles of polymersome in the presence and absence of cysteine. (c) Exogenous H₂S levels in NHEK cells determined using a fluorescent probe. (d) Live/Dead staining analysis of bacteria after the treatment of polymersome. (e-f) In vivo wound healing rates of *S. aureus*-infected diabetic wound site treated with polymersome + Cystine and other control groups. (g) Bacterial colonies obtained from infected wounds on Day 10 treated with different groups [66]. Copyright 2021, American Chemical Society.
gastrointestinal mucosa, which showed the potential in the treatment of colonic diseases, such as inflammatory bowel disease and colorectal cancer [173,174]. In addition, the research on gut microbiota has colonic diseases, such as inflammatory bowel disease and colorectal diabetes, and autism [175]. Thus, delivery of exogenous H\textsubscript{2}S through polymeric carriers to regulate gut microbiota is an approach worth exploring.

3.6. Therapies for other diseases

Like myocardial ischemia we mentioned above, ischemic diseases such as limb ischemia and ischemic stroke, are usually associated with hostile inflammatory response in the ischemic area caused by the production of large amounts of reactive oxygen species [176]. If not rescued timely, they may cause serious injuries and even death. H\textsubscript{2}S has shown the abilities to relieve oxidative stress [177], promote angiogenesis [16], and inhibit cellular apoptosis [178], which are benefit for treating ischemia. In an attempt to treat limb ischemia, Sung et al. prepared DATS loaded H\textsubscript{2}S releasing PLGA microparticles (DATS@MPs) through an oil-in-water single emulsion method [68]. Compared with free DATS, DATS@MPs enabled prolonged intracellular H\textsubscript{2}S generation, favoring long-lasting therapeutic effects. After intramuscular injection to the ischemic limb of mouse model, Sung et al. showed that the DATS@MPs group had the lowest oxidative stress level at the ischemic tissue level compared with free DATS, which was highly associated with the increase of capillary and arteriole densities at the ischemic limb. Meanwhile, the DATS@MPs group showed the lowest oxidative stress level at the ischemic tissues, illustrating the cytoprotective effect enabled by sustained H\textsubscript{2}S release.

Diabetes is characterized by disorders of glucose metabolism, which may induce serious complications, posing a major social health threat. In recent years, growing evidences have indicated that H\textsubscript{2}S homeostasis plays an important role in diabetes [179]. H\textsubscript{2}S could provide a protective effect on islet \( \beta \) cells from oxidative stress and elevated inflammations, to maintain the regular function of islet \( \beta \) cells [20]. In addition, H\textsubscript{2}S could relieve hyperglycemic endothelial dysfunction, which may be of great significance to maintain diabetic blood vessel patency and prevent the development of diabetic complications [179]. Polymeric nanomedicines open a promising option for the management of diabetes [180]. Aimed at the high cellular oxidative stress during diabetes, administrating antioxidants to regulate the redox balance have proven to be an effective approach [181]. Thus, we suppose that delivering H\textsubscript{2}S by means of polymeric carriers is worth exploring for alleviating diabeties and its complications. Noteworthy, the role of H\textsubscript{2}S in diabetes is complicate, and H\textsubscript{2}S could also affect insulin secretion of islet \( \beta \) cells by opening K\textsubscript{ATP} channel [182]. Therefore, the role of H\textsubscript{2}S at different stages of diabetes should be further explored to provide guidance for exogenous H\textsubscript{2}S delivery.

In recent years, H\textsubscript{2}S also showed therapeutic effect on neurodegenerative diseases, such as Alzheimer’s disease. Neurodegenerative diseases are highly associated with oxidative stress [183], and delivering antioxidants through polymeric nanomedicines is explored as a method for treating neurodegenerative diseases [184]. As mentioned above, H\textsubscript{2}S could prevent oxidative stress through various pathways. In addition, recent studies revealed that H\textsubscript{2}S showed neuroprotective effects in Alzheimer’s disease by inhibiting the hyperphosphorylation of Tau protein [185], while the regulation of Tau pathology has shown great potentials on the treatment of Alzheimer’s disease [186]. Therefore, polymeric H\textsubscript{2}S delivery systems deserve to be explored for treatment of neurodegenerative diseases represented by Alzheimer’s disease. Note-worthy, one important property they should be endowed is blood-brain barrier penetrability.

4. Conclusion and future prospects

The past two decades have witnessed the rise of studies on the physiological effects of H\textsubscript{2}S, opening a promising option for the treatment of various human diseases. Since the biological effects of H\textsubscript{2}S are highly associated with its concentrations, there is urgently needed to develop strategies for elaborately regulated H\textsubscript{2}S delivery. To meet the requirements of precision medicines, intelligent polymeric H\textsubscript{2}S delivery systems capable of targeting the lesions specifically, responding to pathological microenvironments smartly and employing multi-model imaging technologies for real-time theranostics are actively explored, showing excellent accuracy and opening a new option for the next generation of H\textsubscript{2}S therapy. Here, we provide a comprehensive overview of intelligent polymeric H\textsubscript{2}S delivery systems and their therapeutic potentials towards cardiovascular diseases, inflammatory diseases, tissue defect, cancers, bacteria-associated diseases, ischemic diseases, diabetes and neurodegenerative diseases.

In recent years, the development of advanced bioimaging technology provides great opportunities for establishing intelligent polymeric H\textsubscript{2}S delivery systems that integrate diagnosis, treatment, and real-time monitoring of various chronic diseases. We hope that visualized H\textsubscript{2}S therapy could be realized by deep deconstruction of the pathological microenvironments, rational design of polymer architectures and elaborate integration of specific functional moieties. However, the development of intelligent polymeric H\textsubscript{2}S delivery systems is still in the infancy stage, and there is still a long way to achieve their clinical translation. Accurate diagnosis depends on the discovery and analysis of more relevant biomarkers. Effective treatment also requires a deeper study on the dose-dependent biological effects of H\textsubscript{2}S. We are convinced that the incorporation of precision medicines and H\textsubscript{2}S therapy would promote the revolutionary development of the next generation of therapies.

In addition to their potential in precision medicines, some issues are also worth noting. The understanding of H\textsubscript{2}S biology is constantly being updated in recent years, which may lead to breakthroughs in the treatment of some chronic diseases, such as neurodegenerative diseases, diabetes and imbalance of gut microbiota. The further expansion of H\textsubscript{2}S therapy also depends on the development of H\textsubscript{2}S donors with improved biosafety and optimized activating mechanisms. In addition, since other RSS\textsubscript{s} (such as persulfide and H\textsubscript{2}Se [187]) and their selenium analogue such as H\textsubscript{2}Se [188] have also been proven to exert specific regulating effects in various physiological processes, precision medicine of these RSS\textsubscript{s} therapies is worthy of further exploration.

CRediT authorship contribution statement

Fan Rong and Tengjiao Wang contributed equally. Fan Rong: Writing - Original Draft, Visualization. Tengjiao Wang: Conceptualization, Investigation, Writing - Original Draft, Funding acquisition. Qian Zhou: Writing - Review & Editing. Haowei Peng: Writing - Original Draft. Jingtian Yang: Writing - Review & Editing. Quli Fan: Supervision, Peng Li: Conceptualization, Supervision, Funding acquisition, Writing - Review & Editing, Project Administration.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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