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Review article

Intelligent polymeric hydrogen sulfide delivery systems for therapeutic applications

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ABSTRACT

Hydrogen sulfide (H_2S) 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_2S are highly associated with its concentrations. At relatively low concentration, H_2S shows beneficial functions. However, long-time and high-dose donation of H_2S would inhibit regular biological process, resulting in cell dysfunction and apoptosis. To regulate the dosage of H_2S delivery for precision medicine, H_2S delivery systems with intelligent characteristics were developed and a variety of biocompatibility polymers have been utilized to establish intelligent polymeric H_2S delivery systems, with the abilities to specifically target the lesions, smartly respond to pathological microenvironments, as well as real-timely monitor H_2S 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_2S delivery systems in cardiovascular therapy, inflammatory therapy, tissue regenerative therapy, cancer therapy and bacteria-associated therapy. Strategies for precise H_2S therapies especially imaging-guided H_2S theranostics are highlighted. Since H_2S donors with stimuli-responsive characters are vital components for establishing intelligent H_2S delivery systems, the development of H_2S donors is also briefly introduced.

1. Introduction

Hydrogen sulfide (H_2S) 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_2S 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_{ATP}) channels [1], suppression of nuclear factor κB (NF-κB) signaling [2] and regulation of cellular redox [3]. Thus, H_2S was identified as one of the endogenous gaseous signaling molecules (generally called "gasotransmitter") like nitric oxide (NO) and carbon monoxide (CO) [1,4]. Notably, H_2S is a weak acid and there is a dynamic equilibrium among H_2S, hydrosulfide ion (HS^-) and sulfide ion (S^{2-}) under physiological conditions [5] (in which S^{2-} is unlikely to be involved in the biological regulating effects as recent study suggested that S^{2-} may be not a relevant species in water [6]). It's still unclear whether H_2S or the HS^- or both contribute to the observed bioactivities [7]. In this review, the term "H_2S" will refer to the equilibrium mixture of these total reactive sulfur species (RSSs).

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Abbreviations

3-MST 3-Mercaptopyruvate sulfurtransferase
ACS14 2-Acetyloxybenzoic acid 4-(3-thioxo-3*H*-1,2-dithiol-5-yl) phenyl ester
ADSC Adipose-derived stem cell
ADT Anetholedithiolethione
ALG-CHO Partially oxidized alginate
AML Anetholedithiolethione-loaded H_2S delivery magnetic nanoliposome
APTC 2-Aminopyridine-5-thiocarboxamide
BSA Bovine serum albumin
BSA@MnS Bovine serum albumin modified γ-phase MnS nanotheranostic
CA Cardiac arrest
CAP-w-FC Diallyl trisulfide loaded gelatin capsules with foaming ability
CBS Cystathionine-β-synthase
CD44 Cluster of differentiation 44
c-di-GMP Cyclic-diguanylate-guanosine monophosphate
C-FE 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-γ-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 triamine pentaacetic acid
DTT Dithiolthiones
E. coli *Escherichia coli*
EPR Enhanced permeability and retention
ESIPT Excited-state intramolecular proton transfer
GSH Glutathione
GYY4137 Morpholin-4-ium-4-methoxyphenyl(morpholino) phosphinodithioate
H_2S Hydrogen sulfide
HA Hyaluronic acid
hMSC Human bone marrow stromal cell
HS^- Hydrosulfide 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_{ATP} channel Adenosine triphosphate-sensitive potassium channel
LBL Layer-by-layer
L-Cys L-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-κB Nuclear factor κB
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 Photoacoustic
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_2S donor
PTT Photothermal therapy
RA Rheumatoid arthritis
ROS Reactive oxygen specie
RSS Reactive sulfur specie
S. aureus *Staphylococcus aureus*
S^{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-α Tumor necrosis factor alpha
UC Ulcerative colitis
US Ultrasound
UV Ultraviolet
VEGF Vascular endothelial growth factor
α-CHCA α-Cyano-4-hydroxycinnamic acid

Generally, H_2S is endogenously synthesized by a number of enzymes responsible for L-cysteine (L-Cys) metabolism, including cystathionine-γ-lyase (CSE), cystathionine-β-synthase (CBS), 3-mercaptopyruvate sulfurtransferase (3-MST), and could also be produced through some non-catalytic routes [8]. Owing to its high lipophilicity, H_2S could freely penetrate biological membranes without any specific receptor mediation [4,9]. H_2S is also involved in several intracellular chemical reactions, which are important basis of its biological effects [8]. For example, H_2S could chelate with metalloproteins or induce *S*-persulfidation of cysteine residues, which in turn modulates protein activities [10,11]. In addition, H_2S participates in many intracellular redox reactions including the reduction of disulphide bonds and acts as antioxidant to scavenge free radicals [8]. Physiological concentration of H_2S usually shows a typical "protective" effect that could protect cells and tissues from harmful oxidative injures, through a combination of antioxidant and antiapoptotic signals [12]. In cardiovascular system, H_2S 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_2S serves as synaptic modulator and neuroprotectant [12]. H_2S also promotes endothelial cell proliferation and angiogenesis [15,16], thus enhancing tissue regeneration. In addition, H_2S shows complex effects in inflammation [17] and cancers [2], and

involves in some diseases such as Alzheimer's disease [18], Parkinson's disease [19] and glycometabolic disorders [20]. It should be noted that H_2S follows dose-dependent biological effects. Physiological low concentration of H_2S has beneficial and cytoprotective effects. When the biosynthesis of H_2S was inhibited, or the administration of H_2S is too excessive, the equilibrium of physiological RSSs would be changed drastically, and the stimulatory effect of H_2S would be superseded by an inhibitory effect [21].

The widespread discovery of the physiological effects of H_2S has led to the development of H_2S therapies. Inhalation therapy is the most conspicuous method for delivering exogenous H_2S and has shown protective effect against ventilator-induced lung injury [22]. However, the delivery rate and dosage of gaseous H_2S need to be strictly controlled, and the short half-life of H_2S limits the therapeutic delivery to deep lesions [23]. Compounds that could release H_2S (also known as H_2S donors) have become useful chemical tools for studying of H_2S therapies. Inorganic sulfide salts are the simplest H_2S donors and the most frequently used alternatives to gaseous H_2S during research, but they release H_2S immediately once in aqueous solution, which is difficult to mimic endogenous H_2S. To achieve controlled H_2S delivery, a series of H_2S 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_2S 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_2S 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_2S delivery systems, mainly by physically encapsulating or chemically conjugating H_2S 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_2S delivery systems is that the H_2S 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_2S donors.

More recently, against the dose-dependent therapeutic effects of H_2S, researchers have dedicated themselves to the development of H_2S 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_2S 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_2S in a controlled manner could be endowed. The strategy to induce multistage *in vivo* reaction is promising for achieving precise and efficient H_2S therapy. Moreover, the utilization of materials with imaging capability (*e.g.*, conjugated polymer) make it possible for imaging guided H_2S theranostics, to real-time monitor H_2S release and lesion condition.

In this review, we overview the recent advances of intelligent polymeric H_2S 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_2S.

2. H_2S donors categorized by different activation mechanisms

H_2S donor has become a useful tool for studying therapeutic effects of H_2S and an important basis for constructing intelligent polymeric H_2S delivery systems. Thus, we discuss the classification of H_2S donors first, mainly focusing on the stimuli-responsive mechanisms and the application scopes of different donors (Fig. 1). In addition, polymeric H_2S donors have been actively explored for controlled H_2S delivery, showing enhanced stability and bioavailability over their small molecular counterparts [74–76]. In this part, the methods for incorporating H_2S donors with polymeric carriers would also be discussed.

2.1. Sulfide salts as direct sources of H_2S

Sulfide salts, such as Na_2S and NaHS, are the simplest H_2S donors and currently the most used alternatives to evaluate the therapeutic potential of exogenous H_2S. Though generally classified as H_2S donors, these sulfides salts are direct sources of H_2S [24]. Once dissolved in water, they would hydrolyze and generate an equilibrium between H_2S, HS^- and S^{2-} immediately, and afterward a rapid volatilization of H_2S would occur. Since high-dose administration of sulfide salts is usually required for studying the biological effects of H_2S, it would cause the initial concentration of H_2S higher than physiological level and then decrease rapidly [24]. This is contradictory to the strictly modulated production of endogenous H_2S, usually cannot sustain therapeutic effects and may induce side effects. In order to achieve controlled H_2S delivery, polymeric carriers could be employed to encapsulate these sulfide salts [57,77]. Unlike Na_2S and NaHS, some other sulfide salts (MnS, FeS, ZnS, etc.) have poor water solubility, but could hydrolyze slowly to generate H_2S 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_2S.

2.2. Hydrolysis-activated H_2S donors

Hydrolysis-activated H_2S donors are able to release H_2S spontaneously in aqueous solution. Lawesson's reagent and its derivatives are phosphorodithioate containing H_2S donors with slow releasing property. Among them, the most well-known is morpholin-4-ium-4-methoxyphenyl(morpholino)phosphinodithioate (GYY4137), which has been utilized in many studies about the physiological effects of H_2S [80]. Another type of phosphorodithioate containing H_2S donor is JK donors possessing a unique acidic pH accelerated H_2S releasing behavior [81]. To further regulate H_2S delivery, phosphorodithioate containing H_2S donors were generally incorporate with polymeric systems through physical encapsulation [32,47,55]. Dithiocarbamates could also be activated by acidic pH to release H_2S, which have been incorporated with polymeric carriers for therapeutic application [34]. These acid pH-responsive H_2S 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_2S donors

Many H_2S donors could be reduced by thiol containing bioactive compounds such as cysteine (Cys) and glutathione (GSH) to release H_2S. These donors are particularly suitable for controlled delivery of H_2S to the pathologically redox microenvironments. *N*-(benzoylthio)benzamides developed by Xian et al. [82] undergo a thioester exchange reaction to form N-SH intermediates, which further react with these compounds to produce H_2S. *S*-aroylthiooximes (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_2S. The H_2S releasing profile of the above two donors could be regulated by tuning the substituents 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_2S donors through postpolymerization approaches [28,73]. Naturally occurring polysulfides, represented by diallyl trisulfide

Table 1
Summary of intelligent polymeric H_2S delivery systems.

Polymeric carriers	H_2S donors	Intelligent abilities	Therapeutic potentials	References
Large porous microspheres	ACS14	Lung accumulation	Relief of pulmonary arterial hypertension	[39]
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 transporting, brain-targeting, MRI	Cerebral and myocardial protection after cardiac arrest	[44]
Polymeric hydrogel	α-Thioetherketone	UV responsive	Antithrombosis	[45]
SDS and SBC loaded gelatin capsule	DATS	*In 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	SPRC	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	Arylthioamide	Thiol responsive	Angiogenesis	[51]
Polymeric micelles	ADT	N/A	Angiogenesis	[52]
Polycaprolactone nanofibers	JK1	pH responsive	Wound healing	[32]
Hyaluronic acid hydrogel	JK1	pH responsive	Wound healing	[53]
Sodium alginate sponge	JK1	pH responsive	Wound healing	[54]
Silk fibroin porous scaffolds	GYY4137	N/A	Bone tissue engineering	[55,56]
Phase-change material-loaded wound dressing	Na_2S	Thermal responsive	Diabetic wound healing	[57]
Enzyme-functionalized albumin	Thiosulfate cyanide sulphurtransferase	*In-situ* enzymic H_2S generation	Cardiac tissue repair	[58]
PEG-cholesteryl conjugate	Trisulfide	Thiol responsive	Anticancer effects	[59]
Polymeric micelles	SATO	Cys responsive	Anticancer effects	[28]
Magnetic nanoliposomes	ADT	Magnetic guided, US and MRI dual model imaging	Anticancer effects	[60,61]
BSA modified MnS nanoparticles	Metastable-phase MnS	pH responsive, MRI imaging	Anticancer effects	[62]
FeS embedded BSA nanoclusters	FeS	pH responsive, MRI imaging	Anticancer effects	[63]
F127 nanoparticles	Polysulfide	GSH responsive, ratiometric PA imaging	Triple-negative breast cancer treatment	[35]
PEG-modified conjugated polymer nanoparticles	Polysulfide	GSH responsive, NIR IIfluorescence 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	SATO	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 responsive	Ameliorating cellular oxidative stress	[69]
Aggregates of mPEG and cholesteryl conjugates	Trisulfide	Thiol responsive	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]
Polycaprolactone microfibers	*N*-(benzoylthio)benzamide	Thiol responsive	Protecting cell from oxidative damage, cells proliferation	[72]
Polymeric micelles	Arylthioamide	Thiol responsive	Spatiotemporally confined cell signaling	[29]
Polymeric nanoparticles	SATO	Cys responsive, bioimaging	N/A	[73]

(DATS), undergo a thiol-promoted cleavage of polysulfide bond and form hydrosulfide intermediates, which further react with thiol containing compounds to produce H_2S [84]. Polysulfide linkers have been introduced to the backbones or side chains of polymers to enable controlled H_2S delivery for various biological applications [59,69,70,85]. Synthetic acyl perthiols are also S-S bond containing H_2S donors [24] and have been modified on the end group of polymers [86]. In addition, arylthioamides could release H_2S 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_2S donors upon exposure to thiol containing compounds [88]. In comparison with these thiol containing compounds specific H_2S 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_2S, showing unique advantage in hypoxia conditions [89].

2.4. Enzyme-activated H_2S donors

Utilizing enzyme-activated H_2S donors has many advantages for targeted H_2S delivery to enzyme-overexpressed microenvironments of lesions. Trimethyl lock group containing H_2S 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_2S. In addition, the bis (4-nitrobenzyl)sulfanes could be reduced by nitroreductase and produce hydroxylamino- or amino-aryl derivatives to generate geminal dithiols through self-immolation, which could be further hydrolyzed to generate H_2S [90]. Dithiolthiones (DTTs), represented by anetholedithiolethione (ADT), were generally considered as hydrolysis-activated H_2S donors [91]. However, recent studies have revealed that H_2S release of ADT could occur through an enzymatic process in the presence of liver microsomes and reduced nicotinamide adenine dinucleotide

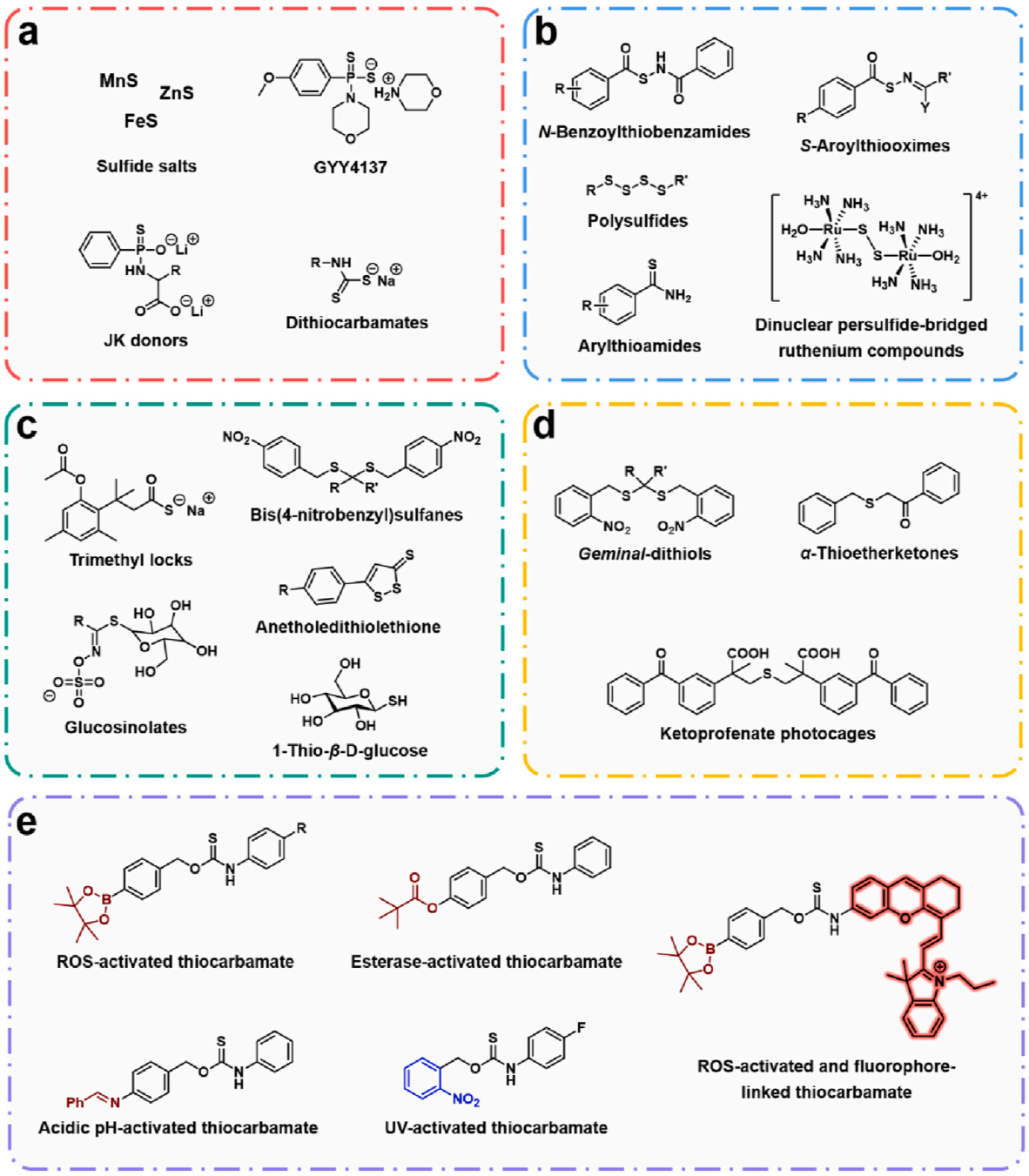

Fig. 1. Chemical structures of H_2S donors. (a) Hydrolysis-activated H_2S donors. (b) Thiols-activated H_2S donors. (c) Enzyme-activated H_2S donors. (d) Light-activated H_2S donors. (e) COS precursors as H_2S donors.

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_2S donors [94]. A more recent study demonstrated that 1-thio-β-D-glucose could act as a H_2S/H_2O_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_2O_2 to generate sulfenic acids (RSOH) that could react with H_2S for persulfidation more efficiently [95].

2.5. *Light-activated H_2S donors*

In recent years, strategies using exogenous stimuli as triggers to regulate H_2S delivery are being actively developed. Among these exogenous stimuli, light could trigger the H_2S release without perturbing native biochemical process, minimize off-target effects though direct spatiotemporal control, showing great advantages in the tissue-specific delivery of H_2S [24]. Light-activated H_2S donors usually contain photoremovable protecting groups, which could be deprotected under light irradiation at appropriate wavelength to release H_2S. *o*-Nitrobenzyl caged geminal dithiols [96] and ketoprofenate caged H_2S donors [97] are reported to release H_2S under ultraviolet (UV) light. In addition, α-thioetherketones are UV light-activated prodrugs of thioaldehydes, which could further release H_2S in the presence of amines [45].

p-Hydroxyphenacyl photocaged H_2S donors could respond to visible light to release H_2S [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_2S donors are mostly activated by UV or visible light with short wavelength, showing poor tissue penetration ability and potential injury to normal tissues. Thus, H_2S 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_2S donors

COS could be quickly hydrolyzed to H_2S by carbonic anhydrase that is ubiquitously distributed in human tissues. The connection between COS and H_2S has led to the study on COS generating compounds as H_2S donors for biological applications. Matson et al. reported that *N*-thiocarboxyanhydride (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 thiocarbamate/thiocarbonate could response to reactive oxygen species (ROSs) to activate self-immolative process to generate H_2S *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 pivaloyloxymethyl 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_2S 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-amplified depolymerization to release multiple equivalents COS in response to per equivalent of H_2S [113].

3. Therapeutic applications of intelligent polymeric H_2S delivery systems

3.1. Cardiovascular therapy

H_2S has demonstrated critical effects on cardiovascular system [114]. Study on isolated blood vessels exhibited that H_2S 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_2S 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_2S could act as a potent antioxidant, and up-regulate the GSH production to protect myocardial cells from oxidative damage together [12]. In addition, H_2S 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_2S delivery for treating cardiovascular diseases. Xian et al. developed a series of controllable H_2S donors and evaluated the cardioprotective effects against MI-R injury [81,116,117]. Compared with small molecular H_2S donors, nanosized polymeric H_2S 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_2S intracellularly and prevent cardiomyocyte apoptosis in an *in vitro* ischemia model, more effective than NaHS and ADT-OH [43]. Sun et al. loaded the polysulfide H_2S 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/cardiopulmonary 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_2S is a potent regularizing factor that could significantly reduce the myocardial infarcted size and improve survival rate in acute myocardial infarction [119,120]. Liu et al. reported a stem cell loaded conductive hydrogel with H_2S delivery capacity for myocardial infarction treatment (Fig. 2a) [42]. ALG-TA-APTC copolymer was formed by grafting H_2S donor 2-aminopyridine-5-thiocarboxamide (APTC) and tetraaniline (TA) oligomer onto partially oxidized alginate (ALG-CHO), for endowing H_2S 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_2S 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_2S 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_2S 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_2S 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_2S could be delivery to the lung through inhalation, it is difficult to mimic slow and constant H_2S release *in vivo* in this way. To overcome this problem, Zhang et al. developed a H_2S 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-thioxo-3*H*-1,2-dithiol-5-yl) phenyl ester (ACS14), a H_2S donor comprising of a dithiolethione 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_2S 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_2S. *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

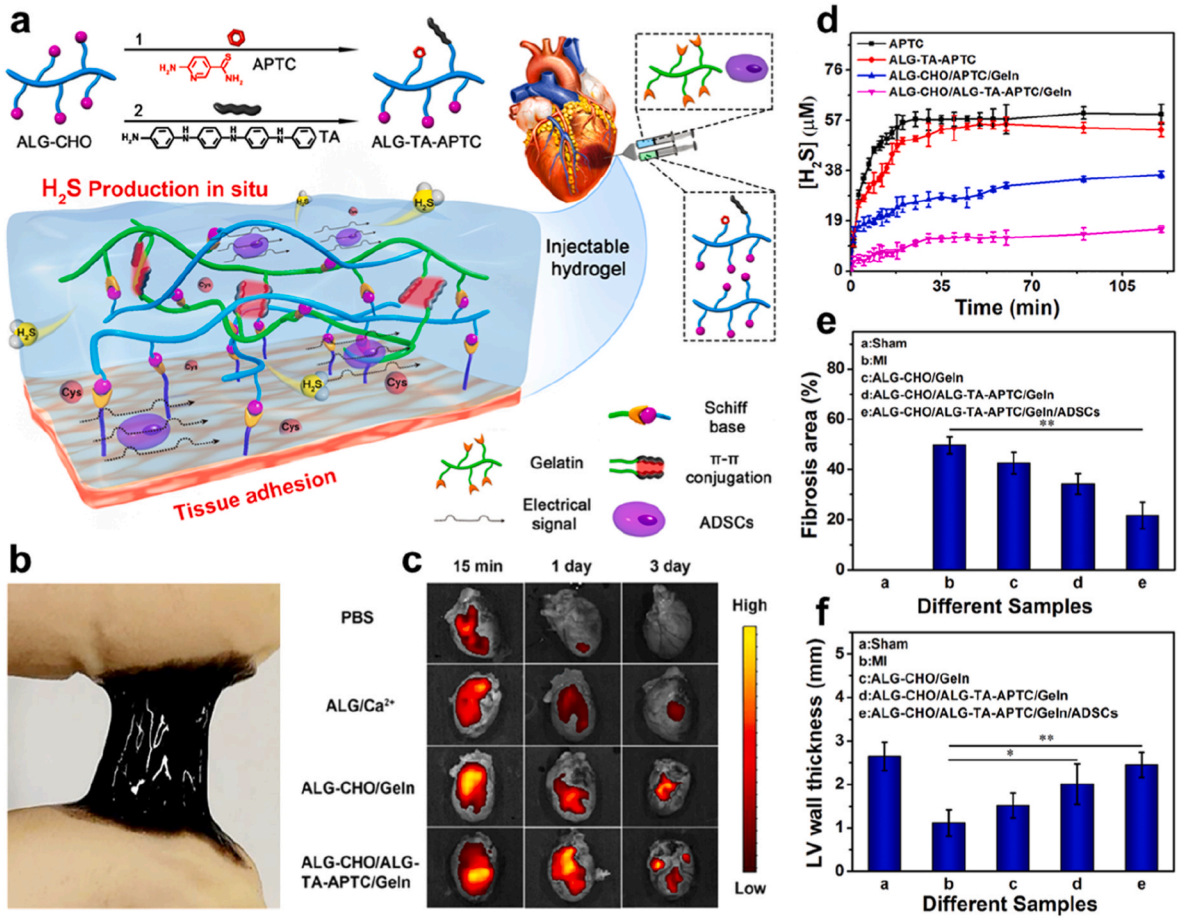

Fig. 2. Structure, preparation, and therapeutic properties of H_2S delivery conductive hydrogel. (a) Scheme illustrating the formation of ADSC-loaded H_2S delivery conductive hydrogel. (b) Photograph showing the potent adhesive property of ALG-CHO/ALG-TA-APTC/Geln hydrogel. (c) Stem cell retention in the MI zone after injection. (d) H_2S-releasing profile *in vitro*, in which macromolecular H_2S prodrug embedded hydrogel showed the slowest H_2S release. (e) Fibrosis area and (f) LV wall thickness after treatment of different hydrogels (* indicates a significant difference between the experimental group and the MI group, $^*p < 0.05$, $^{**}p < 0.01$) [42]. Copyright 2019, American Chemical Society.

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_2S 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_2S (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 μmol/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. 3f) and thrombus weight (Fig. 3g). To evaluate the *in vivo* therapeutic effects of the H_2S 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_2S 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_2S in inflammation is complex. Studies have shown that H_2S exerts anti-inflammatory effects by reducing the expression of many pro-inflammatory cytokines, chemokines and enzymes to inhibit the activation of NF-κB pathways, suppressing the leukocyte adhesion and recruitment, driving macrophage differentiation towards the anti-inflammatory M2 phenotype, and inducing apoptosis in neutrophils [124]. H_2S could also reduce the formation of edema [127] and relieve pain caused by inflammation [128]. It has been reported that H_2S donor-conjugated non-steroidal antiinflammatory drugs (NSAIDs) exhibit improved efficacy and reduced toxicity compared with the parent NSAIDs [129]. However, H_2S could also exhibit

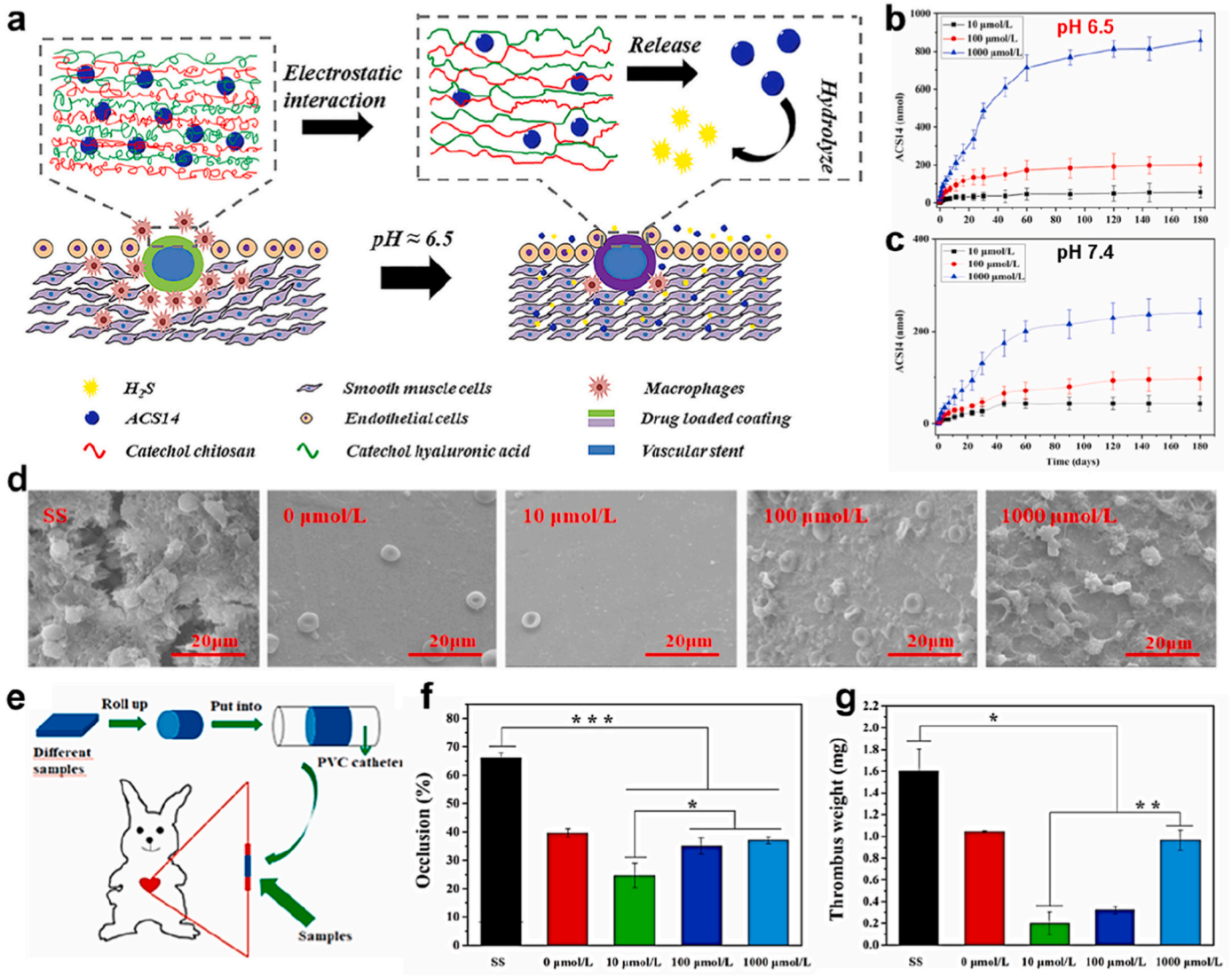

Fig. 3. Preparation of H_2S delivery coating and its therapeutic effects as cardiovascular implant. (a) Intelligent coating release H_2S in a weakly acidic for regulating vascular remodeling. H_2S donor release profiles in (b) pH 6.5 and (c) pH 7.4. (d) Coagulation of different samples with varying content of H_2S donor after *ex vivo* experiments on isolated arteries and veins of rabbits. (e) Schematic diagram of the *ex vivo* experiments. (f) Blood flow obstruction rate and (g) thrombus weight after *ex vivo* experiment (n = 3, $*p < 0.05$, $**p < 0.01$, $***p < 0.001$) [41]. Copyright 2021, Elsevier Ltd.

pro-inflammation effects on a number of pathological processes [130]. The reduced inflammatory response could be observed after treatment of H_2S synthase inhibitors [131]. Hasegawa et al. reported that PEG-ADT conjugate and ADT-containing micelle capable of delivering H_2S could enhance the pro-inflammatory cytokine TNF-α [49,50]. The contradictory effects of H_2S 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_2S 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_2S modulator that could stimulate H_2S generation *in vivo via* CSE/H_2S signaling pathways, named SPRC@PLA [48]. After subcutaneous injection of SPRC@PLA, a sustained elevation of plasma H_2S concentration was observed, different with the rapid production and fast decrease of H_2S by injecting free SPRC. Further research showed that SPRC@PLA could increase the expression of CSE to enhance the generation of H_2S, 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_2S delivery hydrogel for IDD treatment [47]. JK1, a H_2S donor that could undergo an acidic pH-accelerated hydrolysis to release H_2S, 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_2S *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 leucocytes to the vascular endothelium and their migration to the inflamed bowel. The garlic-derived natural H_2S donor, DATS, exhibited anti-inflammatory effects in both *in vitro* and *in vivo* studies [132,133]. However, due to its poor water solubility, appropriate administrating 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

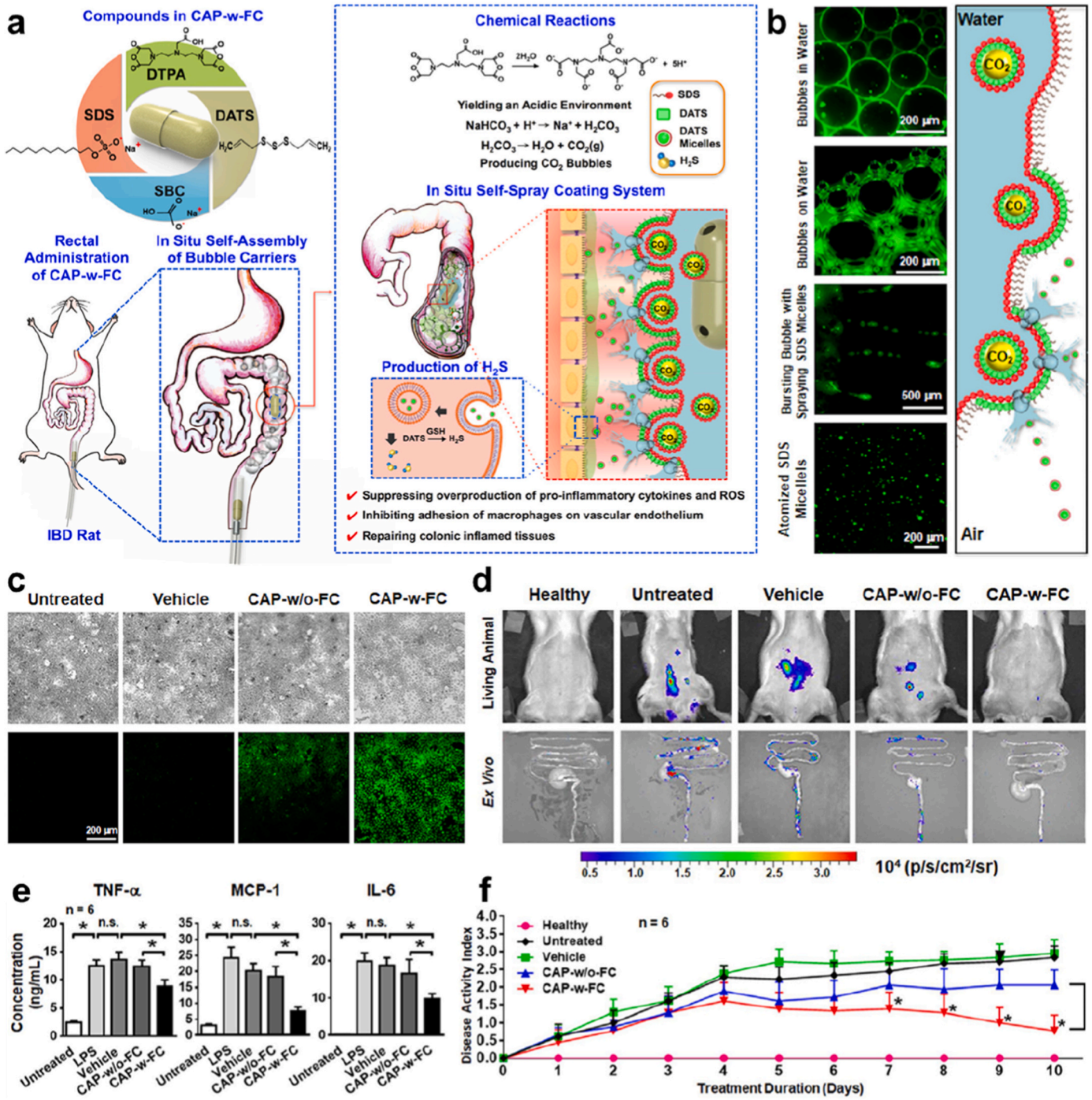

Fig. 4. Formulation, mechanism of action of *in situ* self-spray coating system, as well as its anti-inflammation effects *in vitro* and *in vivo*. (a) Schematic illustrations of dispersion of a coating of DATS-loaded micellar particles on luminal surface of colon to repair colonic inflamed tissues. (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 H_2S 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-a, 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.

(Fig. 4a). CAP-w-FC was rectally administered to rat with UC. After the gelatin capsule was dissolved in the intestinal fluid, the acid initiator reacted with water rapidly to yield an acidic environment, inducing decomposition of foaming agent SBC to produce CO_2 bubbles. The bubbles were stabilized immediately by a self-assembled nanofilm of SDS, which subsequently served as a carrier for hydrophobic DATS. 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_2S fluorescence probe showed that DATS was uniformly internalized by colonic epithelial cells and converted to H_2S, 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_2S 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 K_{ATP} channel, to facilitate angiogenesis, which is vital to the tissue regenerative process [16]. Meanwhile, the inflammation modulating and oxidative stress suppressing abilities of H_2S also contribute to its promotional role in tissue regeneration [53,72]. In recent years, intelligent polymeric H_2S 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_2S 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_2S 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_2S in cell signaling pathways [134]. Thus, the angiogenesis effect is expected to be amplified by establishing H_2S and NO co-delivery systems. Lee et al. reported a H_2S and NO co-delivery nanoparticle formed by the self-assembly of thiobenzamide-functionalized methoxy poly(ethylene glycol-*b*-lactic-*co*-glycolic-*co*-hydroxymethyl propionic acid), loading *N*-diazeniumdiolated 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_2S 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_2S 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_2S delivery polycaprolactone (PCL) fibrous material as wound dressing [32]. When lowered the pH from 7.4 to 6.0, the faster H_2S 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_2S 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_2S 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 dimeters of the SA-based sponge were barely changed after swelling, showing excellent dimension stability to avoid wound laceration. H_2S 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_2S exhibits complex effects on cancer [2]. H_2S could act as a bioenergetic stimulator to promote glucose uptake and glycolysis efficiency to provide the energy of cancer cells. Furthermore, H_2S 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_2S has been demonstrated in numerous types of cancer cells, which has also become potential targets in anticancer therapy to develop H_2S-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_2S were performed, anticancer effects are usually observed. The anticancer property of H_2S could be partly attribute to the uncontrolled cellular acidification caused by the H_2S-mediated glycolysis enhancement [2]. In addition, H_2S could suppress the cell signaling pathways that are abnormally activated during cancer development, such as NF-κB pathways [143]. H_2S 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_2S seems to work specifically on cancer cells, with no obvious impacts on normal cells. In 2017, Matson et al. reported a H_2S 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_2S delivery systems should be formulated based on the pathological conditions of tumor

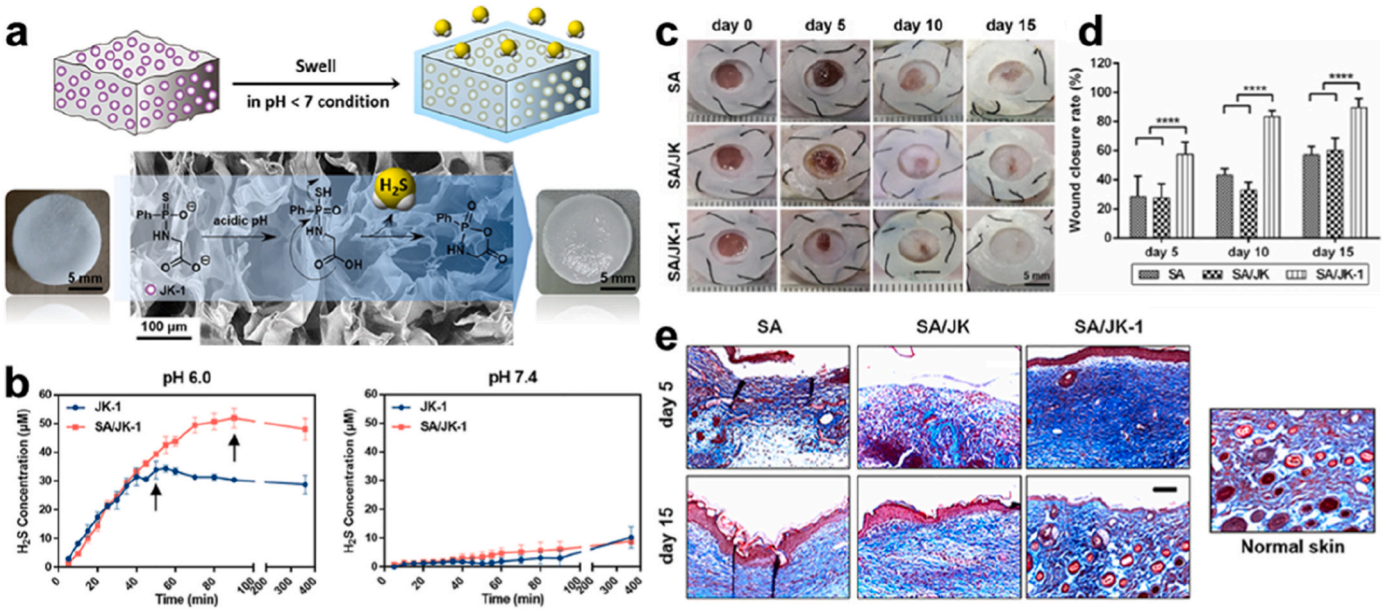

Fig. 5. Acidic pH accelerated H_2S release from the SA sponge and its promoting effect on wound healing. (a) Diagram illustrating the pH dependent H_2S delivery SA sponge dressing. (b) H_2S release profiles of H_2S donor loaded SA (SA/JK-1) and donor alone (JK-1) in pH 6.0 and pH 7.4, in which acidic pH accelerated H_2S generation was observed. (c) Wound healing property of sponge dressing in mice model, in which SA/JK represented the control sponge loaded with a JK compound that cannot release H_2S. (d) Closure rate of wounds, $^{****}p < 0.0001$, n = 4–6. (e) Images showed the representative collagen deposition of wounds [54]. Copyright 2020, Elsevier Ltd.

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 44 (CD44), 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 H_2S donor-doxorubicin conjugate developed by Riganti 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 H_2S delivery by modulating macromolecular architectures. A TME responsive zwitterionic H_2S 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 H_2S, 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 H_2S 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 H_2S delivery system.

In addition to the targeted and TME responsive polymeric H_2S delivery systems, the utilization of external stimuli (light and magnetic field, *etc.*) to regulate H_2S 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 H_2S and Mn^{2+} ions simultaneously [62]. The released Mn^{2+} could not only act as contrast agent for MRI, but also catalyze Fenton-like reaction to convert H_2O_2 into toxic hydroxyl radical at tumor tissues, showing synergistic anticancer effects with H_2S. Besides, Gu et al. developed a ADT-loaded H_2S 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 H_2S 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 H_2S bubbles could sensitize the ultrasound (US) imaging signal, to monitor the dynamic process of intratumoral H_2S production (Fig. 6c). Furthermore, therapeutic US intensity could disrupt the H_2S bubbles and enhance the physical bombing effect on tumors. The intratumorally generated high concentration of H_2S could rapidly travel through deep tumor membrane barrier to enhance antitumor effect. In their following research, the mechanisms of tumor cell death induced by H_2S bubbling were elucidated [61]. The gradual generated H_2S 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

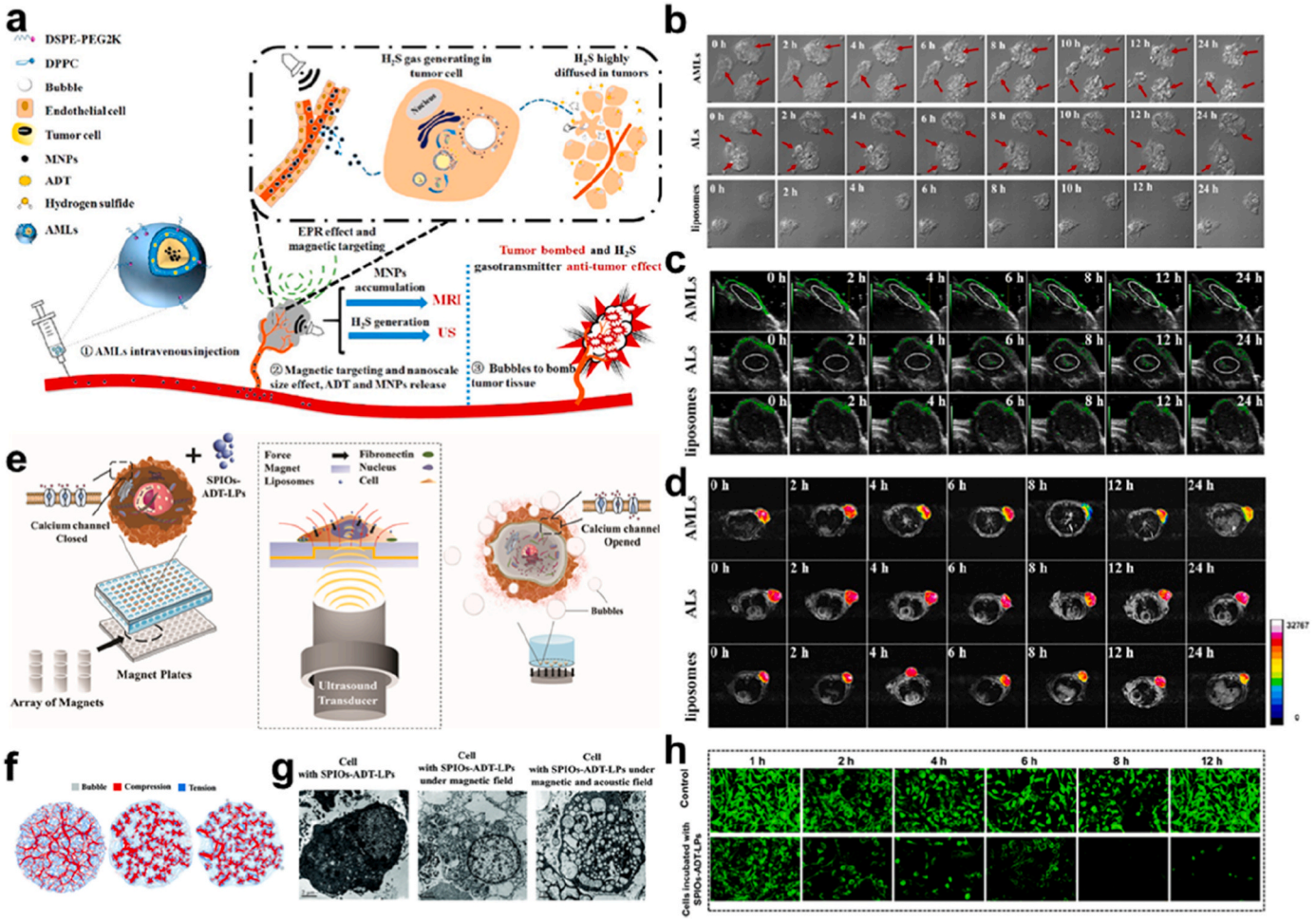

Fig. 6. Anticancer effects of AMLs through magnetic targeting, H_2S bubbling, as well as MRI and US dual imaging monitoring. (a) Scheme illustrating the composition of AML and its synergetic H_2S generation, tumor bombing and MRI/US dual-model imaging theranostic mechanisms. (b) Cellular morphology changes 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.

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_2S delivery systems. Our group proposed a ratiometric photoacoustic (PA) monitored and TME initiated H_2S therapy for the detection and treatment of triple-negative breast cancer (TNBC) [35]. Ratiometric PA probe cyanine (CY) and polysulfide H_2S donor (PSD) were encapsulated in self-assembled polymeric nanoparticle formed by amphipathic block polymers (Pluronic F127). The thiol abundant TME triggered PSD to release H_2S, 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_2S 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_2S delivery systems in our following research [64]. A PEG-grafted conjugated polymer (CP-PEG) was synthesized, which was then employed for loading polysulfide H_2S donor 2,2′-dipyridyl tetrasulfide (Pry-Ps) to prepare H_2S 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. 7h) for cancer cell killing and simultaneous NIR-II fluorescence (Fig. 7e) for tracing the tumor and monitoring the entire therapeutic process (Fig. 7g). More importantly, due to the generation of H_2S 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.

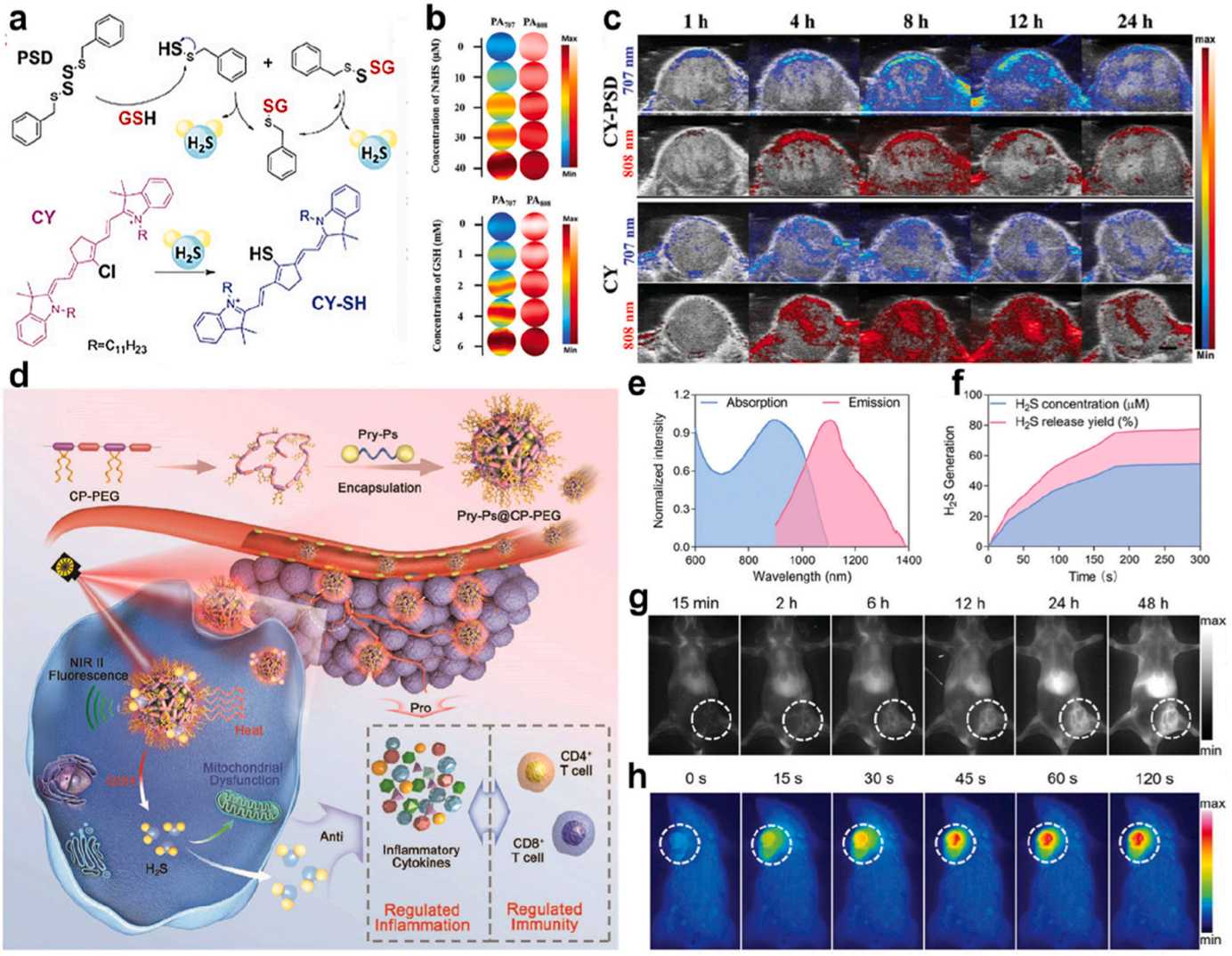

Fig. 7. Polysulfide-loaded polymeric H_2S delivery systems for PA or NIR-II fluorescence guided cancer therapeutics. (a) Mechanism of H_2S generation from PSD with GSH and response process of CY to H_2S. (b) PA signal changes for CY nanoparticles (15 μM) at 707 and 808 nm with different concentrations of NaHS (0–40 μM) (above), as well as PA signal changes of CY-PSD nanoparticles (15 μM) at 707 and 808 nm with GSH (0–6 mM) (below). (c) PA imaging of H_2S in tumor-bearing mice before and after systemic administration of CY-PSD and CY nanoparticles [35]. Copyright 2020, Wiley-VCH. (d) Schematic illustration of the NIR-II fluorescence traced inflammation nanoregulator for dual-functional H_2S and photothermal therapy with modulated immunogenicity. (e) The emission and absorption spectra of Pry-Ps@CP-PEG. (f) GSH-activated H_2S releasing kinetics of Pry-Ps@CP-PEG (40 mg L^{-1}). (g) The NIR-II fluorescence imaging of 4T1-tumor-bearing mice with Pry-Ps@CP-PEG *via* intravenous injection (λ_{ex} = 808 nm), in which white circles represent the injection site of tumor cells on breast pad. (h) The thermal imaging of tumor region (white circles) [64]. Copyright 2021, Wiley-VCH.

3.5. Bacteria-associated therapy

Compared with H_2S generated by mammals, bacteria derived H_2S 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_2S and generate metabolic energy [148,149]. H_2S-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_2S 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_2S seems not so definite as NO and CO. Indeed, high concentration of H_2S (close to millimolar level) is able to induce severe oxidative damage to bacteria [159]. But such high concentration of H_2S would also induce cytotoxicity and inflammation to mammals [8]. Therefore, H_2S is generally not considered to be potential antibacterial agent like NO and CO. In contrast, H_2S could act as cytoprotective agent to protect bacteria from harmful oxidative stress imposed by antibiotics [150]. One major mechanism is H_2S-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_2S 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_2S, but the hydrogen polysulfanes (*e.g.*, H_2S_2 and H_2S_3) and other RSSs [162,163].

Nevertheless, recent advances about the interaction between H_2S and bacteria has led to the revaluation of its potential in antibacterial therapy. Though the direct antibacterial effect of H_2S is limited, H_2S 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_2S-releasing agents in the treatment of bacterial infections through anti-inflammatory pathways. In addition,

H_2S could exhibit excellent synergistic therapeutic effects towards hard-to-heal infected wounds. Recently, Du et al. developed a H_2S 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*-aroylthiooxime)] [P(Lys-*stat*-SATO)] to form the corona. In the presence of cysteine, the polymersome could generated H_2S gradually for up to 12 h (Fig. 8b). Intracellular generation of H_2S in normal human epidermal keratinocytes (NHEK) cells was also observed using a H_2S 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 H_2S 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 H_2S may act as an important biofilm disruptor at proper concentration. H_2S 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 H_2S 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 H_2S-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, H_2S is able to enhance the production of NO by inducting the expression of endothelial NO synthase and stimulating its activity [169,170]. Whether H_2S-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 H_2S in human body. H_2S in gastrointestinal tract is able to influence many physiological and pathophysiological processes [171]. On the one hand, the bacteria-derived H_2S 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 H_2S into the colon could influence the state of microbiota and promote harmonious coexistence of the bacteria with the

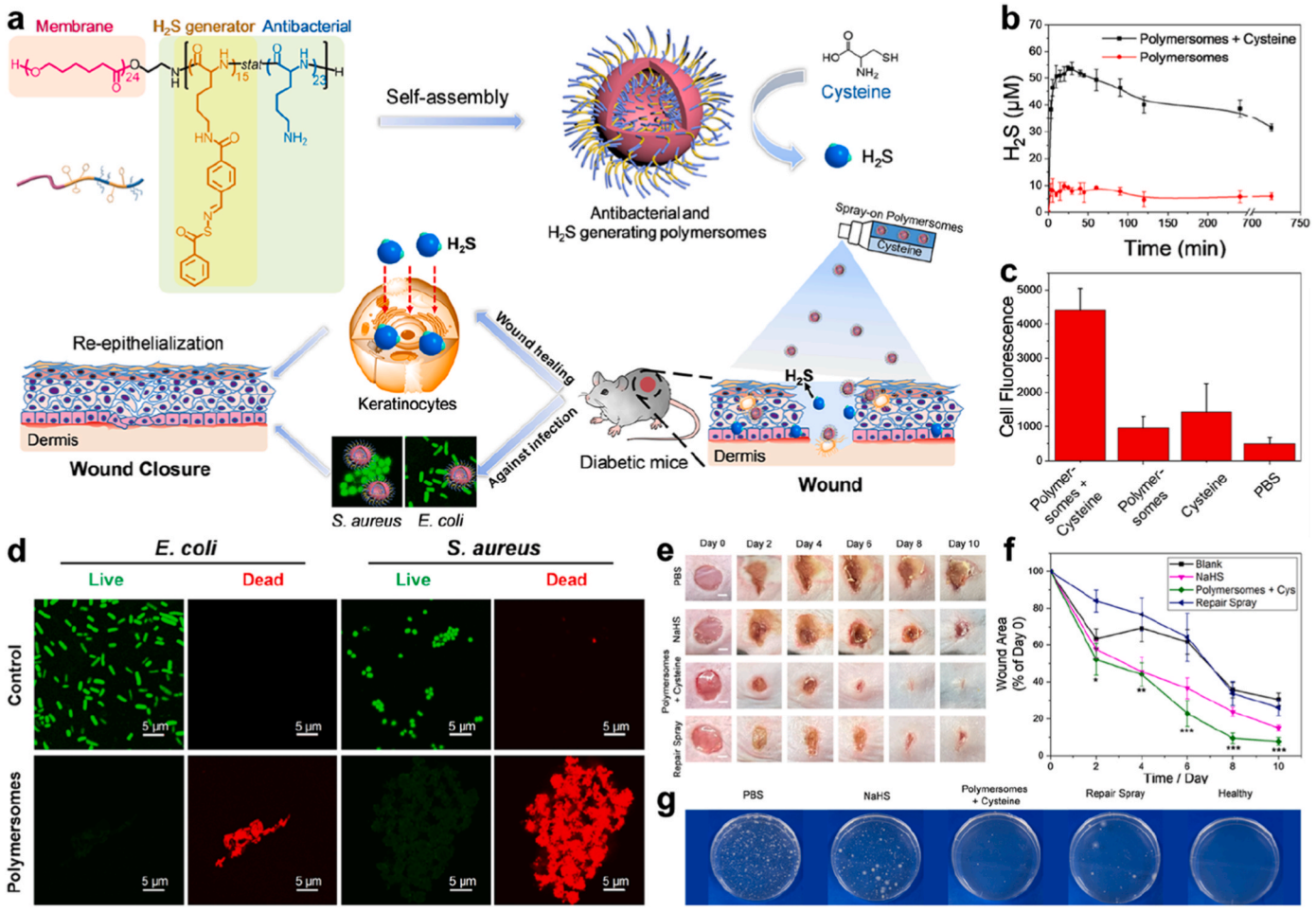

Fig. 8. H_2S delivery polymersome for infected diabetic wound healing. (a) Schematic illustration of the formation and mechanism of action of the H_2S delivery polymersome against infected diabetic wound. (b) H_2S releasing profiles of polymersome in the presence and absence of cystine. (c) Exogenous H_2S 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 revealed that bacteria in gastrointestinal tract have a profound impact on human health. Imbalance of gut microbiota will not only induce gastrointestinal tract disorder, but also lead to a number of diseases residing in organs far from the gut, such as obesity, allergy, type 1 diabetes, and autism [175]. Thus, delivery of exogenous H_2S 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_2S 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_2S releasing PLGA microparticles (DATS@MPs) through an oil-in-water single emulsion method [68]. Compared with free DATS, DATS@MPs enabled prolonged intracellular H_2S generation, favoring long-lasting therapeutic effects. After intramuscular injection to the ischemic limb of mouse model, DATS@MPs exhibited blood perfusion 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_2S 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_2S homeostasis plays an important role in diabetes [179]. H_2S could provide a protective effect on islet β cells from oxidative stress and elevated inflammations, to maintain the regular function of islet β cells [20]. In addition, H_2S 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_2S by means of polymeric carriers is worth exploring for alleviating diabetes and its complications. Noteworthy, the role of H_2S in diabetes is complicate, and H_2S could also affect insulin secretion of islet β cells by opening K_{ATP} channel [182]. Therefore, the role of H_2S at different stages of diabetes should be further explored to provide guidance for exogenous H_2S delivery.

In recent years, H_2S 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_2S could prevent oxidative stress through various pathways. In addition, more recent studies revealed that H_2S 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_2S delivery systems deserve to be explored for treatment of neurodegenerative diseases represented by Alzheimer's disease. Noteworthy, 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_2S, opening a promising option for the treatment of various human diseases. Since the biological effects of H_2S are highly associated with its concentrations, there is urgently needed to develop strategies for elaborately regulated H_2S delivery. To meet the requirements of precision medicines, intelligent polymeric H_2S 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_2S therapy. Here, we provide a comprehensive overview of intelligent polymeric H_2S 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_2S delivery systems that integrate diagnosis, treatment, and real-time monitoring of various chronic diseases. We hope that visualized H_2S 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_2S 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_2S. We are convinced that the incorporation of precision medicines and H_2S 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_2S 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_2S therapy also depends on the development of H_2S donors with improved biosafety and optimized activating mechanisms. In addition, since other RSSs (such as persulfide and H_2S_n [187]) and their selenium analogue such as H_2Se [188] have also been proven to exert specific regulating effects in various physiological processes, precision medicine of these RSSs 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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