Recent development of hydrogen sulfide-releasing biomaterials as novel therapies: a narrative review

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Key Words:
biomaterials; cardiovascular disease; H_2S donors; hydrogen sulfide; wound healing

From the Contents

ABSTRACT

Hydrogen sulfide (H_2S) has been reported as an endogenous gasotransmitter that contributes to the modulation of a myriad of biological signalling pathways, which includes maintaining homeostasis in living organisms at physiological concentrations, controlling protein sulfhydration and persulfidation for signalling processes, mediating neurodegeneration, and regulating inflammation and innate immunity, etc. As a result, researchers are actively exploring effective approaches to evaluate the properties and the distribution of H_2S in vivo. Furthermore, the regulation of the physiological conditions of H_2S in vivo introduces the opportunity to further study the molecular mechanisms by which H_2S regulates cellular functions. In recent years, many H_2S-releasing compounds and biomaterials that can deliver H_2S to various body systems have been developed to provide sustained and stable H_2S delivery. Additionally, various designs of these H_2S-releasing biomaterials have been proposed to aid in the normal conduction of physiological processes, such as cardioprotection and wound healing, by modulating different signalling pathways and cell functionalities. Using biomaterials as a platform to control the delivery of H_2S introduces the opportunity to fine tune the physiological concentration of H_2S in vivo, a key to many therapeutic applications. In this review, we highlight recent research works concerning the development and application of H_2S-releasing biomaterials with a special emphasis to different release triggering conditions in in vivo studies. We believe that the further exploration of the molecular mechanisms underlying H_2S donors and their function when incorporated with various biomaterials will potentially help us understand the pathophysiological mechanisms of different diseases and assist the development of H_2S-based therapies.

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Introduction

Hydrogen sulfide (H_2S), which had been previously regarded as a lethal toxic pollutant for centuries, is currently being explored as an endogenous gasotransmitter with the capability to not only contribute in the modulation of a myriad of biological signalling pathways but also to maintain homeostasis in living organisms at physiological concentrations.[1-5] Over the past decades, many experiments have been performed to investigate the respective role of H_2S in both physiological and pathophysiological activities in mammals.[6-9] Specifically, this small molecule diffuses freely through the cell membrane to initiate a variety of responses independent of transporters, membrane receptors or second messenger systems, and regulate many cellular functions through a series of intracellular signalling processes.[10]

There is sufficient evidence to indicate the correlation between low concentration of endogenous H_2S and many pathophysiological diseases; namely, obesity, marked endothelial dysfunction, insulin resistance, high blood pressure, diabetes, exacerbated cardiac injury after ischemia/reperfusion injury, Alzheimer's disease, asthma, wound healing, and cancers.[11-20] Whether or not the H_2S-generating enzymes are

directly impaired in their respective molecular mechanisms does not differentiate between the presence or progression of these disease processes; therefore, the ability to re-establish the physiological concentration of aqueous H_2S *in vivo* will facilitate further exploration into the molecular mechanism of H_2S and how it regulates cellular functions.

Although there are a variety of H_2S donors reported in studies mentioned above, including conventional inorganic donors like NaHS and Na_2S and newly developed H_2S donor with specific triggers, these donors are often with several issues such as instantaneous release profiles, low water solubility, and lacking capacity of *in situ* delivery.[21, 22] One promising strategy to address these issues is to incorporate these donors into biomaterials, either by physical entrapment or through covalent conjugation to polymers or macromolecules. In this review, by using the PubMed and Google-Scholar as the search engines, H_2S, biomaterials and clinical terms of diseases as key words, we choose those literatures published after 2010 and focus on the recent development of novel biomaterials incorporating with the H_2S-donor motifs for the controlled release of H_2S *in vivo*. In particular, the synthesis and potential clinical applications of such materials are highlighted. More detailed introductions of the physiological roles and functions of H_2S can be found in some other excellent review articles published recently.[7, 9, 23-26]

Homeostasis of Hydrogen Sulfide in Mammals

H_2S is a colorless, flammable, water-soluble gas with strong rotten egg smell. In aqueous solutions, H_2S is a volatile, weak acid that dissociates to form H^+, HS^- and S^{2-} ($H_2S \leftrightarrow H^+ + HS^- \leftrightarrow 2H^+ + S^{2-}$).[27] In mammals, H_2S is produced endogenously from cysteine, serine, homocysteine and other substrates primarily through the actions of three major enzymes (**Figure 1**). Cystathionine-β-synthase is mainly localized in the nervous system, brain and liver; cystathionine-γ-lyase (CSE) is mainly localized in the cardiovascular system to produce H_2S; and 3-mercaptopyruvate sulfurtransferase (3-MST) is predominantly localized in mitochondria.[5, 20] In addition, the activities of gut microbiota, glycolysis and phosphogluconate of glucose, the glutathione and "sulfane sulfur" pools may also contribute to the maintenance of H_2S concentrations in plasma and tissue (**Figure 1**),[11, 28-30] where sulfane sulfur is descriptive of the extremely reactive sulfur atom that is bonded to a divalent sulfur molecule, and thiocysteine and glutathione persulfide are two examples of biologically important compounds that contain a sulfate sulfur within their chemical makeup.[11]

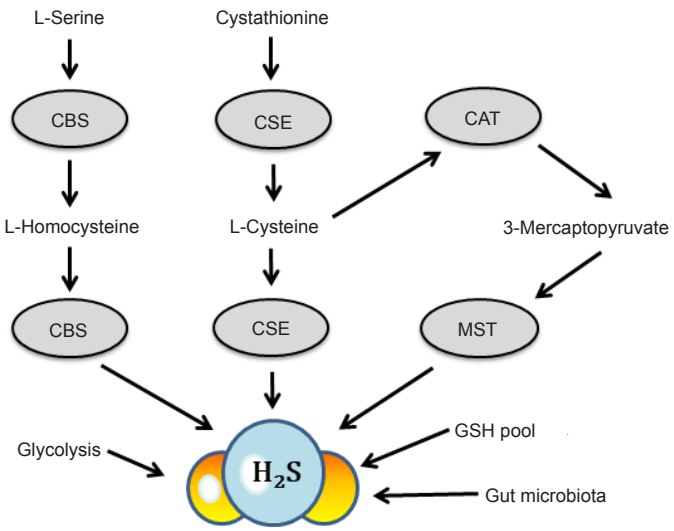

Figure 1. Biosynthesis and catabolism of H_2S. In mammals, H_2S is produced endogenously from cysteine, serine, homocysteine, and other substrates primarily through the actions of three major enzymes. CBS is mainly localized in the nervous system, brain and liver; CSE is mainly localized in the cardiovascular system to produce H_2S; MST is predominantly localized in mitochondria. In addition, the activities of gut microbiota, glycolysis and phosphogluconate of glucose, the GSH and "sulfane sulfur" pools may also contribute to the maintenance of H_2S concentrations in plasma and tissue.[11, 28-30] CAT: cystine aminotransferase; CBS: cystathionine-β-synthase; CSE: cystathionine-γ-lyase; GSH; glutathione; H_2S: hydrogen sulfide; MST: mercaptopyruvate sulfurtransferase.

Kenneth R. Olson[31] has reviewed different methods to detect the concentrations of H_2S within different samples of plasma/blood. The distribution of H_2S varies in different tissues, fresh blood or plasma within animals. In blood, the concentration of H_2S has been reported to be ranging from 30–100 μM.[32-34] The H_2S concentrations within brain tissue, the aorta and other homogenized samples from specific regions, in which H_2S may play significant roles, are higher than that within the blood, indicating that H_2S is an autocrine and paracrine messenger.[35-37]

Due to its volatile nature, the stabilization of H_2S concentrations within *in vitro* experimentation is difficult because the equilibrium will shift to the left in the absence of glutathione, "sulfane sulfur"

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pools and gut microbiota. Several reports have been published showing that in cell culture wells, the H_2S concentrations will be halved in five minutes; this escape will be even faster when there is a bubbled tissue bath.[38-41] Coupled with the lipophilic characteristics of H_2S, direct intraperitoneal injections or blood administrations as described in previous reports will result in the rapid diffusion of H_2S out of the blood and into the lungs.[42] These bottlenecks have driven researchers to further explore the properties and delivery of H_2S with novel approaches, including the inventions of new H_2S donors and complexes of biomaterials capable of sustained and stable *in vitro* or *in situ* delivery of H_2S.

Chemistry of Hydrogen Sulfide Donors and Release Mechanisms

For the controlled release of H_2S, many donors have been developed in the last decade. The conventional inorganic donors, including Na_2S or NaHS, limit the prospects for mechanistic studies and medical applications due to their fast and uncontrolled H_2S release. To overcome this drawback, researchers have developed multiple types of H_2S donors with distinct properties, such as pH-sensitive donors,[43-45] enzyme-activated donors,[46-48] reactive-oxygen species,[49] and thiol-triggered donors[50, 51] (**Figure 2**).

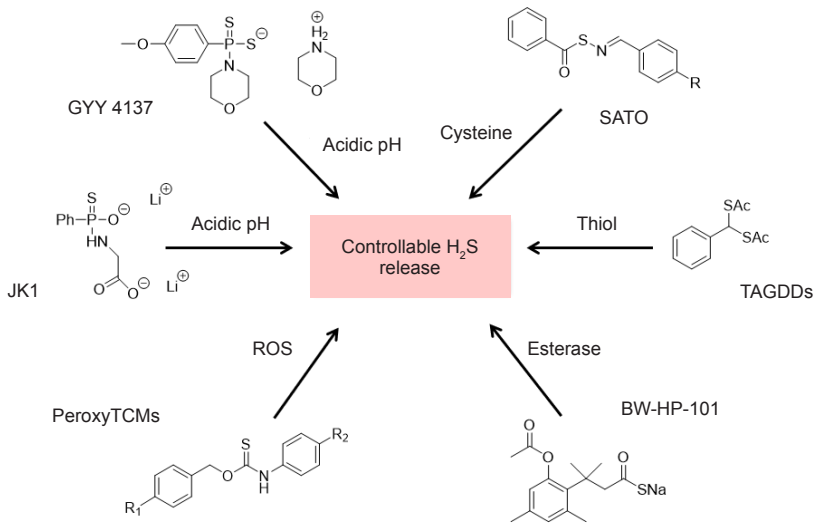

Figure 2. Donor compounds for H_2S release. Recent advances in the development of H_2S donors has revealed multiple types of donors, namely, pH-sensitive donors including JK1 and GYY 4137,[43-45] enzyme-activated donors such as BW-HP-101,[46-48] reactive-oxygen species such as PeroxyTCMs,[49] and thiol-triggered donors including TAGDDs and SATO.[50,51] H_2S: hydrogen sulfide; TAGDD: thiol-activated gem-dithiol-based H_2S donor; SATO: S-aroylthiooxime; PeroxyTCM: PeroxyThioCarbaMate.

Among them, the pH-sensitive H_2S donors have provided a new realm of scientific advances in specific pathophysiological diseases and processes that take place under specific acidic conditions such as acute cutaneous wounds.[52] Upon acute injury to cutaneous tissue, the acidic pH observed at the injury site decreases bacterial growth to help prevent infection; the progression of wound healing yields a gradual return to the physiological pH of 7.4.[53] The longevity of H_2S release under physiological conditions and its acceleration under acidic conditions is an important relationship to consider when developing H_2S donors. Several pH-sensitive H_2S donors have been evaluated for their respective efficacies; moreover, GYY4137 and JK1 are two commonly used pH-sensitive H_2S donors.[43, 44, 50] JKs are a group of pH-sensitive H_2S-releasing compounds created under the manipulation of an intramolecular cyclization reaction and have shown to be efficient at monitoring H_2S release.[45] Including H_2S donors like GYY4137 and JKs can not only aid in the re-epithelialization of cutaneous tissue after trauma but also assists in decreasing inflammation and oxidative stress at the site of injury.[54-58]

Another highly beneficial development in the field of H_2S donors is the creation of enzymatically triggered donors such as BW-HP-101.[46, 50, 59] It can be averse to use triggers that consume thiols or other cellular molecules that risk disrupting the chemical and redox balance of the environment; however, enzymatic triggers allow specific environments to be targeted without consuming these reactants. Additionally, enzyme-triggered donors are advantageous as they rely on the presence of enzymes that are readily available within organisms. BW-HP-101 functions through a cascade initially mediated by an esterase, which is predominantly expressed in liver tissue.[60] Because esterases are key components of drug metabolism, these donors are highly versatile and can be altered to fit different scaffolding foundations among a variety of organ systems. The versatility of BW-HP-101 can be countered with further research into more specific enzyme-triggered donors.

Reactive oxygen species (ROS) are byproducts of electron transport chains located within mitochondria of biological cells; the production of these free radicals is vital to cell function because ROS signalling is imperative to inflammation regulation and cellular homeostasis while ROS can also display cytotoxic effects when being produced in excess.[48] Abundant ROS production has been correlated with several pathophysiological disease processes such as atherosclerosis and lipid peroxidation.[47] H_2S displays cytoprotective properties when introduced to ROS like hydrogen peroxide and has

exhibited anti-apoptotic and antioxidant effects on cells. PeroxyTCM is a recently developed ROS-triggered H_2S donor that has utilized cytoprotective properties to counter the oxidative stress resulting from ROS.[49] However, introducing excess H_2S to cells is extremely toxic and can be detrimental to biological functioning. H_2S-ROS interactions and their role in regulating redox signalling is relatively new and must be further studied.

Thiol-triggered donors, including thiol-activated *gem*-dithiol-based H_2S donors (TAGDDs) and S-aroylthiooximes (SATO), are the most common type of H_2S donors due to the abundance of thiol molecules, such as cysteine, within biological organisms; the broad availability of thiol molecules makes it advantageous for donors to successfully release H_2S across the body.[50, 51] Some types of thiol-triggered donors are activated by the breaking of the S-S bond; this is a relatively simple mechanism that can have many applications upon further research. Polysulfide specifically is constructed from several S-S bonds and therefore has a large reservoir of potential for H_2S donor development. Glutathione, reduced glutathione, is a naturally occurring thiol that has been targeted for similar donor development to serve as a trigger due to its abundance and evidenced quick release of H_2S.[50]

Different Strategies to Synthesize Hydrogen Sulfide-Releasing Biomaterials

Multiple studies have clearly indicated the pivotal roles of pretreatment of H_2S donors in different diseases.[61-63] However, many H_2S donors limit their direct applications due to poor water solubility, toxicity, low renal clearance rate and lacking regional specific release mechanism.[21,64] A variety of biological scaffolds developed in recent years are expected to become an effective means to solve the above constraints on the application of H_2S. Usually, the H_2S donor can be loaded on the biological scaffolds through physical incorporation or chemical conjugation. The resultant H_2S-releasing biomaterials could display a controllable, sustainable, and adjustable H_2S releasing.

Doping biomaterials with H_2S donors

The first strategy to synthesize H_2S-releasing biomaterials is to fabricate biomaterials doping with H_2S donors. This method has the advantages of easy operation, economy and convenient design. Specifically, the creation of biomaterial scaffolds incorporating with H_2S donors can construct micro-environments for the release of H_2S of donors under both *in vitro* and *in vivo* situations. In addition, these material scaffolds could provide various physical and chemical cues for specific cell signalling pathways, further expanding its application prospects in cardiovascular disease, wound healing, and regenerative medicine.[52, 56, 65] As shown in **Figure 3A**, fibrous scaffolds generated by electrospinning, which is a simple, cost-effective, and versatile technique, could be readily doped with H_2S donors resulting in satisfied surface to volume ratio, variable porosity, and flexibility to form various sizes.[66-68] Studies have reported an electrospinning of polycaprolactone (PCL), a structural polymer that can be modified into a three-dimensional scaffolding matrix and chemically doped with H_2S donors like NSHD1 and JK1 to create a fibrous material capable of releasing H_2S under specific pH conditions.[52, 65] These hybrids gave rise to prolonged H_2S releasing time compared to those donors alone.

Acidic linear polysaccharides such as alginate and hyaluronic acid (HA) are biocompatible macromolecules, which are able to form stable aqueous porous hydrogel by various strategies of crosslinking. As shown in **Figure 3B**, H_2S-releasing sponge was fabricated by mixing the pH-dependent H_2S donor JK-1 into an alginate sponge obtained by crosslinking sodium alginate with Ca^{2+}. Those sponge-like materials stand out with their biocompatibility, biodegradability and ability to establish a three-dimensional-structural humid environment within wound regions.[69-71] This approach could be readily employed with different polysaccharide-based hydrogel systems.[56, 57] Similar to those with H_2S-releasing electrospinning fibres, H_2S-releasing hydrogels/sponges could also significantly prolong H_2S release half-lives, which will greatly expand the effective time window and application fields within different donor concentrations.

Integrating H_2S donors into biomaterials

Another strategy to synthesize the H_2S-releasing biomaterials is to directly conjugate H_2S-releasing functional units into different polymers and macromolecules like peptides. This will overcome the polydispersity caused by conventional doping methods. In a pioneer work by Matson and coworkers, a cysteine-triggered H_2S donor SATO was conjugated into amphiphilic polymers to make micelles with a diameter of 20–100 nm (**Figure 4A**). Upon triggering with cysteine, a controlled release of H_2S could be achieved with a prolonged release half-life, long bloodstream circulation and targeted regional specificity.[72, 73] Using a similar strategy, the Matson group[74] developed a peptide-H_2S donor conjugates supramolecular nanofibres loading with cysteine-triggered H_2S donor SATO. These H_2S releasing peptides will spontaneously result in discrete, stable supramolecular nanostructures with the capacity to delivery H_2S (**Figure 4B**).[74] Conjugation of SATO into aromatic peptide amphiphiles hydrogel, enabling controllable H_2S release and mechanical properties of hydrogel, results in a sustainable and controllable H_2S release profile.[75, 76] These H_2S releasing biomaterials represent elegant examples to employ synthetic strategy to empower the biomaterials with an improved H_2S release profile which can be used in a variety of biological applications taking advantage of the cardioprotective, anti-oxidative, and anti-inflammatory effects of H_2S.

Application of Hydrogen Sulfide-Releasing Biomaterials

Cardiovascular disease

Cardiovascular disease was among the first explored areas of H_2S application due to its strong link with hypoxia, ROS production and cardioprotection. A significant decrease in the concentration of H_2S in blood plasma had been observed in patients with coronary heart disease.[77] Briefly, the pathways implicated in the cardioprotective effects of H_2S are multiple, involving K_{ATP} channels, regulation of mitochondrial respiration, and regulation of cytoprotective genes such as

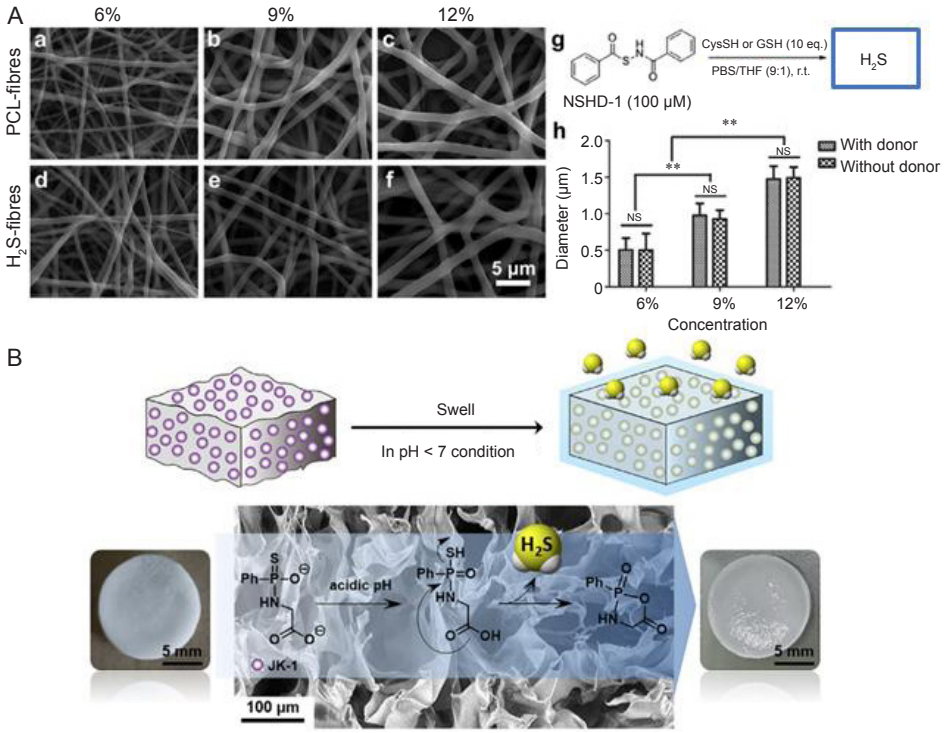

Figure 3. Physical incorporation of H_2S donor into biomaterials. (A) H_2S-release fibres by incorporating thiol-dependent H_2S donor, NSHD-1, in the electrospun PCL-fibres: SEM images of H_2S-fibres (a–c) and PCL-fibres (d–f). All images share the same scale bar (5 μm) in f. (g) The H_2S donor, NSHD-1, can release H_2S in the presence of cysteine or GSH. (h) Fibre diameters plot as a function of solution concentrations. The dopant, NSHD1, has no obvious effect on fibre diameters.[65] (B) H_2S-releasing sponge sodium alginate/JK-1 by incorporating the pH-dependent H_2S donor JK-1 into an alginate sponge obtained by crosslinking sodium alginate with Ca^{2+}.[57] Reprinted from Feng et al.[65] and Zhao et al.[57] Copyright 2015 and 2020, with permission from Elsevier Ltd. GSH: glutathione; NSHD-1: N-(benzoylthio) benzamide; PCL: polycaprolactone; SEM: scanning electron microscope.

nuclear factor erythroid 2-related factor-2 to further modulate the response under hypoxia condition, vasodilatation as well as cryoprotection and anti-inflammatory effects.[78] Studies of effects of H_2S on the cardiovascular system have been detailed and collected in previous literatures.[42, 78, 79] In a rat model of myocardial infarction, it was noted that a treatment of sodium hydrosulfide could significantly decrease the infarct size with a lower mortality risk.[78, 80] Exogenous H_2S exhibits cardioprotection via the alleviation of left ventricular structural impairment in ischemia-induced heart failure.[81] Based on understanding of roles of H_2S in cardioprotection, treatment with inorganic donors like NaHS or other synthesized H_2S-releasing donors, such as s-diclofenac, ADT-OH (5-(4-hydroxyphenyl)-3H-1,2-dithiole-3-thione), JKs and GYY4137, on both cardiomyocytes and animal models could help protect hearts from myocardial ischemia/reperfusion injuries by their intrinsic properties and/or incorporating with biomaterials (**Figure 5**).[45, 81-85] In addition, considering its potential role in anti-inflammatory application,[86-88] H_2S donors like NaHS could attenuate the development of atherosclerosis through a variety of mechanisms; notably the suppression of tumour necrosis factor-α-induced mRNA, expression of intercellular adhesion molecule 1 and vascular cell adhesion molecule 1, mRNA expression of P-selectin and E-selectin, and monocyte adhesion to human umbilical vein endothelial cells.[89]

Integrating H_2S donors with biomaterials can facilitate *in situ* delivery of H_2S and provide both physical and chemical cues for other reactions. Under this strategy, Zhang et al.[90] selected large porous microspheres, a widely studied drug vehicle for pulmonary delivery, loaded with H_2S donor ACS14 (S-aspirin) as an inhalational drug; an observable delay and even reversal in the progression of pulmonary arterial hypertension in a rat model resulted from this experimentation. Wang and Matson[91] utilized peptide-H_2S donor conjugates supramolecular nanofibres saturated with cysteine-triggered H_2S donor SATO to delay the occurrence of the peak time of H_2S release, which was coupled with a prolonged release time as well as the mitigation of the doxorubicin-induced cardiotoxicity of the H9C2 cardiomyocyte. The integration of the SATO donor into aromatic peptide amphiphiles hydrogels was characterized by a secured H_2S release and better mechanical properties. Cell viability and proliferation were subsequently increased and the migration of human umbilical endothelial cells was evidently more profound in studies on human tissue compared to the conventional H_2S donor NaHS.[75, 76] Similar results have been shown in another study using ACS14 with chitosan/HA hydrogel.[92] Liang et al.[93] introduced a partially oxidized alginate grafting H_2S donor 2-aminopyridine-5-thiocarboxamide (ALG-CHO-APTC) which exhibited excellent rheological and adhesion properties to adipose-derived stem cells. The injection of this multifunctional hydrogel into the Sprague-Dawley rat model had significantly upregulated cardiac-

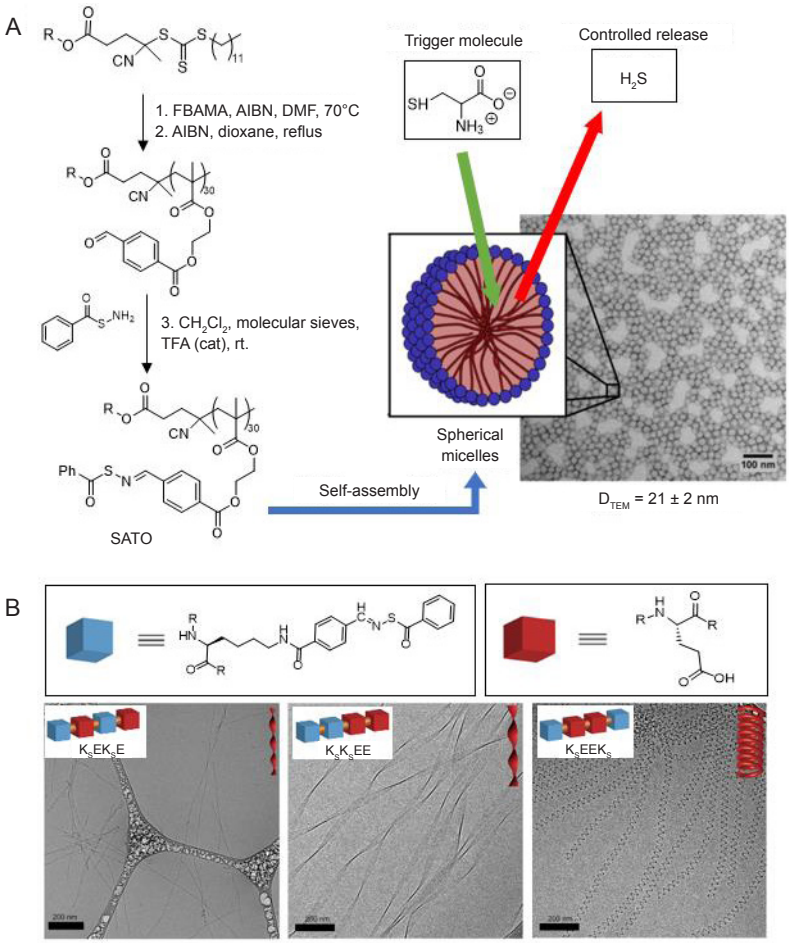

Figure 4. H_2S donor units covalently linked to material backbones. (A) H_2S-releasing SATO-unit was incorporated to the polymer, which could be self-assembled into spherical micelles with an average diameter of 21 ± 2 nm. Reprinted from Foster et al.[72] (B) Three isomeric peptide–H_2S donor conjugates assembled into twisted ribbons and nanocoils in aqueous solution. Reprinted from Wang et al.[74] AIBN: 2,2′-azobis(2-methylpropionitrile; DMF: dimethylformamide; FBEMA: 2-(4-formylbenzoyloxy)ethyl methacrylate; H_2S: hydrogen sulfide; rt: room temperature; SATO: S-aroylthiooxime; SEM: scanning electron microscope; TFA: trifluoroacetic acid.

related mRNA and angiogenic factors while simultaneously downregulating inflammatory factors; furthermore, cardiac function was overall improved. Interestingly, Mauretti et al.[94] introduced a polyethylene glycol-fibrinogen hydrogel loading with serum albumin microbubbles coated with the H_2S synthesis enzyme thiosulfate cyanide sulphurtransferase in a cardiac tissue repairment study. This novel three-dimensional scaffold improved cell growth of human cardiac progenitor cells and set the foundation for further assessment of the effects of H_2S on cardiac muscle regeneration.

Wound healing

The proliferation and differentiation of the epidermis are pivotal to wound healing and are often diminished under various pathological conditions such as diabetes mellitus, chronic skin wounds, and epidermal cancers.[95-97] The impairment of fibroblast proliferation and angiogenesis as well as a dysfunction of keratinocytes have been observed in diabetes mellitus patients and those suffering from chronic wounds;[98-101] however, exogenous and endogenous H_2S could increase the proliferation and differentiation of the epidermis and promote angiogenesis in a dose-dependent manner.[102-107] The inhibition of endogenous H_2S as experienced by a genetically modified $CSE^{-/-}$ mice model significantly decreased the rate of wound healing compared to the $CSE^{+/+}$ wild type mice.[106, 108] Meanwhile, lower level H_2S in plasma of diabetic patients, accompanied with vascular inflammation and overproduction of oxidants, could indicate the potential application of exogenous H_2S in diabetic wound healing.[109, 110] The role and corresponding mechanism of H_2S in wound healing are collected and detailed in previously published reviews.[95, 106, 111]

Although significant advances have been achieved, the applications of H_2S donors are still limited by the open-air and pH-variable wound environments. An ideal wound dressing should be biocompatible, antigen-free, elastic, and anti-inflammatory with the abilities to prevent infections, provide moisture, absorb fluids and exudates, and facilitate cell adhesion and growth factor release.[112-114] To satisfy these requirements, Wang and coworkers have utilized the electrospinning of PCL chemically doped with H_2S donors like NSHD1 (N-(benzoylthio) benzamide) and JK1 to create a H_2S-releasing fibrous material under specific pH conditions.[52, 65] H_2S-fibres can significantly improve the cell viability of

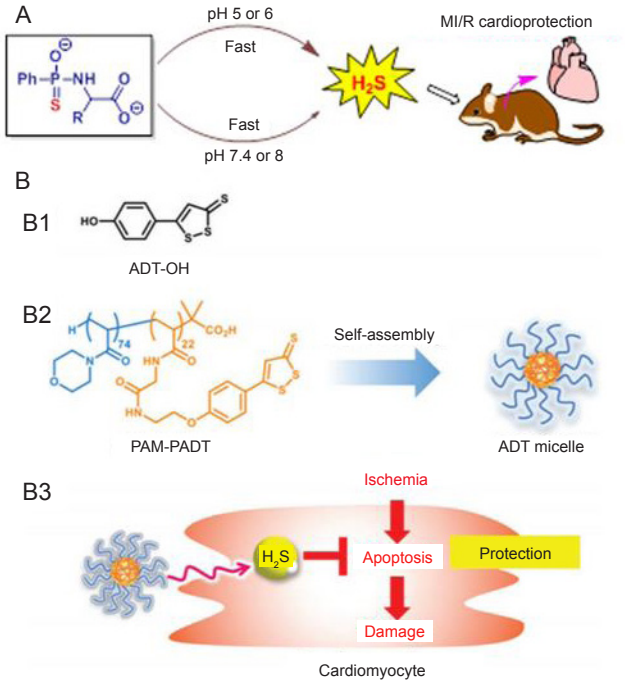

Figure 5. H_2S donors act in cardiovascular disease. (A) JK1 gives rise to faster H_2S release under acidic condition, of which is distinctive feature of ischemia microenvironment compared to normal physiological condition. Reprinted with permission from Kang et al.[45] Copyright © 2016 American Chemical Society. (B) H_2S donor micelles protect cardiomyocytes from ischemic cell death. (B1) Chemical structure of ADT-OH. (B2) A block copolymer having ADT-groups (PAM-PADT) forms ADT micelles by self-assembly. (B3) Intracellular release of H_2S from ADT micelles prevents apoptotic damage of cardiomyocytes under ischemic condition. Reprinted with permission from Takatani-Nakase et al.[85] Copyright © Royal Society of Chemistry 2017. ADT: anethole dithiolethione; ADT-OH: 5-(4-hydroxyphenyl)-3H-1,2-dithiole-3-thione; H_2S: hydrogen sulfide; PAM-PADT: poly (N-acryloy morpholine)-poly anethole dithiolethione.

ROS-treated cells and the re-epithelialization through the upregulation of mRNA expression in genes such as collagen type I and collagen type III commonly expressed during wound healing processes.[65] Because H_2S release has been shown to accelerate under an acidic pH, pH-sensitive H_2S donors like JK1 can be incorporated to PCL scaffolding and subsequently promote the epithelial regeneration and healing when utilized for acute trauma wounds. The accelerated wound healing might be attributed to the increase of the wound closure rates, the augmentation of collagen density in the mice wound model, or the cell viabilities of fibroblasts *in vitro*.[52]

Hydrogels of linear polysaccharides such as alginate and HA are biocompatible, biodegradable stable porous biomaterials and exhibit great potential applications for wound healing.[69-71] An alginate hydrogel incorporated with a H_2S donor such as JK1[57] or dissolved H_2S[115] contributes to the improvement of cell proliferation and migration in addition to angiogenesis with an accelerated wound healing process. Wu et al.[56] introduced a HA hydrogen incorporated with the JK1 H_2S donor (**Figure 6**). Remarkably, compared to either component alone, this HA-JK1 hybrid hydrogel dressing yielded enhanced cell proliferation and angiogenesis as well as macrophage polarization towards M2 phenotype. This result has suggested a downregulation of the inflammation response which could be employed in the treatment of delayed diabetic wounds and other chronic wounds under various pathological conditions.

Lian et al.[116] utilized blended recombinant spider silk protein to make a nanofibrous membrane incorporated with NaHS as a substrate to culture endothelial progenitor cells. This recombinant spider silk protein/NaHS/endothelial progenitor cell complex could significantly enhance wound regeneration efficiency and be utilized in skin tissue regeneration. To further expand upon H_2S-releasing biomaterial functionality, Liu et al.[117] proposed a multi-functional polymersome wound dressing spray, incorporating PCL with SATO and a positively charged peptide; together, the system gives rise to H_2S release and anti-bacterial properties at the same time and aids diabetic wound healing in improving angiogenesis, employing antibacterial properties and encouraging the proliferation of endothelial and epidermal cells.

Other clinical applications

H_2S-releasing biomaterials can be employed in various physiological and pathophysiological situations outside direct application in cardiovascular disease or wound healing processes. In experiments with Staphylococcus aureus, which is commonly found at the wound site, fabricated SATO-aromatic peptide amphiphiles biofilm has shown significant antimicrobial effects.[118] This indicates that this biofilm hydrogel can be applied in situations where antimicrobial properties are critical for the treatment process. Injection into the intervertebral disc joint cavities in rat models experiencing intervertebral disc degeneration, a collagen-JK1 hydrogel expressed the ability to protect the disc from degeneration

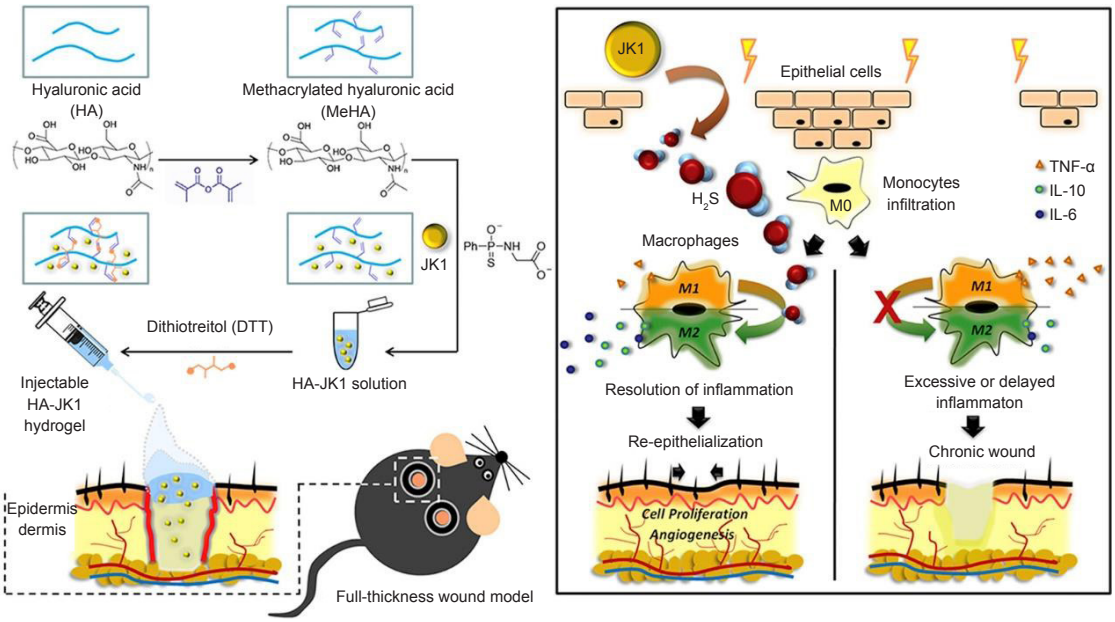

Figure 6. Schematic illustrating the preparation of injectable HA-JK1 hydrogel and its application to full-thickness dermal wound. (Left) JK1, as H_2S donor, was incorporated in the HA based injectable hydrogel, which can be used in the mouse wonder model system. (Right) The local low pH condition near the wound could promoted the fast release of H_2S of JK1, which could effectively accelerate the wound healing through promoting cell proliferation, angiogenesis and more importantly, suppressing inflammation via inducing M2 macrophage polarization. Reprinted from Wu et al.[56] Copyright 2019, with permission from Elsevier Ltd. H_2S: hydrogen sulfide; HA: hyaluronic acid; IL: interleukin; TNF-α: tumour necrosis factor-α.

via inhibiting the apoptosis of nucleus pulposus cells and in turn, alleviating the degradation of the disc's extracellular matrix.[119] In addition, when cultured with mesenchymal stem cells, Cacciotti et al.[120] have shown that when poly lactic acid nanofibres are doped with a H_2S donor derived from garlic oil-soluble extract, a strong biocompatibility, antimicrobial activity, and protective properties against ROS were observed. Raggio et al.[121] introduced a silk fibroin scaffold loading with GYY4137, to bone tissue engineering with better displayed biocompatibility and no cytotoxicity. Apart from the treatment applications for these diseases we mentioned above, anti-cancer effect of H_2S-releasing biomaterial has arisen attentions of many researchers because H_2S as an antioxidant can suppress tumour growth by blocking proliferation of cancer cells, and by modulating differentiation of cancer-associated fibroblasts.[122-124] In Dao et al.'s work,[125] polyethylene glycol-cholesteryl conjugate polymer doping with trisulfide as H_2S donor has shown attenuation of intracellular ROS and collagen type I production in breast cancer and potential in future clinical chemotherapy applications. Liu et al.[126] reported an anethole dithiolethione-loaded magnetic nanoliposome) delivery system, which can facilitate *in situ* drug delivery of H_2S and magnetic resonance imaging of tumour at the same time. In summary, the recent advances of H_2S-releasing biomaterials in applications as summarized in **Table 1** will pave the ways to further mechanism studies and clinical applications.

Conclusion

There was accumulating evidence from the last decade that demonstrated the potential of H_2S-releasing biomaterials for various biomedical applications. Further exploration of the molecular mechanisms underlying H_2S donors and their function when incorporated with various biomaterials will potentially help us to understand the pathophysiological mechanisms of different diseases and assist the development of H_2S-based therapies. On the other hand, there is still a desperate need to develop novel H_2S-release donor molecules and biomaterials to address the demand for different therapies. In particular, recent progress in biomaterials science and technology will provide more opportunities to develop customized H_2S-releasing biomaterials with improved biocompatibility and optimized H_2S release profiles which can offer better answers to clinical challenges.

Author contributions

JF and QW conceived of the overall outline of the paper. JF, EP and QW contributed to the conception and design of all figures and the related literature survey. All authors contributed to the writing of the final manuscript.

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Conflicts of interest statement

No conflicts to disclose.

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Table 1. Summary of applications of H_2S donors and H_2S-releasing biomaterials

Application	H_2S donor/ biomaterials	Research model	Effects/outcome	Proposed mechanism	Reference
Cardioprotection	NaHS	Murine infarction model	Infarcted size and mortality significantly decreased	Upregulation of Bcl-2, demoted expression of Bax, IL-1β and Caspase 3	80-82, 84
	JKs	H9C2 cardiomyoblasts & murine ischemia/ reperfusion model	A dose-dependent inhibition in cell viability; significantly reduced AAR/LV and INS/AAR		45
	S-diclofenac	Rabbit model	Improved reperfusion pressure, anti-ischemic activity, activation of KATP channel		83
	DAT-MSN	Cardiomyocyte, murine infarction model	inhibited myocardial inflammation, greater reduction in the infarct area and preserved cardiac ejection fraction	Same as above	84
	GYY4137	Cardiomyocyte, murine infarction	Infarcted size reduced, improved cardiac functions	Same as above	84
	ADT-OH/ PAM-PADT micelles	Rat cardiomyocytes	Rescue cells from apoptosis		85
	PHDCs/SATO	H9C2 cardiomyoblasts	Mitigated Dox-induced toxicity		91
	ALG-CHO/ APTC/ADSC	ADSC/rat model	Improved heart function	Suppressed TNF-α, upregulation of genes related to angiogenesis and cardiac function	93
	PFHy-MBs/ CST	hCPCs	Improved cell growth		94
Atherosclerosis	NaHS	Apolipoprotein-E K.O. mice model & HUVEC	Antiatherogenic effect with promoted cell viability	Inhibited ICAM-1 and TNF-α signalling	86, 89
	APA/SATO	HUVEC	Improved cell proliferation and migration		75, 76
	Chitosan/ HA hydrogel/ ACS14	Platelet, rat model	Reduced inflammatory and AS lesion		92
Pulmonary arterial hypertension	LPM/ACS14	PAH rat model, HPAEC	Delayed and reversed progression of PAH	Suppressed NF-κB-Snail pathway	90
Wound healing	NaHS	HaCaT cell model, human epidermal melanocytes, HUVEC diabetic mice model	Promoted viability and differentiation	Promoted proliferation and differentiation via ATG5, TRP-1 signalling, angiogenesis via ANG-1, anti-inflammatory effect suppressing IL-6, TNF-α and MMP-9	102-105
	Na2S	HUVEC, diabetic mice model	Suppressed inflammation, promoted migration and proliferation	Upregulation of KATP/ P38/ERK/MAPK/VEGF signalling, and VEGFR2 transcription	106, 108
	NSHD1/PCL fibre	NIH 3T3, H9C2 cell model	Significantly prolonged release time, decreased ROS production		65
	JK1/PCL fibre	NIH 3T3, mice model	Enhanced wound regeneration, prolonged release time		52

Table 1. Continued

Application	H_2S donor/ biomaterials	Research model	Effects/outcome	Proposed mechanism	Reference
	JK1/HA hydrogel	Mice model	Fast wound healing with enhanced cell proliferation and angiogenesis	Macrophage polarization towards M2 phenotype, suppressed TNF-α	56
	JK1/SA hydrogel	L929 cell, rat model	Enhanced wound healing, promoted release profile		57
	H_2S/SA hydrogel	L929 cell, rat model	Promoted wound healing in a dose dependent manner		115
	NaHS/rMaSp fibre	NIH 3T3, mice model	Promoted wound healing with EPC		116
	SATO/PCL fibre	NHEK cells, diabetic mice model	Bacterial inhibition, promoted diabetic wound healing		117
Anti-bacterial	SATO/APA biofilm/ dipeptides	Staphylococcus aureus	Inhibited bacterial growth		118
Intervertebral disc degeneration	JK1/Col hydrogel	Rat model, NP cell	Inhibited inflammatory process and cell apoptosis	Suppressing TNF-α, NF-κB, IL-1β expression and deactivation of P65 signalling	119
Tissue engineering	GaOS/PLA membrane	Cardiac mesenchymal stem cell	Promoted proliferation with reduced oxidative damage		120
	GYY4137/ fibroin scaffold	Mouse fibroblast, hBMSC	Enhanced cell viability		121
Anti-cancer	Trisulfide/ PEG-cholesteryl	MCF7 breast cancer cell	Suppressed tumourigenesis	Normalization of COL-1 expression	125
	ADT/AML	HepG2 cell, mice xenograft model	Reduction of tumour size, facilitate magnetic resonance imaging		126

Note: AAR: area-at-risk; ACS14: S-aspirin; ADSC: adipose-derived stem cell; ADT: anethole dithiolethione; ALG-CHO: partially oxidized alginate; AML: ADT-loaded magnetic nanoliposome; APA: aromatic peptide amphiphiles; APTC: 2-aminopyridine-5-thiocarboxamide; ATG5: autophagy related 5; COL-1: collagen type I; CST: cyanide sulphurtransferase; ADT-OH: 5-(4-hydroxyphenyl)-3H-1,2-dithiole-3-thione; EPC: endothelial precursor cell; ERK: extracellular signal-related kinase; GaOS: casting garlic oil-soluble extract; H2S: hydrogen sulfide; HA: hyaluronic acid; hBMSC: human bone marrow stromal cell; hCPC: human cardiac progenitor cell; HPAEC: human pulmonary artery endothelial cell; HUVEC: human umbilical vein endothelial cell; IL: interleukin; INS: infarct size; LV: lentivirus; MAPK: mitogen-activated protein kinase; MB: microbubble; MMP-9: matrix metallopeptidase 9; NF-κB: nuclear factor κB; NSHD1: N-(benzoylthio)benzamides derivatives 1; PADT: poly anethole dithiolethione; PAH: poly (N-acryloy morpholine); PCL: polycaprolactone; PEG: polyethylene glycol; PFHy: polyethylene glycol-fibrinogen hydrogel; PHDC: peptide-H2S donor conjugate; PLA: poly lactic acid; rMaSp: recombinant spider silk protein; SA: sodium alginate; SATO: S-aroylthiooximes; TNF-α: tumour necrosis factor-α; TRP-1: tyrosinase-related protein-1; VEGF: vascular endothelial growth factor; VEGFR2: vascular endothelial growth factor receptor 2.

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