The Role of Hydrogen Sulfide on Cardiovascular Homeostasis: An Overview with Update on Immunomodulation

Li-Long Pan[1], Ming Qin[1], Xin-Hua Liu[1]* and Yi-Zhun Zhu[2]*

[1] Department of Pharmacology, School of Pharmacy, Fudan University, Shanghai, China, [2] State Key Laboratory of Quality Research in Chinese Medicine and School of Pharmacy, Macau University of Science and Technology, Macau, China

Hydrogen sulfide (H_2S), the third endogenous gaseous signaling molecule alongside nitric oxide (NO) and carbon monoxide, is synthesized by multiple enzymes in cardiovascular system. Similar to other gaseous mediators, H_2S has demonstrated a variety of biological activities, including anti-oxidative, anti-apoptotic, pro-angiogenic, vasodilating capacities and endothelial NO synthase modulating activity, and regulates a wide range of pathophysiological processes in cardiovascular disorders. However, the underlying mechanisms by which H_2S mediates cardiovascular homeostasis are not fully understood. This review focuses on the recent progress on functional and mechanistic aspects of H_2S in the inflammatory and immunoregulatory processes of cardiovascular disorders, importantly myocardial ischemia, heart failure, and atherosclerosis. Moreover, we highlight the challenges for developing H_2S-based therapy to modulate the pathological processes in cardiovascular diseases. A better understanding of the immunomodulatory and biochemical functions of H_2S might provide new therapeutic strategies for these cardiovascular diseases.

Keywords: myocardial ischemia, heart failure, atherosclerosis, inflammation, hydrogen sulfide

INTRODUCTION

Cardiovascular diseases, the leading cause of death worldwide, are multifactorial resulting from disorders of the heart and circulation (Murphy et al., 2015), which cause immense health and economic burdens in all countries (Benjamin et al., 2017). The main risk factors associated with cardiovascular diseases are unhealthy lifestyle and lack of physical activity (American Heart Association Nutrition Committe et al., 2006). Accumulating evidence has demonstrated that the excess risk of cardiovascular outcomes is associated with changing endogenous

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Abbreviations: 3-MP, 3-mercaptopyruvate; 3-MST, 3-mercaptopyruvate sulfurtransferase; AAR, area at risk; ACS, acute coronary syndrome; CAD, coronary artery disease; CAT, cysteine aminotransferase; CBS, cystathionine-β-synthase; CDO, cysteine dioxygenase; CO, carbon monoxide; CSE, cystathionine-γ-lyase; DAO, D-amino acid oxidase; EC, esterified cholesterol; ETHE1, ethylmalonic encephalopathy protein 1; ERK1/2, extracellular signal-regulated kinase 1/2; Foxp3, forkhead box protein P3; H_2S, hydrogen sulfide; HO-1, heme oxygenase-1; ICAM-1, intercellular adhesion molecule-1; iNOS, inducible nitric oxide synthase; IL, interleukin; MI, myocardial infarction; MI/R, myocardial ischemia/reperfusion; NF-κB, nuclear factor-κB; NLRP3, nucleotide-binding domain, leucine-rich-containing family, pyrin domain-containing-3; NO, nitric oxide; Nox4, NADPH oxidase 4; oxLDL, oxidized LDL; PPG, DL-propargylglycine; PPAR-γ, proliferators-activated receptor-γ; ROS, reactive oxygen species; SAP, stable angina pectoris; SQR, sulfur:quinone oxidoreductase; SPRC, S-propargyl-cysteine; STAT3, signal transducer and activator of transcription 3; TC, total cholesterol; TCR, T-cell receptor; TNF-α, tumor necrosis factor-α; Tregs, regulatory T cells; VCAM-1, vascular cell adhesion molecule-1; VEGF, vascular endothelial growth factor; VSMC, vascular smooth muscle cell.

H$_2$S levels (Yang et al., 2008; Kondo et al., 2013; Mani et al., 2013; Wallace and Wang, 2015).

H$_2$S, a colorless gas with characteristic rotten egg smell, is recognized an environmental hazard and a toxic agent for long. In addition, before the discovery that H$_2$S is present in most organ systems in mammals including humans, it was believed that the gas was a byproduct of metabolic processes by microbes in the atmosphere. The pioneering study by the neuroscientist Hideo Kimura demonstrated that H$_2$S at the physiological concentration facilitated hippocampal long-term potentiation in the nervous system, proposing that this gasotransmitter acts as a neuromodulator (Abe and Kimura, 1996). Later, H$_2$S has become recognized widely as the third endogenous gaseous mediator alongside NO and CO for its modulatory effects on many signaling molecules, including kinases, phosphatases, and transcription factors (Abe and Kimura, 1996; Wang, 2002; Sun et al., 2011). Subsequently, it has been found to regulate both physiological and pathophysiological processes but at specific concentrations. Over the past decade, H$_2$S has been found to be synthesized primarily through metabolic processes from cysteine and homocysteine in a variety of tissues where it functions as a signaling molecule (Szabo, 2007). H$_2$S exerts its cellular effects by directly transport across cell membranes by simple diffusion without the need of specific membrane receptors and it is also involved in the modulation of many pathophysiological processes in cardiovascular system (Chunyu et al., 2003; Mathai et al., 2009; Wang et al., 2009; Liu et al., 2012; Pan et al., 2012). So far, a plethora of investigations have been performed on therapeutic values of H$_2$S in cardiovascular diseases, which reveal that H$_2$S at physiological levels has an important role in cardiovascular homeostasis, and inhibitors of endogenous H$_2$S production or H$_2$S donors exert significant effects in cardiovascular diseases, including heart failure, ischemic myocardium, atherosclerosis, and hypertension (Yang et al., 2008; Wang et al., 2009; Calvert et al., 2010; Miao et al., 2016a). Furthermore, empirical studies have elucidated several mechanisms of H$_2$S-mediated cardiovascular protective activities, which include, but are not restricted to, anti-oxidation (Chang et al., 2008; Wang et al., 2009; Huang et al., 2017), anti-apoptosis (Yan et al., 2017), ion channel regulation (Pan et al., 2008; Ma et al., 2015), pro-angiogenesis (Cai et al., 2007), and anti-inflammation (Pan et al., 2011; Wallace and Wang, 2015). The realization of biological importance of H$_2$S in numerous cells, tissues and organs is now shedding light on the pathogenesis of various cardiovascular diseases, and paving the way for innovative therapeutic interventions (Wallace and Wang, 2015; Zheng et al., 2017). Meanwhile, regulation of H$_2$S functions during cardiovascular diseases remains to be better understood.

THE MODULATION OF ENDOGENOUS H$_2$S BIOSYNTHESIS IN CARDIOVASCULAR SYSTEM

Endogenous H$_2$S is produced in mammalian tissues by primarily enzymatic or non-enzymatic pathways (Li et al., 2011; Martelli et al., 2012; Pan et al., 2012; Mani et al., 2014). Current understanding of H$_2$S biology has arisen mostly from research

work focused on enzymatic pathways (Liu et al., 2012; Wallace and Wang, 2015). The majority of endogenous H$_2$S is synthesized by CBS (Szabo, 2007), CSE (Zhao et al., 2001), and 3-MST (Shibuya et al., 2009a,b). CBS and CSE may produce H$_2$S from cysteine alone or from cysteine with homocysteine (Kimura, 2015). 3-MST produces endogenous H$_2$S from one of the following substrates: 3-MP by CAT, thioredoxin, dihydrolipoic acid and D-cysteine along with DAO (Mikami et al., 2011; Yadav et al., 2013). All three H$_2$S-synthesizing enzymes have been reported to be expressed by cardiovascular cells (Yang and Wang, 2015) (**Figure 1**). The distribution of H$_2$S-producing enzymes in mammalian tissues is tissue-specific (Pan et al., 2012). CBS expression predominates in the brain, nervous system, liver, and kidneys, while CSE is a major H$_2$S-synthesizing enzyme present in cardiovascular system under normal physiological conditions (Yang and Wang, 2015). 3-MST, along with CAT, accounts for H$_2$S production in vascular endothelium in cardiovascular system (Shibuya et al., 2009a). In addition to their tissue-specific distribution, the intracellular localization of the three enzymes is different (Pan et al., 2012; Donnarumma et al., 2017). While CBS and CSE are cytosolic enzymes (Pan et al., 2012), 3-MST is present in both the mitochondrial and the cytosol with approximately two thirds of 3-MST found in the mitochondria (Li et al., 2009). Despite these findings, there is no definitive information regarding the relative contributions of each of the three enzymes on circulating and tissue H$_2$S levels (Donnarumma et al., 2017). To maintain an appropriate physiological balance of H$_2$S metabolism, endogenous H$_2$S is inactivated in the biological systems by the enzymes ETHE1, SQR, and CDO, or by means of mitochondrial oxidation, cytosolic methylation, scavenging by glutathione disulfide or other metallo- or disulfide-containing molecules, as well as by release from the lungs (Mani et al., 2014; Donnarumma et al., 2017; Rose et al., 2017).

The critical roles of H$_2$S at its physiologically relevant concentrations on the cardiovascular homeostasis have been well documented (Sun et al., 2011; Liu et al., 2012; Pan et al., 2012; Wang R. et al., 2015; Nagpure and Bian, 2016). The H$_2$S levels in plasma and in organ tissues are regulated strictly by its generation and consumption under physiologic conditions (Liu et al., 2012). The H$_2$S concentrations vary in different cells, tissues and organs and maintained within a certain range (Pan et al., 2012). Physiological levels of H$_2$S range from 15 nM to 300 μM *in vivo* and the wide range of H$_2$S levels may be due to variable detection methods used and the tissues analyzed (Liu et al., 2012; Hackfort and Mishra, 2016). Notably, significant changes of endogenous H$_2$S levels (change of H$_2$S-producing enzyme expression or its activity) have been clearly correlated to the pathogenesis of cardiovascular diseases, including heart failure, myocardial ischemia and atherosclerosis as indicated by both experimental and clinical evidence (Jiang et al., 2005; Feng et al., 2015; Gao et al., 2015; Wang W. et al., 2015; Yang and Wang, 2015; Kanagy et al., 2017; Li et al., 2017). Supplementation with exogenous H$_2$S or modulation of endogenous H$_2$S production markedly attenuates myocardial injury and improves cardiac function. For example, administration of SG1002 (a novel H$_2$S
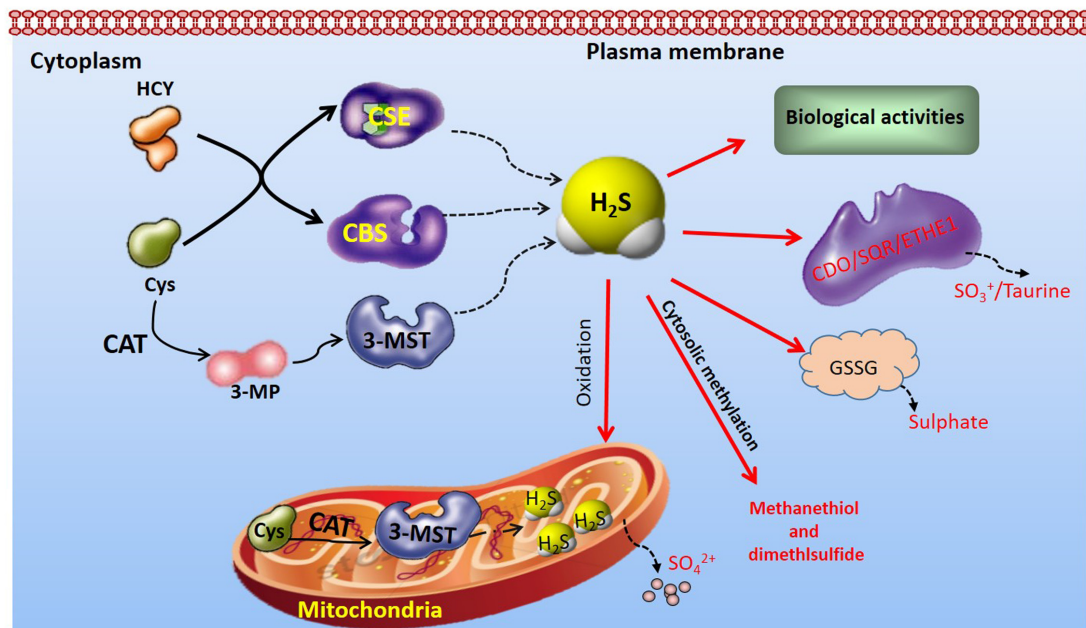
FIGURE 1 | Overview of H₂S-producing enzymes distribution and endogenous H₂S metabolism CBS and CSE, distributed in the cytoplasm, produce H₂S from Cys alone or from cysteine with HCY. In contrast, endogenous H₂S production by 3-MST is primarily from 3-MP, which is produced from cysteine and α-ketoglutarate by CAT. 3-MST is distributed in both mitochondria and cytoplasm. The endogenous H₂S is inactivated in the biological systems by the enzymes ETHE1, SQR, and CDO, or by means of mitochondrial oxidation, cytosolic methylation, scavenging by GSSG or other metallo- or disulfide-containing molecules. 3-MP, 3-mercaptopyruvate; 3-MST, 3-mercaptopyruvate sulfurtransferase; CAT, cysteine aminotransferase; CBS, Cystathionine β-synthase; CDO, cysteine dioxygenase; CSE, cystathionine γ-lyase; Cys, cysteine; HCY, homocysteine; ETHE1, ethylmalonic encephalopathy protein 1; GSSG, glutathione disulfide; SQR, sulfur:quinone oxidoreductase.

prodrug, 400 mg) is reported to result in increased H₂S levels and circulating NO bioavailability, and decreased circulating natriuretic peptide levels in patients with heart failure (Polhemus et al., 2015).

IMMUNEREGULATORY EFFECTS OF H₂S IN CARDIOVASCULAR DISEASES

The physiological and biomedical importance of H₂S has been recognized in the cardiovascular homeostasis. Accumulating evidence has demonstrated the beneficial effects of H₂S-based therapies in cardiovascular disorders, including atherosclerosis, ischemic and heart diseases, which have been well addressed earlier by high-quality reviews (Szabo, 2007; Jin et al., 2010; Liu et al., 2012; Wang, 2012; Polhemus and Lefer, 2014). The roles of H₂S in modulating inflammatory and immune processes during cardiovascular diseases have been emerging. H₂S has been shown to regulate various immune cell functions, such as T-cell activation and proliferation, monocyte and polymorphonuclear cell apoptosis, leukocyte adhesion and infiltration, and inflammatory cytokine release by immune cells. Recent evidence has highlighted that H₂S also actively regulates immuno-inflammatory processes in cardiovascular diseases. The current review focuses on immune-inflammatory modulation in H₂S-mediated cardiovascular homeostasis in conditions including myocardial ischemia, heart failure, and atherosclerosis.

MYOCARDIAL ISCHEMIA

Myocardial infarction is the leading cause of death worldwide with a yearly incidence of 1 million cases (Mozaffarian et al., 2015). During the deprivation of oxygen-carrying blood, combined with nutrient starvation, cardiomyocytes become insensitive to oxygen, leading to MI (Ghaderi et al., 2017). For those patients who undergo acute MI, the most effective therapeutic intervention is timely and effective myocardial reperfusion *via* revascularization combined with routine medical therapy (Hausenloy and Yellon, 2013). However, myocardial reperfusion can itself trigger cardiomyocyte death, an important complication of reperfusion therapy for MI, known as myocardial reperfusion injury (Boag et al., 2017). To date, no effective treatment has been identified. Among the pathological mechanisms underlying MI/R injury, inflammation and inflammatory cell infiltration, together with the activation of innate and adaptive immune responses, are the hallmarks of MI and reperfusion injury (Yellon and Hausenloy, 2007; Nahrendorf et al., 2010; Coggins and Rosenzweig, 2012; Frangogiannis, 2012; Swirski and Nahrendorf, 2013; Liu et al., 2016). Accumulating evidence suggests that modulation of excessive inflammation activation by negative regulation of toll-like receptor signaling and recruitment of inflammatory cells represents a promising therapeutic approach for MI and reperfusion injury (Yellon and Hausenloy, 2007; Coggins and Rosenzweig, 2012).

As the third endogenous gasotransmitter, H$_2$S has emerged as an important mediator in maintaining cardiovascular homeostasis. Our group demonstrated for the first time that decreased plasma H$_2$S levels were associated with increased infarct size and mortality. Administration of sodium hydrogen sulfide (NaHS, an exogenous H$_2$S donor) decreased the infarct size of the left ventricle and MI-associated mortality in rats (Zhu et al., 2007). However, the changes of H$_2$S levels during myocardial ischemia are still controversial. Ali et al. (2016) observed that serum H$_2$S was significantly increased in ST-elevation acute MI patients. Li et al. (2016) have shown that plasma H$_2$S levels decreased after acute MI surgery in rats. This observation is consistent with the previous study that either exogenous H$_2$S administration or modulation of endogenous H$_2$S production reduced myocardial ischemia-reperfusion injury in experimental models through restoration of H$_2$S levels after ischemia (Elrod et al., 2007). The controversial results on serum H$_2$S levels in ischemic myocardium cannot be readily explained by the different detection methods or the different species tested. However, the inconsistent results of serum H$_2$S indeed merit further investigations.
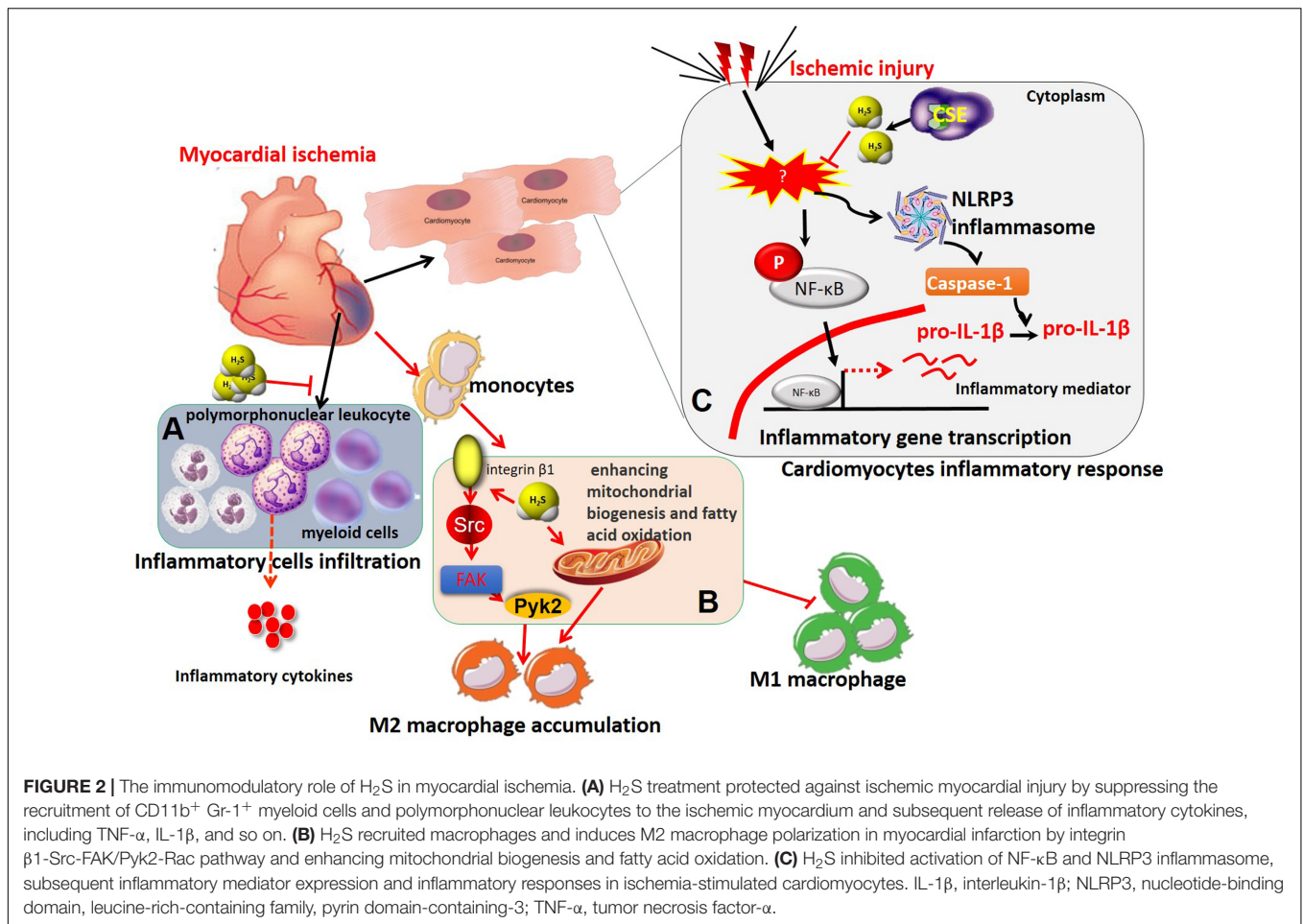
In myocardium, enhanced H$_2$S levels, whether by H$_2$S supplementation or increased endogenous H$_2$S production, have been found to protect the heart against ischemic injury. The exact cardioprotective mechanism of H$_2$S has yet to be clarified but a number of molecular mechanisms have been identified, including vasodilation, anti-inflammation, antioxidation, anti-apoptosis, and modulation of cellular metabolism (Pan et al., 2012). MI and reperfusion injury trigger a complex immune-inflammatory responses in the injured myocardium, including inflammatory leukocyte infiltration and release of cytokines, such as IL-6, IL-8 and TNF-α. Recently, several studies, including our own, have demonstrated that H$_2$S plays an important role in immune-inflammatory processes during MI and reperfusion injury (Elrod et al., 2007; Sodha et al., 2009; Miao et al., 2016a,b) (**Figure 2**). Neutrophils and leukocytes migrate into the infarcted myocardium during the first few hours after the onset of ischemia and peak after 1 day (Yellon and Hausenloy, 2007). Exogenous H$_2$S administration or overexpression of the H$_2$S-producing enzyme CSE significantly decreased leukocytes and neutrophil infiltration within the ischemic zone and markedly reduced myocardial inflammatory cytokine production during MI and reperfusion injury (Elrod et al., 2007). Additionally, exogenous H$_2$S therapy was shown to attenuate cardiomyocyte apoptosis in the AAR of heart in a rat model of MI/R, whereas it decreased polymorphonuclear leukocyte accumulation and inflammatory mediators in the AAR from rat hearts subjected to regional MI/R (Sivarajah et al., 2009). Meanwhile, recruited monocytes/macrophages persist for days in the infarct area and contribute to inflammation, phagocytosis, proteolysis, angiogenesis, and collagen deposition (Nahrendorf et al., 2010). Modulated macrophage infiltration decreased inflammation, diminished interstitial fibrosis and improved cardiac remodeling and dysfunction (Nahrendorf et al., 2010). In a murine MI model subjected to pre- and post-coronary artery occlusion, exogenous H$_2$S treatment reduced the recruitment of CD11b^{+} Gr-1^{+} myeloid cells to the myocardium, inhibited their migration

from the splenic reservoir, and decreased serum TNF-α and IL-1β levels, thereby protecting against ischemic myocardial injury (Zhang et al., 2014). Recently, our study demonstrated that exogenous H$_2$S treatment increased macrophage infiltration into the infarcted myocardium at the early stage of MI in both wild type and CSE-deficient mice (Miao et al., 2016b). In this study, exogenous H$_2$S treatment promoted the migration of macrophages *in vitro*. Meanwhile, exogenous H$_2$S treatment induced the activation of phosphor-Src, -Pyk2, -FAK[397], and -FAK[925]. Moreover, exogenous H$_2$S treatment induced internalization of integrin β1 on macrophage surface and promoted migration of macrophages and activation of Src signaling (Miao et al., 2016b). In our very recent study, we further demonstrated that exogenous H$_2$S treatment ameliorated post-MI pathological cardiac remodeling and dysfunction in wild-type and CSE-deficient mice, decreased infarct size and mortality, and promoted M2 polarization of macrophages at the early stage of MI (Miao et al., 2016a). Notably, adoptive transfer of exogenous H$_2$S-treated bone marrow-derived macrophages into wild-type and CSE-deficient mice with depleted macrophages also improved MI-induced cardiac dysfunction. A similar profile was also observed by Ji et al. (2017) that exogenous H$_2$S treatment promoted microglia switch from a pro-inflammatory M1 phenotype to the modulatory M2 phenotype in ischemic stroke mice. Further mechanistic investigations demonstrated that exogenous H$_2$S-induced M2 polarization of macrophages was achieved by enhanced mitochondrial biogenesis and fatty acid oxidation (Miao et al., 2016a).

In addition to regulatory effects of H$_2$S on immune cell infiltration and phenotype switch, it also directly inhibits inflammatory responses in ischemic myocardium. For example, we found that *S*-propargyl-cysteine (SPRC, a novel endogenous H$_2$S modulator) markedly attenuated LPS-induced TNF-α, ICAM-1, and iNOS expression in cardiomyocytes through modulation of CSE/H$_2$S pathway by impairing inhibitory κBα (IκBα)/nuclear factor-κB (NF-κB) inflammatory signaling and by activating PI3K/Akt signaling pathway (Pan et al., 2011). In addition, Toldo et al. (2014) revealed that Na$_2$S (a H$_2$S donor) administration during MI/R *in vivo* or *in vitro* prevented the activation of nucleotide-binding domain, leucine-rich-containing family, pyrin domain-containing-3 (NLRP3) inflammasome and caspase-1, a macromolecular complex responsible for sensing tissue injury or 'danger' and amplifying the inflammatory responses. Moreover, the NLRP3 inflammasome-inhibiting effects of H$_2$S were completely abolished with deletion of microRNA-21, demonstrating that H$_2$S suppressed myocardial inflammatory responses by inhibition of NLRP3 inflammasome activation and was dependent on microRNA-21 (Toldo et al., 2014) (**Figure 2**).

HEART FAILURE

Heart failure is an inability of the heart to adequately meet the metabolic needs of the body, a clinical disease causing significant morbidity and mortality. Heart failure is the final

FIGURE 2 | The immunomodulatory role of H₂S in myocardial ischemia. **(A)** H₂S treatment protected against ischemic myocardial injury by suppressing the recruitment of CD11b⁺ Gr-1⁺ myeloid cells and polymorphonuclear leukocytes to the ischemic myocardium and subsequent release of inflammatory cytokines, including TNF-α, IL-1β, and so on. **(B)** H₂S recruited macrophages and induces M2 macrophage polarization in myocardial infarction by integrin β1-Src-FAK/Pyk2-Rac pathway and enhancing mitochondrial biogenesis and fatty acid oxidation. **(C)** H₂S inhibited activation of NF-κB and NLRP3 inflammasome, subsequent inflammatory mediator expression and inflammatory responses in ischemia-stimulated cardiomyocytes. IL-1β, interleukin-1β; NLRP3, nucleotide-binding domain, leucine-rich-containing family, pyrin domain-containing-3; TNF-α, tumor necrosis factor-α.

outcome of conditions with varying etiologies. Atherosclerosis, risk factors, and comorbidities such as diabetes and obesity, many of which have an inflammatory component, typically precede MI injury (Odegaard and Chawla, 2013). The smoldering immune-inflammatory response impedes infarct healing by interfering with resolution of local inflammation and delaying the reparative phase (Swirski and Nahrendorf, 2013). Although the prognosis of patients with acute MI is largely determined by the extent of myocardial tissue loss, immune-inflammation also plays a critical role in the evolution of MI-induced cardiac remodeling and may tip the balance in favor of heart failure. Kondo et al. (2013) reported that the myocardial and circulating H₂S levels were markedly reduced in experimental models of heart failure. In addition, they found that CSE-deficient mice exhibited greater cardiac dilatation and dysfunction compared to wild-type mice after transverse aortic constriction. In contrast, cardiac-specific CSE transgenic mice maintained cardiac structure and function after transverse aortic constriction. Recently, we also demonstrated that SPRC (a novel endogenous H₂S modulator) therapy prevented doxorubicin-induced heart failure partially via regulation of gp130/STAT3 pathways. All these data suggest that both exogenous and endogenous H₂S exhibit cardioprotective effects in heart failure.

In heart failure, accumulating experimental and clinical evidence points to a gradual state of immune-inflammatory activation accompanied by the progression of ventricular dysfunction with leukocyte activation and release of inflammatory mediators. For example, the inflammatory biomarker C-reactive protein, and inflammatory cytokines, such as TNF-α and IL-6, increase systemically in heart failure, and leukocytosis is associated with disease progression (Shirazi et al., 2017). Our previous study demonstrated that exogenous H₂S administration markedly inhibited inflammatory cytokine expression in an *in vivo* model of heart failure associated with improving cardiac function and attenuating myocardial fibrosis (Pan et al., 2013). This potent beneficial pharmacological effects of H₂S, at least partially, was associated with decreased Nox4/ROS/ERK1/2 signaling and increased HO-1 expression (Pan et al., 2013). In addition, H₂S also inhibited chronic inflammatory responses and attenuated myocardial hypertrophy in experimental models of myocardial infarction and pressure overload induced via transverse aortic constriction (Nishida et al., 2012). Furthermore, exogenous H₂S treatment also reduced recruitment of CD11b⁺Gr-1⁺ cells in infarct myocardium and peripheral blood and attenuated cardiac dilation in chronic ischemia-mediated infarcted myocardium in mice (Wu et al.,

2017). These findings support the emerging view that H$_2$S has potent immuno-inflammatory regulatory activities in ischemia-induced heart failure, resulted in reduced interstitial fibrosis, cardiac hypertrophy as well as improved overall survival (**Figure 3**).

Angiogenesis is a complex biological process that leads to increased blood flow and promotes cardiac repair and myocardium survival during heart failure. Therefore, promoting myocardial angiogenesis is a novel therapeutic strategy for the treatment of heart failure (Bao et al., 2013; Wang and Cai, 2016). In recent years, the gasotransmitter H$_2$S has become apparent that it is capable of mediating angiogenesis and improving cardiac function after heart failure (Givvimani et al., 2011; Polhemus et al., 2013). In a mouse model of transverse aortic constriction-induced heart failure, chronic H$_2$S treatment with diallyl trisulfide improved left ventricular remodeling and function by inducing angiogenesis via upregulation of VEGF and endothelial NO synthase. Additionally, the study also indicated that H$_2$S upregulated the endogenous antioxidants, GPx1 and HO-1 (Polhemus et al., 2013). These results were further confirmed by our previous study that chronic H$_2$S therapy with SPRC induced angiogenesis by a mechanism involving STAT-3 interacting with VEGF receptor 2 in a rat model of chronic myocardial ischemia (Kan et al., 2014). Recruitment of monocytes/macrophages to the site of injury not only promote inflammatory responses and pathological tissue remodeling but is also required for the resolution of inflammation and regenerative activities, such as angiogenesis (Lavine et al., 2014; Howangyin et al., 2016). One proposed explanation for these observations is that distinct macrophage subpopulations may mediate inflammatory (M1) and reparative (M2) macrophage activities (Lavine et al., 2014; Kolluru et al., 2015; Miao et al., 2016a). H$_2$S modulates monocytes/macrophages phenotypes, which produces beneficial effects in angiogenesis in chronic ischemic diseases. Although there is no direct evidence that H$_2$S modulates macrophage phenotype in heart failure, Kolluru et al. (2015) using femoral artery ligation model has demonstrated that CSE dysregulation or deficiency as well as endogenous H$_2$S production have a significant effect on monocytes/macrophage recruitment and subsequent expression of angiogenetic factors (bFGF and VEGF) under ischemic conditions. Yet exogenously administering H$_2$S or modulation of endogenous H$_2$S production promoted monocyte/macrophage recruitment and angiogenetic factor expression, leading to angiogenesis and restored blood flow (Kolluru et al., 2015). However, the contribution of M1 vs. M2 macrophages in H$_2$S-mediated angiogenetic responses in heart failure has yet to be clarified in future investigation. In addition, CD4$^+$T lymphocyte deficiency delays the transition from M1 to M2 macrophages and impairs healing of the heart (Hofmann et al., 2012). Likewise, depletion of dendritic cells disturbs resolution of inflammation (Hofmann et al., 2012; Swirski and Nahrendorf, 2013). There is still lack of direct evidence for an immunoregulatory role of H$_2$S on immune cell phenotypes in heart failure. Given that leukocytes play a key role in heart failure, the immunoregulatory function of H$_2$S on different immune cell subsets merits further investigations.
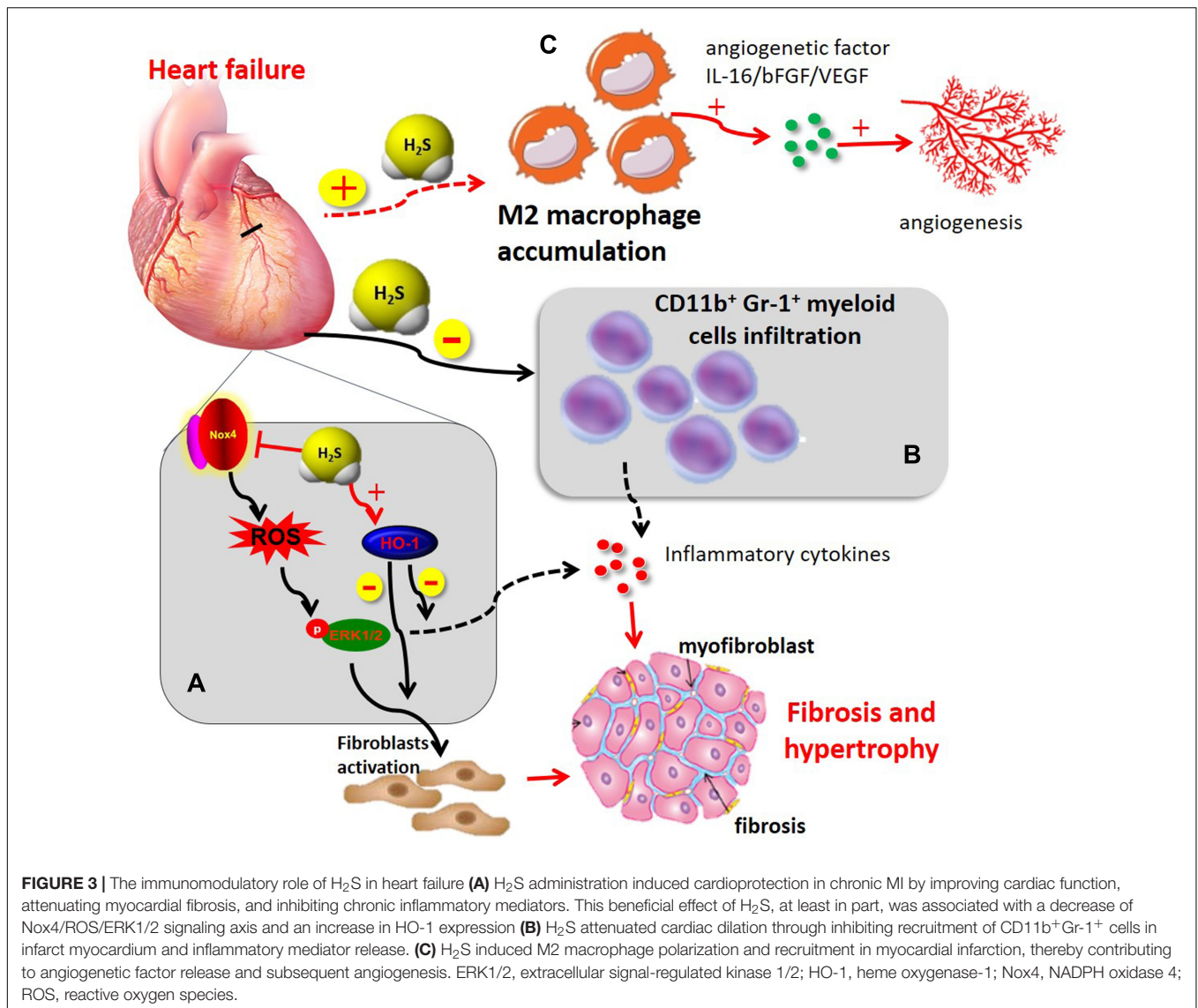
Taken together, preclinical evidence suggests that H$_2$S significantly improve cardiac function in the setting of heart failure via immunoregulatory activities, including modulating immune cell phenotypes, suppressing inflammatory responses and inflammatory cell infiltration, which represents a therapeutic strategy for heart failure (**Figure 3**).

ATHEROSCLEROSIS

Atherosclerosis, a vascular disease at the susceptible sites in medium and large-sized arteries, is the pathological basis of coronary heart disease and the major cause of death in developed countries. The development of atherosclerosis is a complex multifactorial process that involves vascular inflammation, VSMC proliferation and migration, thrombus formation, as well as abnormal immune responses including monocyte infiltration and differentiation, and lesion-resident macrophage conversion into foam cells (Pan et al., 2012). Through the factors that initiate plaque formation and are currently being debated, it is no longer news that atherosclerosis is more than a mere cholesterol storage disease. Immune inflammation in the pathogenesis of atherosclerosis has now gained widespread recognition (Libby and Hansson, 2015).

Recent studies have suggested that dysfunctional CSE and reduced endogenous H$_2$S levels are linked to the pathogenesis of atherosclerosis (Wang et al., 2009; Mani et al., 2014). Exogenous H$_2$S treatment protects rat aortic VSMC from hyperhomocysteine- or ROS-induced cytotoxicity, which is considered independent of atherogenic risk factors (Yan et al., 2006). In a genetic model of hyperhomocysteinemia, CBS$^{-/-}$ApoE$^{-/-}$ mice exhibited accelerated aortic atherosclerosis compared with ApoE$^{-/-}$ mice after 6 months of age in the absence of dietary manipulation (Wang et al., 2003). Since only 2% of CBS$^{-/-}$ApoE$^{-/-}$ mice survived up to 6 months of age, the pathophysiological relevance of CBS$^{-/-}$ to H$_2$S metabolism in atherosclerosis is not clear (Wang et al., 2003). At the same time, CSE expression and H$_2$S production were reduced during neointimal hyperplasia in carotid artery in rats, and that exogenous H$_2$S treatment markedly reduced neointimal formation (Meng et al., 2007). Furthermore, Wang et al. (2009) reported that plasma H$_2$S level and H$_2$S production in atherosclerotic aortic tissues were decreased in ApoE$^{-/-}$ atherosclerotic mice. Exogenous H$_2$S treatment resulted in elevated plasma H$_2$S level and reduced the atherosclerotic plaque size in the aortic root of ApoE$^{-/-}$ mice, whereas DL-propargylglycine (PPG, a potent CSE inhibitor) reduced plasma H$_2$S level and enlarged plaque size in the aorta (Wang et al., 2009). Furthermore, atherogenic diet feeding to ApoE$^{-/-}$ CSE$^{-/-}$ mice exacerbated the development of atherosclerosis compared to mice with only ApoE or CSE deficiency. Treatment of CSE$^{-/-}$ mice with exogenous H$_2$S inhibited the progression of atherosclerosis (Mani et al., 2013), which provided clear evidence that supports a protective role of H$_2$S against atherosclerosis.

Initially, exploration of the immune-inflammatory aspects of atherogenesis focused on the intima, the site where

FIGURE 3 | The immunomodulatory role of H_2S in heart failure **(A)** H_2S administration induced cardioprotection in chronic MI by improving cardiac function, attenuating myocardial fibrosis, and inhibiting chronic inflammatory mediators. This beneficial effect of H_2S, at least in part, was associated with a decrease of Nox4/ROS/ERK1/2 signaling axis and an increase in HO-1 expression **(B)** H_2S attenuated cardiac dilation through inhibiting recruitment of CD11b^{+}Gr-1^{+} cells in infarct myocardium and inflammatory mediator release. **(C)** H_2S induced M2 macrophage polarization and recruitment in myocardial infarction, thereby contributing to angiogenetic factor release and subsequent angiogenesis. ERK1/2, extracellular signal-regulated kinase 1/2; HO-1, heme oxygenase-1; Nox4, NADPH oxidase 4; ROS, reactive oxygen species.

atheromata take root. As probing has deepened, researchers have come to recognize that influence arising from all three layers of arteries can affect the pathophysiology of this disease (Libby and Hansson, 2015; Gistera and Hansson, 2017). Indeed, immune-inflammatory responses participate in atherosclerosis by modifying the arterial tree at various levels (Libby and Hansson, 2015). Accumulating evidence has indicated that H_2S is involved in the immune-inflammatory processes in atherosclerosis in a number of preclinical models of atherosclerosis (**Figure 4**). The vascular endothelial dysfunction, characterized by the loss or dysregulation of the homeostasis, is considered an important early event in the development of atherosclerosis (Mani et al., 2014). Endothelial dysfunction is associated with increased oxidative stress, adhesion molecules expression, synthesis of inflammatory and pro-thrombotic factors, and abnormal modulation of vascular tone (Mani et al., 2014). Wang et al. (2009) demonstrated that ICAM-1 levels

were significantly increased, accompanied by increased size of the atherosclerotic plaque in ApoE$^{-/-}$ atherosclerotic mice. The ICAM-1 levels and atherosclerotic plaque were reduced in aortas of ApoE$^{-/-}$ mice following treatment with exogenous H_2S. The inhibitory mechanism of H_2S on ICAM-1 expression was addressed in endothelial cells *in vitro*, where exogenous H_2S was shown to inhibit NF-κB activation (Wang et al., 2009). We also studied the protective effects of exogenous H_2S on TNF-α-induced dysfunction in human umbilical vein endothelial cells *in vitro* (Pan et al., 2012). Mechanically, exogenous H_2S inhibited TNF-α-induced ICAM-1 and VCAM-1 protein expression, P-selectin and E-selectin mRNA expression, as well as monocyte adhesion to endothelial cells (Pan et al., 2012). Similarly, Feng et al. (2017) found that CSE/H_2S pathway was significantly downregulated in the development of pulmonary vascular endothelial inflammation. H_2S treatment could reduce pulmonary vascular pressure, relieve pulmonary
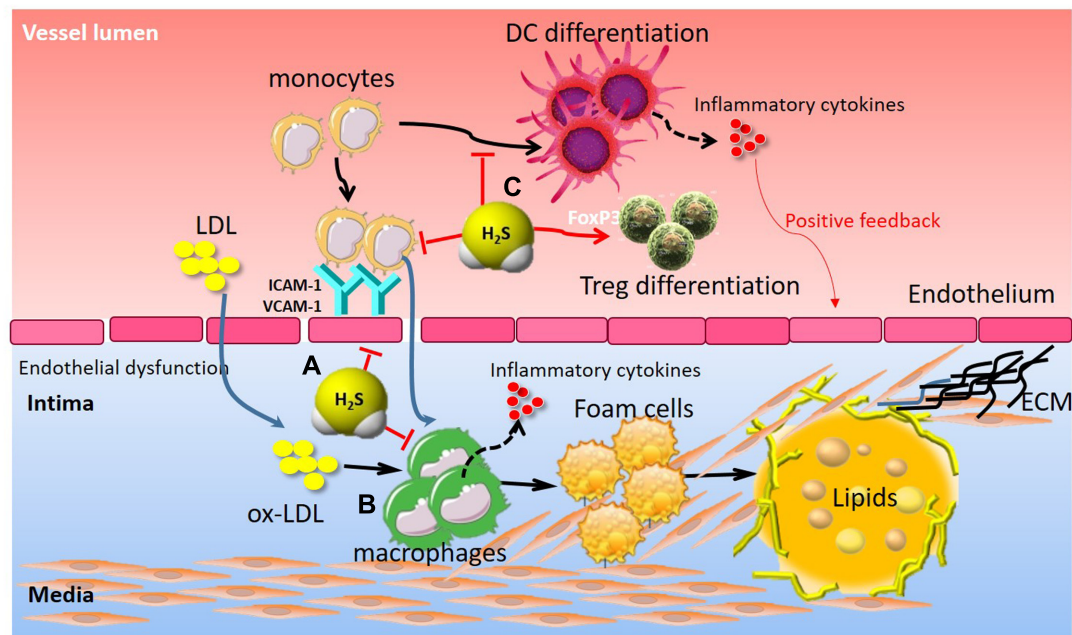
FIGURE 4 | The immunomodulatory role of H_2S in atherosclerosis. **(A)** H_2S attenuated endothelial dysfunction, adhesion molecules (ICAM-1, VCAM-1) expression, and leukocyte adhesion. **(B)** H_2S inhibited monocyte activation and foam cell formation, thereby contributing to inflammatory cytokine release, VSMC proliferation and subsequent atherosclerotic plaque formation. **(C)** H_2S suppressed monocyte differentiation into inflammatory dendritic cells and induced CD4$^+$Foxp3$^+$ Treg cell differentiation, thereby contributing to vascular immune homeostasis. Treg, regulatory T cell; ICAM-1, intercellular adhesion molecule-1; VCAM-1, vascular cell adhesion molecule-1.

vascular remodeling, inhibit pulmonary vascular endothelial cellular inflammation, and attenuate the NF-κB signaling pathway in pulmonary arterial endothelial cells. In contrast, Zanardo et al. (2006) demonstrated that suppression of endogenous H_2S production, by CSE blockade using β-cyano-L-alanine, led to enhanced leukocyte adhesion, leukocyte infiltration, and edema formation while H_2S donors produced opposite effects.

Macrophage is thought to play an important role in atherosclerosis by generating lipid-laden foam cells and by secreting inflammatory mediators (Moore and Tabas, 2011). Macrophage uptake of oxidized-low density lipoproteins (oxLDL) contributes to formation of lipid-laden "foam cells," the primary component of atherosclerotic lesions (Moore and Tabas, 2011). However, H_2S plays an inhibitory role in macrophage-derived foam cell formation. *In vitro*, Wang et al. (2013) demonstrated that oxLDL may down-regulate the CSE/H_2S pathway, which exerts an anti-inflammatory effect on oxLDL-stimulated macrophage by suppressing JNK/NF-κB signaling. Treatment with exogenous H_2S or upregulation of endogenous H_2S by CSE overexpression markedly attenuated oxLDL-mediated inflammatory responses and JNK/NF-κB signaling activation (Wang et al., 2013). Du et al. (2014) further elucidated that the sulfhydration of free thiol group on cysteine 38 in NF-κB p65 served as a molecular mechanism by which H_2S inhibited NF-κB activation in oxLDL-induced macrophage inflammation. In addition, H_2S also abrogated oxLDL-induced macrophage foam cell formation.

Mechanistically, H_2S inhibited oxLDL-induced intracellular lipid accumulation, reduced TC, EC, and EC/TC ratio in macrophages by down-regulating expressions of CD36, scavenger receptor A and acyl-coenzyme A: cholesterol acyltransferase-1 (Zhao et al., 2011). In agreement with these findings, H_2S treatment attenuated high glucose + oxLDL-induced foam cell formation (Xie et al., 2016). The protective effect of H_2S can be, at least in part, attributed to Nrf2 activation via Keap1 *S*-sulfhydration at Cys151. Furthermore, H_2S significantly inhibited macrophage accumulation and reduced the aortic atherosclerotic lesion in ApoE$^{-/-}$ mice. However, PPG demonstrated the opposite effect: enlarging the lesion area and macrophage accumulation in the lesions of ApoE$^{-/-}$ mice (Lin et al., 2016). H_2S supplementation also reduced lesion zone and macrophage infiltration in diabetic LDLr$^{-/-}$ mice. The expression of adhesion molecules and macrophages/monocyte recruitment in sub-endothelial space are critical for the initiation and development of atherosclerotic lesions. The preferential accumulation of Ly-6C^{high} monocytes in the growing atheromata relied on the C-C chemokine receptor type 2 (CCR2)-monocyte chemotactic protein-1 (CCL2), CX3CR1-CX3CL1, and CCR5-CCL5 (Gao et al., 2015), and neutralizing these axes in mice almost abolished atherosclerosis *via* reduced macrophage infiltration and increased plaque stability (Moore and Tabas, 2011). *In vivo*, Zhang et al. (2012) observed that H_2S treatment downregulated CX3CR1 and CX3CL1 expression on macrophages through modulation of the transcription factors PPAR-γ and NF-κB. They also demonstrated that, by interfering with the CX$_3$CL1/CX$_3$CR1

dyad, supplementation of mice with the exogenous H$_2$S reduced the development of atherosclerotic plaques (Zhang et al., 2012). They further found in a clinical study that plasma H$_2$S level was markedly reduced, whereas plasma CCL2 and CX3CL1 levels were substantially increased in patients with ACS compared to patients with SAP or non-CAD patients (Gao et al., 2015). Furthermore, patients with ACS exhibited significantly higher proportions of CD14$^+$CCR2$^+$CX3CR1$^+$ (intermediate monocytes, Mon2) and CD14$^+$CCR2$^-$CX3CR1$^+$ monocytes (non-classical monocytes, Mon3) but a lower percentage of CD14$^+$CCR2$^+$CX3CR1$^-$ monocytes (classical monocytes, Mon1) than patients with SAP or non-CAD did Gao et al. (2015). Lastly, they identified that plasma H$_2$S level was negatively correlated with the proportion of Mon2 monocyte subsets, suggesting that impaired endogenous H$_2$S synthesis in ACS may facilitate monocyte subset conversion from Mon1 to Mon2 or Mon3, leading to atherosclerotic plaque instability, and the development of ACS (Gao et al., 2015). However, the precise mechanism by which H$_2$S regulates monocyte phenotypes in CAD remains to be better understood. Similarly, in methionine/choline-deficient diet-induced experimental steatohepatitis in mice, H$_2$S treatment significantly prevented CX$_3$CR1$^+$CD11b$^+$/F4$^-$80$^+$ cell accumulation and decreased circulating and hepatic TNF-α levels (Sutti et al., 2015). These CX$_3$CR1$^+$ cells were further characterized by the co-expression of inflammatory monocyte (Ly6C, CD11b) and dendritic cell (CD11c, MHCII) markers as well as by a sustained TNF-α production, suggesting that H$_2$S could prevent monocyte differentiation into inflammatory monocyte-derived inflammatory dendritic cells and limit their M1 polarization (Sutti et al., 2015).

T-helper (Th) cells play a critical role in mediating adaptive immunity. During TCR activation in a particular cytokine milieu, naive CD4$^+$T cells may differentiate into different lineages of Th cells, including Th1, Th2, Th17, and Treg cells. Accumulating evidence has shown that peripheral activation of Treg and subsequent recruitment to atherosclerotic plaque limit the lesion progression in experimental models by down-regulating inflammatory responses which include multiple mechanisms (Libby et al., 2013; Delgado-Maroto et al., 2017). However, minor populations of Foxp3$^+$ Treg cells were found in human atherosclerotic plaques at all stages of the disease (Gistera and Hansson, 2017). Transfer of Foxp3$^+$ Treg cells decreased atherosclerosis in hypercholesterolaemic mice (Gistera and Hansson, 2017). More recently, Yang et al. (2015) found that reduced H$_2$S levels were responsible for impaired CD4$^+$Foxp3$^+$ Treg cell differentiation and function as well as immune dysfunction in mice. Treatment of H$_2$S donor rescued Treg-cell-deficient phenotypes of immune dysfunction in CBS$^{-/-}$ mice and WT Treg cell infusion could partially rescue autoimmunity in CBS$^{-/-}$ mice (Yang et al., 2015). The immune regulatory mechanisms by H$_2$S are that H$_2$S affected sulfhydration of nuclear transcription factor Y subunit beta (NFYB) to control NFYB complex binding to the *Tet1* and *Tet2* promoters, forming a H$_2$S-NFYB-Tet axis to regulate Treg differentiation and immune homeostasis (Yang et al., 2015). Furthermore, H$_2$S can enhance TCR-dependent T cell activation

and IL-2 expression. H$_2$S also enhances T cell proliferation and lineage determination *via* altering cytoskeletal actin dynamics and increasing the reorientation of the microtubule-organizing center (Miller et al., 2012), suggesting that H$_2$S represents a novel immunomodulatory molecule for T cell responses. Therefore, it may be a novel therapeutic approach for chronic immune-inflammatory responses in atherosclerosis *via* targeting H$_2$S metabolism.

CHALLENGES FOR H$_2$S RESEARCH AND FUTURE PERSPECTIVES

Since the first demonstration of the expression of H$_2$S-producing enzymes in the mammalian system, there have been numerous experimental studies conducted on the role of H$_2$S modulation, by ways of overexpression/inhibition of H$_2$S-synthesizing enzymes or H$_2$S donor, on cardiovascular homeostasis (Salloum, 2015). Mechanisms underlying H$_2$S signaling have been uncovered; however, a lot of unknowns on how H$_2$S influences cardiovascular homeostasis remain to be further investigated. Immune-inflammatory responses play a decisive role in different phases of cardiovascular diseases (Gistera and Hansson, 2017; Jones et al., 2017). Data from basic studies support immunoregulatory functions of H$_2$S and therefore the potential of H$_2$S to modulate the immune-inflammatory response to prevent cardiovascular disorders, including ischemic heart disease, atherosclerosis, heart failure, and so on. In other cardiovascular diseases such as hypertension, H$_2$S has been demonstrated to play an important role (Yang et al., 2008). As arterial inflammation and immune dysregulation are involved in the pathogenesis of the disease (Smith and Ferguson, 2016) and H$_2$S has been shown to maintain immune homeostasis, it could be postulated that H$_2$S may play a positive role in such condition. So far literature has been limited to provide further evidence and hence is not covered in the current review, which merit future investigation and verification.

Both pro- and anti-inflammatory effects of H$_2$S have been reported. In numerous studies including our studies, H$_2$S has been characterized for its anti-inflammatory role (Cao and Bian, 2016; Zhou et al., 2016; Feng et al., 2017). In contrast, recent work from different groups has shown a key role of H$_2$S as an inflammatory mediator (Li et al., 2011; Bhatia, 2015). These contradictory observations may result from different experimental settings and approaches, such as cell culture and/or *in vivo* disease models. However, a number of elegant studies suggest that H$_2$S is a potent anti-inflammatory molecule, specifically in the cardiovascular diseases (Polhemus and Lefer, 2014; Miao et al., 2016a). Although the data are debatable, they suggest that H$_2$S may be a double-edged sword and controversies are warranted to encourage future studies to better understand the biological significance of this gaseous molecule in cardiovascular homeostasis. We believe that resolving these issues would drastically advance H$_2$S research.

H$_2$S has a number of biological effects on cardiovascular systems. However, the molecular targets of H$_2$S remains to be fully uncovered. K$_{ATP}$ channels in many cellular systems are

accountable for the effects of H$_2$S. In other cases, H$_2$S seems not to act on the same channels. Until now, the potential molecular targets for H$_2$S are likely to include intracellular proteins or enzymes (such as p66Shc, phospholamban, protein tyrosine phosphatase 1B, mitogen-activated extracellular signal-regulated kinase 1, ATP synthase subunit α, etc.), and transcription factors (such as NF-κB, kelch-like ECH-associating protein 1, specific protein-1 and interferon regulatory factor-1, etc.) as well as membrane receptors (vascular endothelial growth factor receptor 2, insulin receptor, and epidermal growth factor receptor) in cardiovascular system (Li et al., 2011; Ge et al., 2014; Wang et al., 2016). Underlying these functions are the atomic biology, interaction between sulfur atoms and target molecules. In this regard, Tao et al. found a molecular switch in H$_2$S-targeting receptor, the cysteine1024 (Cys1024)-S-S-Cys1045 disulfide bond, in the intracellular kinase domain of vascular endothelial growth factor receptor 2 (Tao et al., 2013), which has prompted the field of H$_2$S biology to a new landmark. Although remarkable progress has been made in delineating the role of the potential targets by H$_2$S in cardiovascular homeostasis, one challenging question that remains in this field is the identification of more precise protein targets that mediate numerous physiological functions. These proteins propose novel targets for therapeutic intervention and drug design in cardiovascular homeostasis, which may accelerate the development and application of H$_2$S related drugs in the future.

Modulation of endogenous H$_2$S levels as a novel potential therapeutic strategy for cardioprotection in patients undergoing cardiovascular disorders and the changed H$_2$S-producing enzymes expression/activities have been directly related to the endogenous H$_2$S generation. Meanwhile, the three H$_2$S-generating enzymes have been broadly localized in cardiovascular system (Pan et al., 2012). Downregulation of the three H$_2$S-producing enzymes is associated with chronic cardiovascular pathologies (Kanagy et al., 2017; Merz et al., 2017). Unfortunately, the H$_2$S-producing enzymes responsible for H$_2$S production and biological function in cardiovascular homeostasis are not clear and consistent in current literature (Kuo et al., 2016; Li et al., 2016). Meanwhile, the roles of H$_2$S degradative enzymes ETHE1, SQR and CDO in cardiovascular immune homeostasis remain largely unexplored and merit further investigation (Rose et al., 2017).

Over the last decade, considerable evidence has been collected, which points to a functional role for H$_2$S in cardiovascular homeostasis, representing a novel promising therapeutic strategy for cardiovascular diseases. However, the majority of the cardiovascular studies involving H$_2$S have been investigated and established in healthy, juvenile, and small animals, making them far removed from the clinical setting of the typical cardiovascular diseases. Meanwhile, improved understanding on the protective actions of H$_2$S, together with rapid development of novel H$_2$S donors (Polhemus and Lefer, 2014; Hackfort and Mishra, 2016; Zheng et al., 2017), has raised heightened enthusiasm for the translational studies. Currently,

there are three cardiovascular H$_2$S trials on clinicaltrials.gov. Therefore, it will be expedient to move one step forward to confirm rigorously the therapeutic effects of H$_2$S in larger animal models before making a complete transition to the clinic.

As with the development of small molecule H$_2$S donors, there are organ-specific issues that need to be considered. Given its ubiquitous nature, it is not surprising that H$_2$S has important functions in a wide range of physiological and pathophysiological processes. H$_2$S delivery will produce a wide range of biological activities, including unwanted side effects. Therefore, the speed and amount of H$_2$S release from different donors should be controllable. Otherwise, a novel H$_2$S donor that could specifically target an organ system would alleviate undesirable effects. Because the cardiovascular system is a circulatory system, the cardiovascular-specific delivery of H$_2$S maintained cardiovascular homeostasis is one of the key challenges being explored in the field.

CONCLUSION

H$_2$S is a ubiquitous gasotransmitter and plays a critical role in immune homeostasis in cardiovascular disorders. Significant changes of endogenous H$_2$S levels (change of H$_2$S-producing enzyme expression or its activity) have been clearly correlated to immune-inflammatory responses in a variety of cardiovascular diseases. We have summarized the latest knowledge on the immune-inflammatory modulatory functions of H$_2$S in cardiovascular diseases and discussed the possible cellular and molecular mechanisms by which it exerts cardiovascular protective actions as well as its therapeutic potential for cardiovascular diseases. Although the molecular targets of H$_2$S remain to be fully elucidated, considerable evidence has demonstrated that H$_2$S is a novel immune-modulator in cardiovascular homeostasis. Insights into the molecular targets of H$_2$S in immune-inflammatory processes may help better understanding of the pathophysiology of these diseases.

AUTHOR CONTRIBUTIONS

X-HL and Y-ZZ designed the subject content of the review article. L-LP, MQ, and X-HL conducted initial search of literature, drafted the manuscript, and prepared the figures and tables. X-HL and Y-ZZ had primary responsibility for final content. All authors read and approved the final manuscript.

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