Potential role of hydrogen sulfide in diabetes-impaired angiogenesis and ischemic tissue repair

Zhongjian Cheng, Raj Kishore

Center for Translational Medicine, Lewis Katz School of Medicine, Temple University, 3500 Broad Street, Philadelphia, PA, 19140, USA

Abstract

Diabetes is one of the most prevalent metabolic disorders and is estimated to affect 400 million of 4.4% of population worldwide in the next 20 year. In diabetes, risk to develop vascular diseases is two-to-four-fold increased. Ischemic tissue injury, such as refractory wounds and critical ischemic limb (CLI) are major ischemic vascular complications in diabetic patients where oxygen supplement is insufficient due to impaired angiogenesis/neovascularization. In spite of intensive studies, the underlying mechanisms of diabetes-impaired ischemic tissue injury remain incompletely understood. Hydrogen sulfide (H\textsubscript{2}S) has been considered as a third gasotransmitter regulating angiogenesis under physiological and ischemic conditions. Here, the underlying mechanisms of insufficient H\textsubscript{2}S-impaired angiogenesis and ischemic tissue repair in diabetes are discussed. We will primarily focuses on the signaling pathways of H\textsubscript{2}S in controlling endothelial function/biology, angiogenesis and ischemic tissue repair in diabetic animal models. We summarized that H\textsubscript{2}S plays an important role in maintaining endothelial function/biology and angiogenic property in diabetes. We demonstrated that exogenous H\textsubscript{2}S may be a therapeutic agent for endothelial dysfunction and impaired ischemic tissue repair in diabetes.

1. Introduction

Diabetes is one of the most prevalent metabolic disorders and is estimated to affect 400 million of 4.4% of population worldwide in the next 20 year [1]. Diabetes has a 2- to 4-fold increased risk to develop vascular diseases compared to non-diabetes [2]. Refractory wounds and critical ischemic limb (CLI) are two of major ischemic vascular complications in diabetic patients where oxygen supplement is insufficient due to impaired angiogenesis/neovascularization. Accumulative studies demonstrated that impaired biology/function and angiogenic property of endothelial cells (ECs) play a critical role in diabetes-induced deficiency of angiogenesis/neovascularization [3-5]. However, the underlying mechanisms remain incompletely understood.

Insufficient gasotransmitters, including nitric oxide (NO) and 1) carbon monoxide (CO) have been considered as crucial regulators of EC dysfunction in diabetes [6]. In the last decades, hydrogen sulfide (H\textsubscript{2}S), a “toxic gas with strong odor of rotten eggs”, has been found in biological system and considered as the third gasotransmitters regulating many biological functions [7]. Especially, insufficient production of H\textsubscript{2}S has been linked to different pathogenesis of cardiovascular diseases such as hypertension, endothelial dysfunction, myocardial infarction and ischemic limb injury [4,5,8-10], and emerged as an important regulator in diabetes-impaired endothelial cell (EC) function/biology, angiogenesis, wound healing and ischemic lamb repair [4,5]. Administration of H\textsubscript{2}S rescued endothelial dysfunction in diabetic animal models [11]. Recently, we provided strong evidence that insufficient production of H\textsubscript{2}S plays a crucial role in diabetes-impaired microvascular endothelial function and angiogenesis in ischemic hindlimb (IHL) of db/db mice [4,5]. In this review, we will summarize the current understanding of the role of H\textsubscript{2}S in diabetes-impaired EC function, angiogenesis, wound and IHL repair.

2. Endogenous H\textsubscript{2}S biosynthesis

In mammalian tissues, H\textsubscript{2}S is mainly produced by three pyridoxal-5’-phosphate (PLP)-dependent enzymes, cystathionin-\gamma-synthase (CBS), cystathionine-\gamma-lyase (CSE) and 3-mercaptopropionate sulfurtransferase (3-MST) in the transulfuration pathway of homocysteine metabolism [12-15]. CBS is predominantly expressed in the central nervous system whereas CSE is abundantly expressed in cardiovascular system [16]. Protein expression of CSE was detected in cultured bovine aortic ECs and human umbilical vein ECs, and endothelial layer of vascular tissues in

* Corresponding authors.
E-mail addresses: zcheng@temple.edu (Z. Cheng), tuf51785@temple.edu (R. Kishore).

https://doi.org/10.1016/j.redox.2020.101704
Received 15 June 2020; Received in revised form 12 August 2020; Accepted 24 August 2020
Available online 29 August 2020
2213-2317/Published by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).
wild-type mice [4, 5, 17]. H₂S is produced in both vascular ECs and VSMCs mainly by activation of CSE [5, 17–21]. Recent studies have shown 3-MST, along with cysteine aminotransferase (CAT), which produces H₂S in the brain as well as in the vascular endothelium (Fig. 1) [15, 22]. Physiological level of H₂S is in wide range between 15 nM and 300 μM depending on detection methods and the tissues analyzed [23–31]. In fact, the concentration of free H₂S in vascular tissues is around 100 times greater than that in the other tissues [26, 32], implying that H₂S is critical in the regulation of vascular homeostasis, endothelial function and angiogenic property of ECs.

In addition to enzymatic synthesis pathways, endogenous H₂S can also be produced through non-enzymatic processes which have not been well understood or characterized. Studies have reported that many factors are involved in non-enzymatic production of H₂S, including glucose, glutathione, inorganic and organic polysulfides and elemental sulfur [33]. H₂S can be generated from glucose either via glycolysis or from phosphoglyconate via NADPH oxidase or reacting with sulfur-containing amino acid methionine, homocysteine or cysteine [34]. H₂S can also be produced by direct reduction of glutathione and elemental sulfur through reducing equivalents of the glucose oxidation pathway [35]. Moreover, thiourea results from a reduction reaction involving pyruvate is an intermediate of sulfur metabolism from the glucose oxidation pathways [36]. Using a florescent probe, we found that H₂S production in ECs is also related to downregulation of CSE levels [50]. Understanding the mechanisms of non-enzymatic impaired EC function may provide therapeutic targets for ischemic tissue injury in diabetes.

One of the underlying mechanisms of diabetes-impaired H₂S production is suggested to be related to hyperglycemia-enhanced H₂S consumption through mitochondria-derived reactive oxygen species (ROS) signaling pathways in ECs [50]. ROS scavenger or mitochondrial uncoupling agents prevented H₂S consumption in high glucose-treated ECs [50]. Another underlying mechanism may be related to downregulation/inactivation of H₂S synthesis enzymes [5, 44, 47, 48]. In good accordance with above studies, we also provide strong evidence that superoxide generation was enhanced whereas H₂S production was reduced in the lung ECs and/or small mesenteric arteries of db/db mice (Table 1) [5]. Moreover, we demonstrated that decreased H₂S production in microvascular ECs is also related to downregulation of CSE levels although studies to understand the underlying mechanisms of diabetes-downregulated CSE level are warranted [5]. Taken together, diabetes is associated with increased ROS-linked H₂S consumption and CSE-mediated H₂S reduction which might be related to increased

3. H₂S signaling mechanisms

H₂S exerts its biological effects mainly via three routes: 1. Reactive oxygen species (ROS)/reactive nitrogen species (RNS) scavenging; 2. Metal center interaction; 3. S-persulfidation [40]. Compared to the first two routes, S-persulfidation, normally called S-sulfhydration, is the key process for H₂S-mediated biological effects. S-sulfhydration is the process in which a thiol (R-SH) is converted into a persulfhydrol (R–SSH). S-sulfhydration modulates the biological activity of proteins by decreasing the pKa and increase in nucleophilicity of persulhydrids with respect to thiols [41]. S-sulfhydration modification as a new post-translational modification is involved in many pathophysiological process including cell survival/death, differentiation, proliferation/hypertrophy, metabolism, endoplasmic reticulum (ER) stress, vascular relaxation, inflammation, oxidative stress [42]. Recently, insufficient Keap1 S-sulfhydration in ECs has been suggested to be involved in pathogenesis of atherosclerosis in STZ-induced diabetic low-density lipoprotein receptor (LDLR)−/− mice [43]. S-sulfhydration modification of targeted proteins from H₂S may provide novel targets for therapeutic/prevention of ischemic tissue repair in diabetes.

4. H₂S in diabetes

The synthesis of H₂S is known to be reduced in diabetic patients and animal models [43, 44]. Plasma H₂S was significantly decreased in high fat-diet-induced diabetic LDLR−/− mice [43]. In streptozotocin (STZ)-induced diabetic rats, blood H₂S level were lower compared with age-matched non-diabetic rats [45]. Endogenous H₂S production was also found to be reduced in type 2 diabetic animals [5, 46, 47]. Plasma H₂S levels were significantly reduced in non-obese diabetic mice [46]. Renal CSE and CBS expression and H₂S production are markedly lowered in spontaneous diabetic Akita mice [44]. Deficient CSE delayed the onset of STZ-induced type 1 diabetes, and diabetes was accompanied by increased pancreatic CSE and CBS protein expression [48]. Recently, we examined H₂S production in small mesenteric arteries of type 2 diabetic db/db mice and non-diabetic db/+ mice with two different methodologies [5]. Using a florescent probe, we found that H₂S production in small mesenteric arteries was decreased to 65% in db/db mice compared with that in db/+ mice. By RP-HPLC detection, we also found that free sulfide levels were reduced to 63.7% (45.9 pM/mg) in the small mesenteric arteries of db/db mice compared with that of db/+ mice [5]. By gas chromatography chemiluminescence and florescent probe, we found that H₂S production was markedly reduced in bone marrow cells (BMCs), plasma and thigh skeletal muscles from db/db mice [4]. We also found that high glucose dose-dependently reduced H₂S production in human microvascular ECs [4]. It has been demonstrated that the negative association between type 2 diabetes and H₂S is reinforced by decreased plasma H₂S levels [45, 49]. Understanding the mechanisms of insufficient H₂S-impaired EC function may provide therapeutic targets for ischemic tissue injury in diabetes.
cardiovascular risk in animal models and experimental models. The underlying mechanisms of diabetes-impaired H$_2$S production are still needed to be explored.

5. H$_2$S as ROS modulator in diabetic ECs

Reactive oxygen species (ROS) generated from ECs is a key factor in the pathogenesis of diabetic complications [51]. H$_2$S was found to be beneficial against oxidative stress via 2 distinct mechanisms: 1) acts as a direct scavenger of ROS; 2) upregulates antioxidant defense system. Accumulative evidence show that H$_2$S prevents diabetes-impaired EC biology/function via inhibition of oxidative stress. H$_2$S reduced ROS formation, improved function and metabolic state of ECs under hyperglycemic condition [50]. H$_2$S decreased ROS production and apoptosis in hyperglycemic ECs [52], and alleviated vascular abnormality in the aorta of diabetic rats via attenuating NADPH oxidase activity [53]. H$_2$S decreased high glucose-induced autophagy in ECs though the nuclear factor erythroid2-related factor 2 (Nrf2)-ROS-S-adenosine monophosphate-activated protein kinase (AMPK) signaling pathway [54]. Administration of sodium hydrosulfide (NaHS) protected excessive autophagy in arterial ECs of db/db mice via enhancing superoxide dismutase/catalase activity [54]. NaHS improved endothelial function and decreased oxidative stress in STZ-treated diabetic mice [55]. Recently, study also provided an evidence that mitochondria-specific H$_2$S donor AP123 and AP39 prevented hyperglycemia-triggered oxidative stress and metabolic abnormalities in microvascular ECs [56].

6. H$_2$S affects metabolism in diabetes and ECs

Although numerous studies reported that H$_2$S production is reduced in diabetes, the role of H$_2$S in the metabolism in diabetes remains controversial. Studies have reported that H$_2$S is essential for maintaining insulin bioactivity and glucose uptake. H$_2$S was required for vitamin D-induced GLUT4 translocation and glucose uptake [57]. H$_2$S reduced production of inflammatory cytokine, a known causal factor for the development of insulin resistance in adipose and other metabolic tissues, from resident adipose macrophages [58]. Endogenous glucose production was reduced in CSE KO mice [59]. H$_2$S may directly stimulate gluconeogenesis via sulphydral of pyruvate carboxylase, a key enzyme in gluconeogenesis [60]. Mitochondria plays a critical role in cell survival and death by regulating ATP synthesis through lipid and glucose metabolism. Increasing evidence indicate that mitochondrial function changes are implicated in diabetes-impaired EC function [61]. It was found that H$_2$S protected the vascular endothelium in hyperglycemia by preserving mitochondria function [50]. Mitochondria-targeted H$_2$S donors AP123 and AP39 increased the electron transport at respiratory complex III and improved the cellular metabolism in high glucose-treated microvascular ECs [56].

7. H$_2$S is an endothelium-derived hyperpolarizing factor (EDHF)

Endothelium is a single layer of squamous ECs that lines the interior surface of blood vessel lumen. Endothelium is the first target of pathological stimuli from blood. Endothelium mediates blood flow homeostasis and fulfills tissue metabolic demands by supplying nutrients and oxygen. Endothelium regulates vasomotor tone and organ perfusion by releasing by releasing vasodilator substances such as nitric oxide (NO), prostacyclin (PGI$_2$), and endothelium-derived hyperpolarizing factor (EDHF), and vasoconstrictor substances, such as angiotensin II, endothelin-1, thromboxane A$_2$ and prostaglandin H$_2$ in response to pathophysiological stimulation [62,63]. EC impairment thus endothelial dysfunction (ED) which is characterized by an impairment of endothelium-dependent vascular relaxation is an early event in the development of cardiovascular disease, EDHF-mediated vascular relaxation is defined by endothelium-dependent relaxation when production of NO and PGI$_2$ is blocked. It is generally accepted that NO predominantly controls relaxation of macro-vasculature, whereas EDHF primarily controls relaxation of micro-vasculature and becomes more important when vessel diameter decreases [64–66]. Although extensively studied, the nature of EDHF remains unclear. Many EDHF candidates have been reported including NO, CO, H$_2$O$_2$, C-type natriuretic peptide, PGI$_2$, EETs, trihydroxyisocitriatesic acid [20,65,67,68]. Current studies support the concept that EDHF-mediated.

Vascular relaxation is elicited by the opening of Ca$^{2+}$-activated potassium channels (K$_{Ca}$) in both ECs and vascular smooth muscle cells (VSMCs) [5,18,19,77]. Several lines of evidence indicate that H$_2$S has a role in the regulation of vascular tone. H$_2$S induced vascular relaxation in aorta [78–80], gastric artery [81], mesenteric artery [5,82], and internal mammary artery [83]. Accumulative evidence indicate that H$_2$S is an EDHF [5,17–20,84–86]. H$_2$S induced cell hyperpolarization by patch clamp [86]. By myograph, H$_2$S induced endothelium-dependent vascular relaxation in the presence of enos inhibitor and cyclooxygenase inhibitor [5,18–20,85]. Moreover, H$_2$S induced vascular relaxation in the presence of eNOS and cyclooxygenase (COX) inhibitor to a greater extent in the rat mesenteric artery than that in the rat aorta [17–19]. Removal of endothelium completely abolished the H$_2$S-induced relaxation in human and rat mesenteric arteries [18,82]. Endothelium-dependent vascular relaxation to acetylcholine in small mesenteric arteries was virtually abolished in the presence of eNOS and COX inhibitor in CSE knockout mice [20,85], suggesting H$_2$S is a EDHF. Moreover, studies also found that the vascular relaxation in response to H$_2$S is activated via activation of ATP-sensitive potassium channel (K$_{ATP}$) in smooth muscle cells [19] and endothelial and/or muscular small- (SK$_{Ca}$), intermediate- (IRK$_{Ca}$) and big- (BK$_{Ca}$) conductance calcium-activated and voltage-sensitive (Kv) potassium channel [87–91].

8. H$_2$S in diabetes-impaired vascular relaxation

H$_2$S exerts protective effects against hyperglycemic stress in the vascular endothelium and exhibits protective effects in animal models of diabetic complication [7,45,49,50,55,92–94]. We and others reported that H$_2$S deficiency plays an important role in the pathogenesis of cardiovascular complications in diabetes [3,5,45,49,50,55,92–95]. Low levels of H$_2$S in the blood of diabetes and overweight patients and STZ-treated rats cause vascular inflammation [45,49]. Exogenous H$_2$S is beneficial for prevention/therapeutics of diabetes-induced cardiovascular complications, such as rescued oxidative stress, endothelial dysfunction and cardiomyopathy in STZ-induced diabetic mice/rats [55,95]; reduced blood pressure and prevented the progression of diabetic nephropathy in spontaneously hypertensive rats [92]; decreased reactive oxygen species (ROS) and vascular inflammation markers in high glucose-treated human monocyes [93]; improved metabolic state and mitochondria function of ECs under hyperglycemia condition [50]. Although many studies reported that H$_2$S production was decreased in diabetes, vascular relaxation response to H$_2$S was enhanced in thoracic aorta, mesenteric, pulmonary and carotid arteries of STZ- or alloxan-induced diabetic animal models [96–98]. Diabetes-enhanced vascular relaxation response to H$_2$S has been suggested to be a compensatory mechanism overcome insufficient H$_2$S production and impaired endothelial function by increasing sensitivity of vasculature to H$_2$S [5,96,99]. However, the molecular/signaling pathways of enhanced EDHF-mediated endothelium-dependent vascular relaxation in response to H$_2$S remain unclear. It has been showed that glibenclamide (K$_{ATP}$ channel blocker) decreased maximum relaxation response to NaHS in the thoracic aorta, pulmonary and mesenteric arteries isolated from either 4- or 12-week-STZ-induced diabetic rats [96]. Moreover, vascular relaxation of rabbit carotid artery in response to NaHS was diminished by charybotoxin (BK$_{Ca}$/IK$_{Ca}$ blocker), 4-amynopiridine (Kv channel blocker) and glibenclamide in the carotid arteries of alloxan-induced diabetic rabbits but not in that of non-diabetic rabbits [97]. However,
Table 1

H₂S levels in diabetes.

| Diabetic patients/animals/cells       | Method for H₂S assay | Sources of H₂S/free sulfide | H₂S in diabetes vs. non-diabetes | Ref. # |
|--------------------------------------|-----------------------|-----------------------------|----------------------------------|--------|
| db/db mice                           | Gas chromatography    | Bone marrow cells           | ↓                                | 4      |
|                                      |                       | Plasma                      | ↓                                |
|                                      |                       | Medial tight muscles        | ↓                                |
| High glucose-treated human microvascular ECs | Fluorescent dye sulfidefluor 7AM | ECs                          | ↓                                | 4      |
| db/db mice                           | Fluorescent dye sulfidefluor 7AM | Mesenteric artery           | ↓                                | 5      |
| db/db mice                           | RP-HPLC               | Mesenteric artery           | ↓                                | 5      |
| Akita mice                           | Spectrophotometer     | Kidney                      | ↓                                | [44]   |
| High glucose-treated mouse glomular ECs | Spectrophotometer     | ECs                         | ↓                                | [44]   |
| High fat diet-induced diabetic LDLR −/− mice | Spectrophotometer     | Plasma                      | ↓                                | [43]   |
| Type 2 diabetic patients and STZ-treated diabetic rats | Spectrophotometer    | Plasma                      | ↓                                | [45]   |
| Non-obese/Ltj diabetic mice          | Spectrophotometer     | Plasma                      | ↓                                | [46]   |
| STZ-treated mice                     | Spectrophotometer     | Aorta                       | ↓                                | [46]   |
| Type 2 diabetic patients             | Spectrophotometer     | Pancreas                    | ↓                                | [49]   |
| High glucose-treated microvascular ECs (bEnd3) | Spectrophotometer     | ECs                         | ↓                                | [50]   |
| Women with Gestational diabetes mellitus | Sulfide-sensitive electrode (PX-270) | Plasma | ↓                                | [69]   |
| High fat diet-induced diabetic mice  | Gas chromatography    | Heart tissue                | ⇧                                | [70]   |
|                                      |                       | Plasma                      | ⇧                                |
| Type 2 diabetic patients             | Spectrophotometry (blood) | Blood                       | ↑                                | [71]   |
|                                      | Methylene blue (plasma) | Plasma                      | ⇧                                |        |
| STZ-treated diabetic rats             | Spectrophotometer     | Vascular smooth muscle cells of thoracic aorta | ↓ | [72]   |
| STZ-treated diabetic rats             | Spectrophotometer     | Plasma                      | ↓                                | [73]   |
| Fructose-fed diabetic rats            | Methylene blue        | Adipose tissue              | ↑                                | [74]   |
| STZ-treated diabetic rats             | –                     | Liver                       | ↓                                | [75]   |
| High glucose treated pancreatic islets | Methylene blue        | Pancreatic islets           | ↓                                | [76]   |
| STZ-treated diabetic rats             | Spectrophotometer     | Plasma, liver, pancreas and kidney | Plasma: ⇧ | Liver: ↓ | Pancreas: ↑ | Kidney: ⇧ | [75] |

4-aminopyridine did not modify the relaxant response to H₂S in the control rat thoracic aorta [19]. In line with above findings, activity and expression of K<sub>Ca</sub> channels were enhanced in the smooth muscle cells of mesenteric artery of OLETF diabetic rats [98]. Recently, we studied the role of H₂S in diabetes-induced ED in the small mesenteric artery of db/db mice [5]. We were the first demonstrating that H₂S is an effective EDHF in the mesenteric arteries of db/db and db/db mice [5], because that l-cysteine and NaHS, precursor and donor of H₂S, induced endothelium-dependent response in the presence of l-NAME (eNOS inhibitor) plus indomethacin (COX inhibitor), respectively [5]. Moreover, in good accordance with previous studies that diabetes enhanced vascular relaxation in response to H₂S [96–98], we also provided strong evidence that EDHF-mediated vascular relaxation to NaHS was enhanced in the small mesenteric artery of db/db mice [100]. Finally we found that K<sub>ATP</sub> blocker, but not any of K<sub>Ca</sub> blockers, blocked enhanced relaxation to NaHS in the small mesenteric arteries of db/db mice [5]. Our study implied that increased EDHF-mediated vascular relaxation to H₂S in the small mesenteric artery of db/db mice is via, at least partially, activation of K<sub>ATP</sub> but not K<sub>Ca</sub>. Exogenous H₂S and/or K<sub>ATP</sub> activators may be beneficial for prevention/treatment of micro-vascular complication in diabetic patients. Further studies to examine the therapeutic effects of H₂S and/or K<sub>ATP</sub> activators on microvascular endothelial function in db/db mouse are warranted.

Taken together, in general, the EDHF-mediated endothelium-dependent vascular relaxation to H₂S is enhanced under diabetic condition. The diabetes-enhanced EDHF-mediated vascular relaxation in response to H₂S is suggested mainly by sensitizing/overexpression of different potassium channels, including K<sub>Ca</sub>, K<sub>ATP</sub> and K<sub>Ca</sub>. Enhanced endothelium-dependent vascular relaxation to H₂S may be complementary effects to overcome insufficient H₂S production and endothelial dysfunction in diabetes. The differences on the role of K<sub>Ca</sub>, K<sub>ATP</sub> and K<sub>Ca</sub> in H₂S-mediated endothelium-dependent vascular relaxation in diabetes may be related to the size and type of vessels, type and severity of diabetes, and species. Whether this complementary effects dependent on the species of animal model and severity/stage of diabetes remain unclear.

9. Low concentration of H₂S mediate vascular constriction

It is noteworthy that low concentration of H₂S has been considered as an endothelium-dependent vascular constriction factor (see review [101,102]). H₂S relaxed phenylephrine-precontracted human internal mammary artery at higher concentrations but induced constriction at lower concentrations [83]. Intravenous infusion of a low concentration of NaHS into the anaesthetized rats significantly increased mean arterial blood pressure [103]. Low concentrations of NaHS induced constriction of aorta from mice/rats [104]. The molecular pathways involved in H₂S-induced vascular constriction were found to be related to decreasing nitric oxide (NO) bioavailability by converting NO to an inactive nitrosothiol and N-nitrosohydrazylamine-N-sulfonate or directly reducing NO production [83,103–105], or down-regulation of cAMP endothelium-independently [106]. The pathophysiological importance of low concentration of H₂S-mediated vascular constriction has been suggested for further investigation [102]. As diabetes markedly reduced H₂S production (Table 1), it would be interesting to study if insufficient H₂S-induced vascular contraction has an impact on impaired blood perfusion in diabetic wound and ischemic hindlimb via restriction of blood/nutrition supply in microvasculature.

10. H₂S in diabetes-impaired angiogenesis

Angiogenesis is defined as a physiological process through which new blood vessels are sprouted from the preexisting blood vessels [107,108]. Angiogenesis is required for delivering nutrients and waste and supplying immune surveillance [100]. The rate of new blood vessels formation varies with biological age and differs between tissues in healthy organisms [109]. Organisms exhibit rapid angiogenesis during embryonic development [110]. In adults, angiogenesis is observed only during embryonic development [110]. In adults, angiogenesis is observed only during embryonic development [110]. In adults, angiogenesis is observed only during embryonic development [110]. In adults, angiogenesis is observed only during embryonic development [110]. In adults, angiogenesis is observed only during embryonic development [110].
pathological stimulation, ECs process an angiogenic program to contribute wound healing and tissue remodeling [107]. Enhancing EC function and angiogenesis thereby improving blood perfusion has been suggested as an alternative approach in the treatment of ischemic tissue injury. The process of angiogenesis is complex which contains a series of cellular and molecular events which includes three steps: 1) enzymatic degradation of capillary basement membrane; 2) EC proliferation, migration and 3) tubulogenesis and the formation of capillaries [112-114], which involves the interaction between pro- and anti-angiogenic factors, growth mediators, cytokines, cells and extra-cellular matrix [115]. Recent studies demonstrated that rather than the amount of single angiogenic factor, balance between endogenous pro- and anti-angiogenic factor plays an important role in the regulation of angiogenesis [116]. Defects in the angiogenic balance may cause a shift towards either excessive or deficient angiogenesis.

Impaired angiogenesis is one of the hallmarks of diabetes which is involved in the pathogenesis of nephropathy, wound and critical limb ischemia in diabetes [4,117-119]. The risk factors involved in diabetes-impaired angiogenesis are suggested to be related to many factors, including hyperglycaemia, chronic inflammation, oxidative stress, hyperglycaemia/advanced glycation end products (AGE), connective tissue growth factors, lipoxidation and its products [120]. The underlying mechanisms of diabetes-impaired angiogenesis remain incompletely understood.

Emerging data support the role of H₂S in the regulation of angiogenesis. H₂S promotes EC proliferation, migration, survival, formation of tubular structure and networks [100,107,121-129]. The sufficient concentrations of H₂S to induce angiogenesis are physiological levels [125,130]. H₂S in a dose-dependent manner promoted human umbilical vein endothelial cells (HUVECs) growth, adhesion, migration, tube formation, and in vivo angiogenesis measured by matrigel plug assay [124,125,129]. Silencing of CSE in HUVECs decreased cell proliferation and tube formation [131]. Administration of H₂S increased proliferation and migration in microvascular ECs and recovered microvessel sprouting in CSE-silenced rat aorta [122]. In addition, administration of 3-mercaptoypyruvate (3-MP), the 3-MST substrate reserved increased Matrigel plug angiogenesis/neovascularization in mice [132]. Many molecules have been suggested to be involved in H₂S-mediated angiogenesis. Most studies focused on the VEGF signaling in angiogenic response [125,133,134]. The pro-angiogenic effect of vascular endothelial growth factor (VEGF) is mediated by the endogenous production of H₂S [125]. Silencing of CSE by siRNA attenuated VEGF-induced angiogenesis [125]. In addition, H₂S stimulated angiogenesis by increasing the activity of endothelial nitric oxide synthesis (eNOS) [121,135], phosphatidylinositol 3 (PI3)-kinase/protein kinase B (AKT) [130], p38/mitogen-activated protein kinase (MAPK) [125], K⁺ATP, signal transducer and activator of transcription 3 (STAT3) [124], and sirtuin 1 (SIRT1)/VEGF/cyclic guanosine 5'-monophosphate (cGMP) cascade [123].

Angiogenesis is impaired in diabetes [4,117]. However, the underlying mechanisms of diabetes-impaired angiogenesis remain unclear. A series of multiple mechanisms, including impaired EC biology/function and growth factor response, were suggested to lead to diminished peripheral blood perfusion and decreased angiogenesis in diabetes. H₂S rescued hyperglycaemia-impaired migration of HUVECs by upregulating miR-126-3p [136]. Hyperglycaemia/diabetes-impaired angiogenesis is associated with an impairment of proangiogenic and bio-energetic effector molecules [137]. H₂S increased angiogenesis in db/db mice is related to decreasing infiltration of neutrophil and macrophage, production of TNF-α, interleukin (IL)-6 [137]. H₂S donor diallyl trisulfide (DATS) improved revascularization in STZ-induced diabetic mice via increasing NO bioavailability [138]. H₂S promoted angiogenesis in db/db mice via improving VEGFR and PDGFR, and Angiopoietin-1 (Ang I) [118,128]. Recently we reported that diabetes impairs angiogenesis in db/db mice via eNOS-pT495-mediated reduction of NO [4].

11. H₂S in diabetes-impaired wound healing

It is well known that in the physiological condition (before injury), the vascularity is quiescence in which blood vessel are adequately perfused to deliver sufficient oxygen/nutrients to the tissue [139,140]. There is a proper balance of pro- and anti-angiogenic factors are expressed to maintain a functional vascular network that neither proliferating nor diminishing [139,140]. However, this homeostasis is interrupted leading to an ischemic/hypoxic state when tissue is injured. Under post-injury, numerous proangiogenic factors are produced for formation of angiogenesis in wounds, such as VEGF and transcriptional activator hypoxia-inducible factor (HIF) which promotes angiogenesis by upregulating target genes such as VEGF-A [141].

Refractory wound is defined by slow healing of wound which is one of major microvascular complications in diabetes. In the wound healing process, impaired EC function/angiogenesis contribute to defects in the oxygen/nutrients supply, thus inhibiting normal healing process [142]. In the process of wound healing, angiogenesis is a crucial step which starts at the 3rd days after wounding [140,143]. Dysfunction of angiogenesis has been linked to impaired wound healing in diabetes [4,117,118,128]. For instance, the prevalence of foot ulcers due to impaired wound healing is predicted to be 25% in diabetic patients [144,145]. Many insufficient angiogenic factors, such as vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF-2) and platelet-derived growth factor (PDGF) are involved in diabetes-impaired angiogenesis/wound healing [146-148]. Moreover, several studies also demonstrated that modulation of anti-angiogenic factors and capillary maturation factors are also involved in the pathogenesis of diabetes-impaired wound healing. For example, circulating levels of anti-angiogenic factor pigment epithelium-derived factor (PEDF) were significantly enhanced in patients with diabetic foot ulcers (DFU) [149], suggesting that enhanced PEDF could negatively impact wound healing in diabetes. Local administration of neutralizing antibodies to Ang 1 on wounded skin reduced maturation of capillary formation in STZ-induced diabetic mice [150]. In addition, several miRNAs (miRs) have also been shown to be involved in diabetic wound healing. miR-27b accelerated the wound healing process in db/db mice [128]. Inhibition of miR-155 reduced oxidative stress, increased angiogenesis and wound healing in STZ-induced diabetic rats [151]. Local administration of let-7b-containing exosomes, nanoscale membrane extracellular vesicles (30–100 nm), from LPS-primed mesenchymal stromal cells decreased inflammatory response and increased wound healing in STZ-induced diabetic mice [150]. miR-191 and -200b expression were increased in diabetic patients with PAD and chronic wounds and positively correlated with higher levels of inflammation associated markers [152,153]. H₂S has been reported to accelerate gastric ulcer and skin burn healing wound healing [125,130,154]. Topical administration of H₂S improved the recovery from burn wounds in wild-type rats and that genetic ablation of CSE delayed healing in mice [125]. H₂S improves angiogenesis and wound healing in db/db mice via increasing transcription of VEGF, EGF, HIF-1α and ENOS, and protein expression of VEGF, PDGF, and phosphorylated VEGFR and PDGFR [128]. H₂S accelerates wound healing in STZ-induced diabetic mice associated with formation of granulation, anti-inflammation, and the increased level of VEGF [155]. H₂S improved diabetic wound healing in ob/ob mice via attenuating inflammation [137]. H₂S precipitated wound to close through inhibition of neutrophil extracellular traps (NET) release-coupled neutrophil death (NETosis) in db/db mice [117]. H₂S improved wound healing via restoration of endothelial progenitor cell functions and activation of Ang 1 in db/db mice [118]. Cysteine/cysteine-rich un-denatured whey protein supplement improved pressure ulcer recovery in diabetic patients [156]. Accumulative evidence indicated that H₂S regulates miR expression (i.e. miR-1, -221, -21, -1 and -133a) [157-160], however, the interaction between H₂S and miRs in diabetic wound healing remain unclear. A recent study suggested that H₂S may rescue diabetes-impaired wound healing via DNMT1 inhibition and
consequently enhanced miR-126-3 production in ECs [161]. Further studies to understand the role of H$_2$S in miRs-mediated EC dysfunction will provide novel insights for prevention/therapeutics ischemic tissue injury in diabetes.

12. H$_2$S in diabetes-impaired critical limb ischemia

The morbidity of critical limb ischemia (CLI) in patients with diabetes, which affects 178 million US adults [1], is extremely high (up to 76% in some studies [162]). Patients with CLI suffer from consequent rest pain, ulcers, cool limbs, and even amputation. Disease severity at the time of presentation and progression of CLI in diabetes has also been noted to be worse [163]. Angiogenesis is a promising target for the treatment of ischemic limbs by providing extra blood for the ischemic region. Pro-angiogenic factors, such as VEGF and basic fibroblast growth factor (bFGF), play an important role in promoting angiogenesis accompanied with enhanced blood perfusion in ischemic limbs of patients [164]. It is also reported that transplantation of bone marrow- or placenta-derived mesenchymal stem cells (MSCs) significantly improved capillary density and blood flow in ischemic hindlimbs of animal models [165,166]. Pro-angiogenic factors released from MSCs could promote angiogenic differentiation, leading to the stimulation of resident progenitor cells (EPCs) to migrate, proliferate, and differentiate into incorporated ECs [167].

In clinics, H$_2$S levels in gastrocnemius tissue were attenuated in the setting of CLI in patients [168]. Administration of H$_2$S was promising for ischemic hindlimb (IHL) repair in animal model. S-propargyl-cysteine, a novel water-soluble modulator of endogenous H$_2$S promoted angiogenesis in IHL of mice via signal transducer and activator of transcription 3 (STAT3)/VEGF signaling [124]. Intraportal injection of low dose, but not high dose, of NaHS significantly improved capillary density, angiographic scores, blood perfusion in IHL which may be mediated by interaction between the upregulated VEGF in the skeletal muscle cells and the VEGFR2 as well as its downstream signaling element AKT in the ECs [129]. H$_2$S improved angiogenesis and blood perfusion in IHL of CSE$^{-/-}$ mice via peroxisome proliferator-activated receptor-$\gamma$ (PPAR-$\gamma$/VEGF axis [169]. DATS enhanced angiogenesis and blood flow in IHL of wild-type mice via stimulation of AKT-eNOS signaling pathway [170]. H$_2$S also limited cellular damage in myotubes and skeletal muscles of ischemic hindlimbs [171].

We examined role of H$_2$S in diabetes-impaired biology/function of bone marrow cell (BMC) and IHL repair in db/db mice [4]. We found that H$_2$S production and CSE expression was significantly reduced in BMCs from db/db mice. Systemic administration of DATS or local transplantation of DATS-treated or CSE-overexpressed BMCs improved capillary density, cell survival and blood perfusion in the IHL of db/db mice [4]. Mechanistically we found that DATS restored NO production and decreased eNOS-pT495 levels in human microvascular ECs. We demonstrated that H$_2$S and overexpression of CSE in diabetic BMCs may rescue their dysfunction and open novel avenues for cell-based therapeutic of CLI in diabetic patients [4]. Consistent with the effects of DATS in IHL of db/db mice, recent study also revealed that administration of DATS improved angiogenesis and IHL repair in STZ-treated mice via NO signaling pathway [138]. However, the underlying mechanisms of downregulation of CSE expression/activity and insufficient H$_2$S-induced eNOS-pT495 in diabetic ECs remain incompletely understood.

13. Conclusion

H$_2$S is an endogenous gas with important physiological function. H$_2$S plays an important role in maintenance of vasculature homeostasis. The evidence presented above shows that H$_2$S, mainly synthesized by CSE or 3-MST, stimulates angiogenetic property of ECs. H$_2$S-induced EDHF-mediated vascular relaxation is enhanced in micro-vasculature in diabetes which may play compensatory effects for overcoming H$_2$S reduction-induced endothelial dysfunction. Diabetes enhances H$_2$S-induced EDHF-mediated vascular relaxation in micro-vasculature by opening potassium channels, including K$_{Ca}$, K$_{ATP}$ and Kv, which varies by type of vessels, diameter of vessels, severity of diabetes and species. Physiological doses of H$_2$S increase angiogenesis by promoting EC growth, survival migration and tube formation. H$_2$S production is reduced in plasma/blood, ECs and bone marrow cells in diabetes. Insufficient H$_2$S production in diabetes impairs angiogenetic property and ischemic tissue injury via, at least partially, interrupting the balance between pro- and anti-angiogenic factors (Fig. 2). Although studies showed that administration of H$_2$S or overexpressing CSE improves EC biology/function, angiogenesis and IHL repair in diabetes, how H$_2$S impacts on the metabolism of EC and contributes to it angiogenic properties in diabetes remain unclear. In addition, studies for significance of translational medicine of H$_2$S on diabetes-impaired angiogenetic and ischemic tissue repair in patients are warranted.

14. Declaration of competing interest

The authors declare no conflict of interest.

Acknowledgments

This study was supported in part by the NIH grants HL091983, HL143892, and HL134608 (R.K.) and American Heart Association grant HL143892, and HL134608 (R.K.) and American Heart Association grant.
References

[1] E.W. Gregg, Y. Li, J. Wang, et al., Changes in diabetes-related complications in the United States, 1990-2010, N. Engl. J. Med. 367 (16) (2012) 1514-1523.
[2] C.S. Fox, S. Coady, P.D. Sorlie, et al., Trends in cardiovascular complications of diabetes, J. Am. Med. Assoc. 292 (20) (2004) 2495-2499.
[3] J.C. van den Born, H.P. Hammes, W. Grefrath, H. van Goor, J.J. Hillebrands, PFG GRK International Research Training Group 1874 Diabetic Microvascular Complications (DIAMICOM), Gasotransmitters in vascular complications of diabetes, Diabetes 65 (2) (2016) 331-345.
[4] Z. Cheng, V.N. Gariikapati, E. Nickoloff, et al., Restoration of hydrogen sulfide production in diabetic mice improves reparative function of bone marrow cells, Circulation 134 (19) (2016) 1467-1483.
[5] Z. Cheng, X. Shen, X. Jiang, et al., Hyperhomocysteinemia potentiates diabetes-impaired EDRF-induced vascular relaxation: role of insufficient hydrogen sulfide, Redox Biol 16 (2018) 215-225.
[6] C.C. Low Wang, C.N. Hess, W.R. Hiatt, A.B. Goldfine, Clinical update: cardiovascular disease in diabetes mellitus: atherooclerotic cardiovascular disease and heart failure in type 2 diabetes mellitus - mechanisms, management, and clinical considerations, Circulation 133 (24) (2016) 2459-2502.
[7] R. Wang, Physiological implications of hydrogen sulfide: a whiff exploration that might interest you, Antioxid. Redox Signal. 17 (1) (2012) 198-210.
[8] B. Donertas, A. J. Z. Lev, Gut microbiota and neuroinflammation in pathogenesis of hypertension: a potential role for hydrogen sulfide, Pharmacol. Res. 153 (2015) 10677-10687.
[9] E. Donnarumma, M.J. Ali, A.M. Rushing, et al., Zofenopril protects against hyperhomocysteinemia-induced atherothrombotic lesion development, Circ. Res. 114 (4) (2014) 626-636.
[10] V. Brancaleone, F. Roviezzo, V. Vellecco, L. De Gruttola, M. Bucci, G. Cirino, S.K. Jain, R. Bull, J.L. Rains, et al., Low levels of hydrogen sulfide in the blood of patients with coronary artery disease: implications for their possible biological activity and utility, Free Radic. Biol. Med. 77 (2014) 88-94.
[11] D. Zhang, J. Du, C. Tang, Y. Huang, H. Jin, H2S-Induced sulfhydration: biological function and detection methodology, Front. Pharmacol. 8 (2017) 608.
[12] Y. Cheng, J.F. Nilsang, G. Tang, K. Cao, R. Wang, Hydrogen sulfide-induced autophagy in endothelial cells by the Nrf2-ROS-AMPK signaling pathway, Cell Biosci. 6 (2016) 33.
[13] K. Ono, T. Akaite, T. Sawa, et al., Redox chemistry and chemical biology of H2S, hypusines, and related thiol species: implications of their possible biological activity and utility, Free Radic. Biol. Med. 71 (2014) 1383-1392.
[14] V. Brancacene, F. Roviozto, V. Vellecco, L. De Gruttola, M. Bucci, G. Cirino, Biosynthesis of H2S is impaired in non-obese diabetic (NOD) mice, Br. J. Pharmacol. 155 (5) (2008) 673-680.
[15] J.Z. Cheng, T. Vaskonen, I. Tikkassen, et al., Endothelial dysfunction and salt-sensitive hypertension in spontaneously diabetic Goto-Kakizaki rats, Hypertension 37 (2 Pt 2) (2001) 431-439.
[16] K. Lin, G. Tang, L. Wang, R. Wang, The pathogenic role of cystathionine gamma-hydrolyase/sulfite in streptozotocin-induced diabetes in mice, Am. J. Pathol. 179 (2) (2011) 869-879.
[17] M. Whitman, K.M. Gooding, J.L. Whatmore, et al., Adiposity is a major determinant of plasma levels of the novel vasodilator hydrogen sulfide, Diabetologia 53 (8) (2010) 1722-1726.
[18] K. Suzuki, G. Ohah, K. Modis, et al., Hydrogen sulfide replacement therapy protects the vascular endothelium in hyperglycemia by preserving mitochondrial function, Proc. Natl. Acad. Sci. U. S. A. 108 (33) (2011) 13829-13834.
[19] F. Giacco, M. Brownlee, Oxidative stress and diabetic complications, Circ. Res. 107 (9) (2010) 1058-1070.
[20] J. Lin, M. Chen, D. Liu, et al., Exogenous hydrogen sulfide protects human umbilical vein endothelial cells against high glucose-induced injury by inhibiting the necroptosis pathway, Int. J. Mol. Med. 41 (3) (2018) 1477-1486.
[21] Y.F. Zheng, D.Z. Dai, Y. Dai, NaHS ameliorates diabetic vascular injury by correcting depressed connexin 43 and 40 in the vasculature in streptozotocin-induced diabetic rats, J. Pharm. Pharmacol. 62 (5) (2010) 615-626.
[22] J. Liu, J. Wu, A. Sun, et al., Hydrogen sulfide decreases high glucose/palmitate-induced autophagy in endothelial cells by the Nrf2-R OS-AMPK signaling pathway, Cell Biochim. 6 (2016) 33.
[23] H.H. Ng, G.S. Vilidz, J.M. Bart, A.A. Miller, O.L. Woodman, J.L. Hart, Chronic NaHS treatment decreases oxidative stress and improves endothelial function in diabetic mice, Diabetes Vasc. Dis. Res. 13 (4) (2016) 246-255.
[24] D. Gero, R. Terrogrossa, A. Perry, et al., The novel mitochondria-targeted hydrogen sulfide (H2S) transporter APT12 and P2X9 protect against hyperglycemic injury in microvascular endothelial cells in vitro, Pharmaco. Res. 113 (Pt A) (2016) 186-198.
[25] L.M. Mann, S.K. Jain, Vitamin D up-regulates glucose transporter 4 (GLUT4) translocation and glucose utilization mediated by cystathionine-gamma-lyase (CSE) activation and H2S formation in 3T3L1 adipocytes, J. Biol. Chem. 287 (50) (2012) 42324-42332.
[26] A.S. Greenberg, M.S. Ohan, Obesity and the role of adipose tissue in inflammation in obesity, Am. J. Clin. Nutr. 83 (2) (2006) 461S-465S.
C.R. Triggle, H. Ding, Endothelium-derived hyperpolarizing factor: is there a role of hydrogen sulfide in the control of vascular tone, Nitric Oxide 81 (2018) 1118

Y. Ju, A. Untereiner, L. Wu, G. Yang, H2S-induced S-sulfhydration of pyruvate carboxylase contributes to gluconeogenesis in liver cells, Biochim. Biophys. Acta 1850 (11) (2015) 2293-2303.

M. Fangare, A. Makino, Microchannel-oriental vascular endothelial cell in diabetes, J. Smooth Muscle Res. 48 (1) (2012) 1–26.

Z. Cheng, X. Yang, H. Wang, Hyperpomocysteinemia and endothelial dysfunction, Curr. Hypertens. Res. 5 (2) (2008) 153–160.

R.F. Purchase, J.V. Zawadzki, The obligatory role of endothelial cells in the relaxation of arterial smooth muscle by acetylcholine, Nature 288 (1980) 373–376.

S. Frutos, P.M. Vanhoucke, Endothelium-derived hyperpolarizing factor: where are we now? Arterioscler. Thromb. Vasc. Biol. 26 (6) (2006) 1215–1225.

C.R. Triggle, H. Ding, Endothelium-derived hyperpolarizing factor: is there a novel chemical mediator? Clin. Exp. Pharmacol. Physiol. 29 (3) (2002) 153–160.

S. Hammer, J. Hoyer, The endothelium-derived hyperpolarizing factor: insights from genetic animal models, Kidney Int. 72 (2) (2007) 145–150.

C.R. Triggle, A. Howarth, Z.J. Cheng, H. Ding, Twenty-five years since the discovery of endothelial hyperpolarizing factor, Biophys. Res. Commun. 465 (4) (2015) 825

S. Kubo, M. Kajiwara, A. Kawabata, Dual modulation of the tension of isolated gastric artery and gastric mucosal circulation by hydrogen sulfide in rats, Exp. Pharmacol. Physiol. 87 (2016) 76.

J.S. Possomato-Vieira, J.S. Chimini, M.L.S. da Silva, C.A. Dias-Junior, Increases in blood flow to gastric artery and gastric mucosal circulation by hydrogen sulfide in rats, Exp. Pharmacol. Physiol. 86 (2018) 1118-1127.

G. Yetik-Anacak, G. Sevin, O. Ozaymik, M.V. Dereci, A. Ahmed, Hydrogen sulfide: a novel mechanism for the vascular protection by resveratrol under oxidative stress in mouse aorta, Vasc. Pharmacol. 87 (2016) 76.

Z. Liu, Y. Han, L. Li, et al., The hydrogen sulfide donor, GYY4137, exhibits anti-tumor effect on human cervical cancer cells, J. Chromatogr. B Analyt Technol Biomed Life Sci 1060 (2017) 103

R.H. Adams, K. Alitalo, Molecular regulation of angiogenesis and vasculogenesis, Trends Cell. Biochem. 389 (1–2) (2014) 249–256.

W.B. Wei, X. Hu, X.D. Zhuang, L.Z. Liao, W.D. Li, GYY4137, a novel hydrogen sulfide-releasing molecule, likely protects against high glucose-induced cytotoxicity by activation of the AMPK/mTOR signal pathway in H9c2 cells, Mol. Cell. Biochem. 389 (1–2) (2014) 249–256.

Z. Cheng, R. Kishore

Z. Liu, Y. Han, L. Li, et al., The hydrogen sulfide donor, GYY4137, exhibits anti-tumor effect on human cervical cancer cells, J. Chromatogr. B Analyt Technol Biomed Life Sci 1060 (2017) 103

R.H. Adams, K. Alitalo, Molecular regulation of angiogenesis and vasculogenesis, Trends Cell. Biochem. 389 (1–2) (2014) 249–256.

W.B. Wei, X. Hu, X.D. Zhuang, L.Z. Liao, W.D. Li, GYY4137, a novel hydrogen sulfide-releasing molecule, likely protects against high glucose-induced cytotoxicity by activation of the AMPK/mTOR signal pathway in H9c2 cells, Mol. Cell. Biochem. 389 (1–2) (2014) 249–256.

Z. Cheng, R. Kishore

Z. Liu, Y. Han, L. Li, et al., The hydrogen sulfide donor, GYY4137, exhibits anti-tumor effect on human cervical cancer cells, J. Chromatogr. B Analyt Technol Biomed Life Sci 1060 (2017) 103

R.H. Adams, K. Alitalo, Molecular regulation of angiogenesis and vasculogenesis, Trends Cell. Biochem. 389 (1–2) (2014) 249–256.

W.B. Wei, X. Hu, X.D. Zhuang, L.Z. Liao, W.D. Li, GYY4137, a novel hydrogen sulfide-releasing molecule, likely protects against high glucose-induced cytotoxicity by activation of the AMPK/mTOR signal pathway in H9c2 cells, Mol. Cell. Biochem. 389 (1–2) (2014) 249–256.

Z. Cheng, R. Kishore

Z. Liu, Y. Han, L. Li, et al., The hydrogen sulfide donor, GYY4137, exhibits anti-tumor effect on human cervical cancer cells, J. Chromatogr. B Analyt Technol Biomed Life Sci 1060 (2017) 103

R.H. Adams, K. Alitalo, Molecular regulation of angiogenesis and vasculogenesis, Trends Cell. Biochem. 389 (1–2) (2014) 249–256.

W.B. Wei, X. Hu, X.D. Zhuang, L.Z. Liao, W.D. Li, GYY4137, a novel hydrogen sulfide-releasing molecule, likely protects against high glucose-induced cytotoxicity by activation of the AMPK/mTOR signal pathway in H9c2 cells, Mol. Cell. Biochem. 389 (1–2) (2014) 249–256.

Z. Cheng, R. Kishore

Z. Liu, Y. Han, L. Li, et al., The hydrogen sulfide donor, GYY4137, exhibits anti-tumor effect on human cervical cancer cells, J. Chromatogr. B Analyt Technol Biomed Life Sci 1060 (2017) 103

R.H. Adams, K. Alitalo, Molecular regulation of angiogenesis and vasculogenesis, Trends Cell. Biochem. 389 (1–2) (2014) 249–256.

W.B. Wei, X. Hu, X.D. Zhuang, L.Z. Liao, W.D. Li, GYY4137, a novel hydrogen sulfide-releasing molecule, likely protects against high glucose-induced cytotoxicity by activation of the AMPK/mTOR signal pathway in H9c2 cells, Mol. Cell. Biochem. 389 (1–2) (2014) 249–256.

Z. Cheng, R. Kishore

Z. Liu, Y. Han, L. Li, et al., The hydrogen sulfide donor, GYY4137, exhibits anti-tumor effect on human cervical cancer cells, J. Chromatogr. B Analyt Technol Biomed Life Sci 1060 (2017) 103

R.H. Adams, K. Alitalo, Molecular regulation of angiogenesis and vasculogenesis, Trends Cell. Biochem. 389 (1–2) (2014) 249–256.
regulating hypoxia-inducible factor-alpha and vascular endothelial growth factor-dependent angiogenesis, J Am Heart Assoc 1 (5) (2012), e004993.

C. Coletta, A. Papapetropoulos, et al., Hydrogen sulfide and nitric oxide are mutually dependent in the regulation of angiogenesis and endothelium-dependent vasorelaxation, Proc. Natl. Acad. Sci. U. S. A. 109 (23) (2012) 9331–9336.

Q. Hu, D. Wu, F. Ma, et al., Novel angiogenic activity and molecular mechanisms of ZYV-803, a slow-releasing hydrogen sulfide-nitric oxide hybrid molecule, Antioxidants Redox Signal. 25 (8) (2016) 496–514.

J. Kan, W. Guo, C. Huang, G. Yao, Y. Zhu, Y.Z. Zha, S-propargyl-cysteine, a novel water-soluble modulator of endogenous hydrogen sulfide, promotes angiogenesis through activation of signal transducer and activator of transcription 3, Antioxidants Redox Signal. 20 (15) (2014) 2303–2316.

A. Papapetropoulos, A. Pyriochou, Z. Altaany, et al., Hydrogen sulfide is an endogenous stimulator of angiogenesis, Proc. Natl. Acad. Sci. U. S. A. 106 (51) (2009) 21972–21977.

D. Polhemus, K. Kondo, S. Bhushan, et al., Hydrogen sulfide attenuates cardiac dysfunction after heart failure via induction of angiogenesis, Circ Heart Fail 6 (5) (2013) 1077–1086.

C. Szabo, A. Papapetropoulos, Hydrogen sulphide and angiogenesis: mechanisms and applications, Br. J. Pharmacol. 164 (3) (2011) 853–865.

G.G. Wang, W. Li, Hydrogen sulfide improves vessel formation of the ischemic adductor muscle and wound healing in diabetic db/db mice, Iran J Basic Med Sci 22 (10) (2019) 1192–1197.

M.J. Wang, W.J. Cai, N. Li, Y.J. Ding, Y. Chen, Y.C. Zhu, The hydrogen sulfide donor NaHS promotes angiogenesis in a rat model of hind limb ischemia, Antioxidants Redox Signal. 12 (9) (2010) 1065–1077.

W.J. Cai, M.J. Wang, P.K. Moore, H.M. Jin, T. Yao, Y.C. Zhu, The novel proangiogenic effect of hydrogen sulfide is dependent on Akt phosphorylation, Cardiovasc. Res. 76 (1) (2007) 29–40.

S. Saha, P.K. Chakraborty, X. Xiong, et al., Cystathionine beta-synthase regulates endothelial function via protein S-sulfhydration, Faseb. J. 30 (1) (2016) 441–456.

C. Coletta, K. Modis, B. Szczerny, et al., Regulation of vascular tone, angiogenesis and cellular bioenergetics by the S-mercaptopyruvate sulfurransulfurase/ISR pathway: functional impairment by hyperglycemia and restoration by L-dopa-lic acid, Mol. Med. 21 (2015) 1–14.

P. Carmeliet, R.K. Jain, Molecular mechanisms and clinical applications of angiogenesis, Nature 473 (7347) (2011) 359–371.

A.K. Olsson, A. Dimberg, J. Kreuger, L. Claesson-Welsh, VEGF receptor signaling - in control of vascular function, Nat. Rev. Mol. Cell Biol. 7 (5) (2006) 359–371.

G.K. Kolluru, S.C. Bir, M.J. Wang, et al., The novel proangiogenic effect of hydrogen sulfide is dependent on Akt phosphorylation, Cardiovasc. Res. 76 (1) (2007) 29–40.

H. Zhao, S. Lu, J. Chai, et al., Hydrogen sulfide improves diabetic wound healing in ob/ob mice via attenuating inflammation, J. Diabet. Complicat. 31 (9) (2017) 1077–1086.

M.G. Tonnesen, X. Feng, R.A. Clark, Angiogenesis in wound healing, J. Invest. Dermatol. 133 (3) (2009) 231–248.

J.L. Wallace, M. Digay, W. McKnight, et al., Emerging role of hydrogen sulfide-microRNA crosstalk in cardiovascular diseases, Am. J. Physiol. Heart Circ. Physiol. 310 (7) (2016) H902–H912.

W.L. Xue, R.Q. Chen, Q.Q. Zhang, et al., Hydrogen sulfide rescues high glucose-induced migration dysfunction in HUVECs by upregulating miR-126-3p, Am. J. Physiol. Cell Physiol. 318 (5) (2020) C857–C869.

F. Dick, N. Diehm, A. Galimanis, M. Husmann, J. Schmidli, I. Baumgartner, Surgical or endovascular revascularization in patients with critical limb ischemia: influence of diabetes mellitus on clinical outcome, J. Vasc. Surg. 45 (4) (2007) 751–761.

J.L. Kulko, K.R. Bailey, S.L. Kardia, T.H. Mosley Jr., E. Boerwinkle, S.T. Turner, Ethnic differences in peripheral arterial disease in the NHLBI Genetic Epidemiology Network of Arteriopathy (GENOA) study, Vasc. Med. 8 (4) (2003) 237–242.

S. Oladipupo, S. Hu, J. Kovalski, et al., VEGF is essential for hypoxia-inducible factor-mediated neovascularization but dispensable for endothelial sprouting, Proc. Natl. Acad. Sci. U. S. A. 108 (32) (2011) 13264–13269.

J. Liu, H. Han, L. Xia, et al., In vitro mesenchymal stem cells enhance angiogenesis by improving the function of endothelial cells in diabetic rats with lower ischemia, PloS One 10 (5) (2015), e0126715.

N. Xie, Z. Li, T.M. Adesanya, et al., Transplantation of placenta-derived mesenchymal stem cells enhances angiogenesis after ischemic limb injury in mice, J. Cell Mol. Med. 20 (1) (2016) 29–37.

F. Lu, X. Zhao, J. Wu, et al., MSCs transplanted with hepatic growth factor or vascular endothelial growth factor improve cardiac function in the infarcted porcine heart by increasing angiogenesis and reducing fibrosis, Int. J. Cardiol. 167 (6) (2015) 2524–2532.

K.N. Islam, D.J. Polhemus, E. Donnarumma, L.P. Brewster, D.J. Lefer, Hydrogen sulfide levels and nuclear factor-erythroid 2-related factor 2 (NRF2) activity are attenuated in the setting of critical limb ischemia (CLI), J Am Heart Assoc 4 (5) (2015).

A. Majumder, M. Singh, A.K. George, J. Behera, N. Tyagi, S.C. Tyagi, Hydrogen sulfide improves postischemic neangiogenesis in the hind limb of cytochrome-c beta-synthase mutant mice via PPAR-gamma/VEGF axis, Phys. Rev. E (2017), e183588.

R. Hayashida, K. Kondo, S. Morita, et al., Diallyl trisulfide augments ischemia-induced angiogenesis via an endothelial nitric oxide synthase-dependent mechanism, Circ. J. 81 (6) (2017) 870–876.

P.W. Henderson, N. Jimenez, R. Ruffino, et al., Therapeutic delivery of hydrogen sulfide for salvage of ischemic skeletal muscle after the onset of critical ischemia, J. Vasc. Surg. 53 (3) (2011) 785–791.

J. Brem, M. Tomic-Canic, Cellular and molecular basis of wound healing in diabetes, J. Clin. Invest. 117 (5) (2007) 1219–1222.

R. Cheng, J.X. Ma, Angiogenesis in diabetes and obesity, Rev. Endocr. Metab. Disord. 16 (1) (2015) 67–75.

W. Qi, C. Yang, Z. Dai, et al., High levels of pigment epithelium-derived factor in diabetes impair wound healing through suppression of Wnt signaling, Diabetes 64 (1) (2015) 1407–1419.

C. Li, T. Yu, Y. Liu, X. Chen, X. Zhang, Topical application of insulin accelerates vessel maturation of wounds by regulating angiopoietin-1 in diabetic mice, Int. J. Low. Extrem. Wounds 14 (4) (2015) 353–364.

J. Ye, Y. Kang, X. Sun, P. Ni, M. Wu, S. Lu, MicroRNA-155 inhibition promoted wound healing in diabetic rats, Int. J. Low. Extrem. Wounds 16 (2) (2017) 74–84.

S. Dangwal, B. Mani, C. Bang, et al., Impairment of wound healing in patients with type 2 diabetes mellitus influences circulating MicroRNA patterns via inflammatory cytokines, Arterioscler. Thromb. Vasc. Biol. 35 (6) (2015) 1480–1488.

N. Nagpal, R. Kishore, miR-191: an emerging player in disease biology, Front. Genet. 5 (2014) 99.

Z. Cheng and R. Kishore, Redox Biology 37 (2020) 101704.