Hydrogen Sulfide in Skin Diseases: A Novel Mediator and Therapeutic Target

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Together with nitric oxide (NO) and carbon monoxide (CO), hydrogen sulfide (H2S) is now recognized as a vital gaseous transmitter. The ubiquitous distributions of H2S-producing enzymes and potent chemical reactivities of H2S in biological systems make H2S unique in its ability to regulate cellular and organ functions in both health and disease. Acting as an antioxidant, H2S can combat oxidative species such as reactive oxygen species (ROS) and reactive nitrogen species (RNS) and protect the skin from oxidative stress. The aberrant metabolism of H2S is involved in the pathogenesis of several skin diseases, such as vascular disorders, psoriasis, ulcers, pigment disorders, and melanoma. Furthermore, H2S donors and some H2S hybrids have been evaluated in many experimental models of human disease and have shown promising therapeutic results. In this review, we discuss recent advances in understanding H2S and its antioxidant effects on skin pathology, the roles of altered H2S metabolism in skin disorders, and the potential value of H2S as a therapeutic intervention in skin diseases.

1. Introduction

The gasotransmitter hydrogen sulfide (H2S), recognized as the third gaseous signalling molecule along with nitric oxide (NO) and carbon monoxide (CO), is produced enzymatically in mammals under physiological conditions [1]. H2S was identified as a toxic gas pollutant with an odour of rotten eggs in the 18th century [2]. In 1996, Abe and Jincun reported the role of endogenous H2S in neuroregulation, which ushered in a new era of H2S and revealed its biological and pharmacological functions [3]. Later, a number of important biological effects of H2S were reported, including its vasorelaxation, antiapoptotic, anti-inflammatory, and antioxidative stress effects [3–6]. Emerging evidence has shown that endogenous H2S exhibits important functions by regulating multiple biological processes, particularly in the skin. Pathophysiological abnormalities related to altered H2S metabolism and function have been demonstrated in various dermatoses, such as psoriasis, vitiligo, and even melanoma [7–11]. In this review, we summarize the latest research progress on H2S-mediated effects, focusing on the most recent results and mechanism of the antioxidant effect of H2S in various skin diseases, to provide new insights into further exploration of its therapeutic targets.

2. Production and Metabolism of H2S in the Skin

2.1. Production of H2S. H2S can be produced by nonenzymatic and enzymatic pathways in mammalian organisms. Nonenzymatic processes are primarily produced by the decomposition of an inorganic substance, which contributes a little to the amount of H2S production. The main generation of H2S in cutaneous tissue mostly depends on enzymatic routes using L-cysteine and homocysteine by two pyridoxal-5'-phosphate-dependent enzymes, cystathionine β-synthase (CBS) and cystathionine γ-lyase (CSE). The pyridoxal-5'-phosphate-independent enzyme, 3-mercaptopropionate...
sulfurtransferase (3-MST), displays enzymatic activity at a pH of 7.4, generating H$_2$S from 3-mercaptopropionate, which is produced by cysteine aminotransferase (CAT) in mitochondria [12–14] (Figure 1).

The structure of the skin is shown in Figure 2. Skin has two main layers. The uppermost one is the epidermis, which is divided into five layers of cells made mostly out of keratinocytes, along with melanocytes, Merkel cells, and Langerhans cells. The dermis is the second one, a subjacent fibrous-collagenous-elastic tissue that hosts vessels, nerves, and sensory receptors. The subcutaneous tissue hypodermis is the deepest layer [15]. However, the precise localization of the H$_2$S-generating enzymes in the different cell types of the skin has not yet been completely determined. Only a few reports revealed that gene expression for the H$_2$S-producing enzymes occurs in normal human epidermal melanocytes and keratinocytes, which are located in the epidermis (rectangular area in Figure 2) [10, 16]. An immunohistochemical (IHC) analysis from human samples showed that CSE, CBS, and 3-MST express in normal human epidermal melanocytes, and all the dysplastic nevi were positive for CSE, negative for CBS, and variable for 3-MST [10]. CSE and 3-MST also express in the cutaneous circulation to regulate vasodilatation in humans [17, 18]. Consequently, H$_2$S is currently accepted to present and exert various effects in skin, but the exact mechanism of H$_2$S production in different cell types of the skin remains to be elucidated.

2.2. Metabolism of H$_2$S. After its enzymatic synthesis, H$_2$S can be either directly released or stored and liberated afterward, which maintains the proper physiological balance of its metabolism. Two forms of sulfur stores have been identified: bound sulfane sulfur and acid-labile sulfur [13, 19].

The exact details of H$_2$S metabolism in the skin have not yet been elucidated. The main pathway of H$_2$S catabolism is thought to occur in mitochondria by oxidation to thiosulfate and sulfate, excretion from the lung or kidney, and methylation via rhodanese and thiol methyltransferase in the cytosol [20–22]. Meanwhile, H$_2$S can interact with methemoglobin to form sulhemoglobin, a possible biomarker of plasma H$_2$S [23].

3. The Role of H$_2$S in Skin Pathophysiology

Recently, an increasing amount of evidence has illustrated the essential roles of H$_2$S in vasodilatation [17], wound healing [24], inflammation [16], antioxidation [8], and the regulation of cancer cells [9, 10, 25] in the skin (Figure 3).

3.1. H$_2$S in Vascular Disorders. In the study of vascular signaling mechanisms in healthy and sick adults, the skin is a representative and accessible regional vascular bed that modulates vascular function [26–28]. Deficits in cutaneous vascular function are highly associated with and predictive of vascular dysfunction in the coronary and renal circulation [29, 30].

CSE and 3-MST have been suggested to be expressed in the human microvasculature [17]. One recent study indicated that NaHS and Na$_2$S may result in a significant dose-dependent increase in vasodilatation in the cutaneous circulation through tetraethylammonium-sensitive calcium-dependent potassium channels and functionally interact with both the COX and NO vasodilatory signalling pathways. Furthermore, as an endothelium-derived hyperpolarizing factor, H$_2$S can also cause local thermal hyperaemia and reflex vasodilatation in cutaneous blood flow [17]. In the past, these functions were thought to be mediated by only endothelial NO synthase and eicosanoid-dependent mechanisms [31, 32].

Emerging evidence suggests that H$_2$S is a physiologic vasodilator and regulator of blood pressure in many other organs and tissues. Rodent experiments showed that knockdown of CSE or treatment with the CSE inhibitor D,L-propargylglycine resulted in marked hypertension [33–36]. In addition, H$_2$S could protect against ischaemia/reperfusion (I/R) injury in the heart, liver, kidney, brain, intestine, stomach, hind limb, lung, and retina [37]. Therefore, targeting H$_2$S or its donors might become a novel preventive and therapeutic strategy for the regulation of multiple vascular pathologies.

3.2. H$_2$S in Inflammatory Disorders. The physical anti-inflammatory role of H$_2$S has attracted extensive attention. Numerous studies have shown that endogenous and exogenous H$_2$S play a critical role in the resolution of inflammation [38]. Additionally, psoriasis is a common T-cell-chronic inflammatory skin disease characterised by red, thickened plaques with overlying silver-white scales. According to Alshorafa et al., the serum levels of TNF-$\alpha$, IL-6, and IL-8 in patients with psoriasis were higher than those in a healthy control group, and the level of H$_2$S was lower than that in the healthy control group. Administration of HaCaT cells with exogenous H$_2$S largely inhibited the TNF-$\alpha$-mediated upregulation of NO, IL-6, and IL-8 in a dose-dependent manner by suppressing activation of the p38, MAPK, ERK, and NF-κB pathways [7].

Moreover, hypoxia of the skin is a common physiopathological characteristic of various skin diseases, such as diabetic ulcers [39, 40], pressure ulcers [41], and varicose ulcers [42], in which inflammation and oxidative stress injury are closely related. Yang et al. used cobalt chloride (CoCl$_2$) as a hypoxia-mimicking agent to treat human skin keratinocytes (HaCaT cells) and demonstrated that 100-800 μM NaHS administration for 30 minutes could confer a cytoprotective effect against chemical hypoxia-induced cytotoxicity and inflammation through inhibiting the reactive oxygen species- (ROS-) activated NF-κB/COX-2 signalling pathway in HaCaT cells [43].

Likewise, evidence suggests that both CSE and CBS alleviate inflammation in the skin [16]. The expression of these enzymes was upregulated in human keratinocytes treated with formaldehyde at subcytotoxic concentrations, and the H$_2$S produced could, in turn, inhibit an increase in proinflammatory factors (such as MMP-1, PGE2, and IL-8), which are involved in early proinflammatory processes. In addition, in mice with the cutaneous Arthus reaction, exposure to NaHS decreased the number of neutrophils recruited to skin lesions and attenuated TNF-$\alpha$ and IFN-$\gamma$ expression in the inflammatory reaction [44].

3.3. H$_2$S in Wound Healing. The proliferation and differentiation of the epidermis are indispensable processes in wound
Figure 1: Production of $\text{H}_2\text{S}$ in the skin. CBS catalyses the generation of cystathionine from the substrates homocysteine and serine and liberates $\text{H}_2\text{S}$ from a combination of cysteine and homocysteine. CSE mainly converts cysteine into $\text{H}_2\text{S}$, pyruvate, and ammonia. 3-MST generates $\text{H}_2\text{S}$ from 3-mercaptopyruvate produced by cysteine aminotransferase. CBS: cystathionine $\beta$-synthase; CSE: cystathionine $\gamma$-lyase; GSH: glutathione; 3-MST: 3-mercaptopyruvate sulfide transferase; CAT, cysteine aminotransferase.

Figure 2: The structure of skin. The uppermost layer is the epidermis, the second layer is the dermis, and the deepest layer is the subcutaneous tissue hypodermis. The area indicated by the rectangle reveals that the epidermis is divided into five layers of cells.
repair that are often dysregulated under pathologic conditions, such as those in psoriasis, epidermal cancers, atopic dermatitis (AD), and delayed wound healing [45, 46]. The proliferation and differentiation of human keratinocytes were found to be promoted by exogenous H\textsubscript{2}S in a dose-dependent manner by autophagy regulation [24]. Endogenous overexpression of CSE or the addition of exogenous NaHS at increasing concentrations (0-100 μM) and for increasing stimulation times (0-6 d) could also increase cell proliferation in primary human epidermal melanocytes [8].

Endogenous H\textsubscript{2}S has been demonstrated to promote wound healing. Researchers found that CSE expression and the H\textsubscript{2}S content are decreased in diabetic foot ulcers and the granulation tissues of wounds [47, 48]. The wound healing process was shown to be significantly delayed in CSE\textsuperscript{−/−} mice compared with CSE\textsuperscript{+/} mice, and blockade of CBS had the same effects, decreasing the wound closure rate and cell migration [49, 50]. In contrast, intraperitoneal treatment with NaHS and 4-hydroxythiobenzamide dramatically improved wound healing through the activation of angiopoietin-1 and restoration of endothelial progenitor cell functions in type 2 diabetic db/db mice [47]. To better understand the underlying mechanism of this effect, a recent study showed that downregulation of neutrophil extracellular trap (NET) release and blockade of ROS-induced MAPK ERK1/2 and p38 activation played an important role in the improved diabetic wound healing caused by Na\textsubscript{2}S [51]. Additionally, H\textsubscript{2}S could promote ischaemic diabetic wound healing via increasing the production of vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), platelet-derived growth factor (PDGF), hypoxia inducible factor-1α (HIF-1α), and endothelial nitric oxide synthase (eNOS) in type 2 diabetic db/db mice [52]. Topical treatment with a 2% NaHS-containing ointment also accelerated wound healing by modulating angiogenesis in the granulation tissues via augmented VEGF levels in rats with streptozotocin-induced diabetes [53].

Furthermore, Zhao et al. suggested that improved wound healing by NaHS treatment in diabetic ob/ob mice was associated with reduced neutrophil and macrophage infiltration; decreased production of TNF-α, IL-6, and MMP-9; and increased collagen deposition in granulation tissues [48]. Thus, the identification of H\textsubscript{2}S as a small-molecule stimulus for cell proliferation and wound healing provides essential information for understanding epidermal repair and disorders and offers potential targets for future therapy.

3.4. H\textsubscript{2}S in Pigment Skin Disorders and Fibrotic Disease. Accumulating evidence suggests that H\textsubscript{2}S may confer protective effects against various types of stimuli-triggered damage.
in different organs, such as the skin, heart, and brain [8, 54, 55]. One of the dominant mechanisms of H2S protection is its antioxidant effect, which is exerted not only by increased reduced glutathione (GSH) but also the direct scavenging of superoxide anion (O2-), hydrogen peroxide (H2O2) [56], and peroxynitrite (ONOO-) [57] to combat oxidative stress.

A recent study showed that 10-100 μM NaHS and the overexpression of CSE could promote cell proliferation and melanocyte regeneration by increasing the production of melanogenic enzymes (MITF, TYR, and TRP-1) in primary human epidermal melanocytes [8]. Melanocyte regeneration and melanin synthesis play important biological roles in pigment skin disorders and processes such as vitiligo, hair greying, and albinism [58, 59]. Synthesized and deposited in melanosomes, melanin can be transported to nearby keratinocytes to induce pigmentation, protecting the epidermis and underlying fibroblasts in the dermis from ultraviolet damage, which results in photoaging, oxidative stress, and even skin cancer [60, 61]. Therefore, pharmacologic regulation of H2S may be a novel strategy for skin disorders caused by the loss of melanocytes and dysregulation of oxidative stress.

Excessive oxidative stress is one of the dominant causes of wound healing impairment [62]. ROS arising from inflammatory cells activates various molecular signalling pathways to block angiogenesis or cytokine secretion to delay wound healing. The antioxidant and cytoprotective effects of H2S are also observed in the skin wound healing process [63, 64]. For example, attenuated ROS and increased VEGF expression are the main reasons for the accelerated wound healing and improved blood flow observed after pretreatment of wounds with NaHS after an operation. NaHS also promotes skin fibroblast and keratinocyte migration by alleviating ROS and increasing mitochondrial membrane potential [65]. In addition, Na2S could improve diabetic wound healing by downregulating NET release and suppressing inflammatory, and accelerated wound healing by downregulating the NF-κB pathway [66]. Taken together, these findings suggest that exogenous H2S supplementation and endogenous H2S overexpression are potential strategies to combat oxidative stress and control inflammation to promote skin wound healing.

In addition, the physical effect of H2S against oxidative stress and inflammation in the development of fibrosis has attracted significant attention [67]. Abnormal H2S metabolism is associated with the pathogenesis of fibrosis, causing damage to the structure and function of tissues and organs. Several in vivo and in vitro studies have shown that both endogenous H2S levels and the expression of H2S-related enzymes in plasma are significantly decreased in fibrotic diseases, but supplementation with exogenous H2S could alleviate the severity of fibrosis in different experimental animal models [68, 69]. The cytoprotective role of H2S in fibrosis is mainly attributed to its antioxidant, antiapoptotic, anti-inflammatory, and fibroblast-inhibitory activities [70-73]. H2S could restore a normal morphologic phenotype in Werner syndrome fibroblasts by attenuating oxidative damage and modulating the mTOR pathway [74]. Wang et al. demonstrated the beneficial effects of H2S on systemic sclerosis-associated skin and lung fibrosis. Intraperitoneal injection of NaHS markedly reduced the expression of fibrotic biomarkers such as α-smooth muscle actin, collagen-I, collagen-III, fibronectin, transforming growth factor-β1, Smad2/3 phosphorylation, and monocyte chemoattractant protein-1 in the lung in a mouse model, suggesting that H2S may be a potential therapy against systemic sclerosis-related organ fibrosis in the clinic [75].

3.5. H2S in Skin Cancers. H2S has a crucial role in multiple types of cancers, including human melanoma [10, 25, 76]. Generally, endogenous H2S or a relatively low concentration of exogenous H2S might promote or maintain cancer cell growth over a relatively short duration, while overexpression of H2S-generating enzymes or exposure to a relatively high level of H2S donor may have an anticancer effect over a relatively long duration [25].

Immunohistochemical (IHC) analysis of over 100 human subjects showed that the CSE level was increased from the transition from nevus to primary melanoma, decreased in metastatic lesions, and almost absent in lymph node metastases, and the expression of CSE and 3-MST was significantly higher than that in normal human epidermal melanocytes [10]. Overexpression of CSE led to spontaneous apoptosis in human melanoma cells by decreasing the levels of antiapoptotic proteins and suppressing the activation of NF-κB. It was also reported that an exogenous H2S donor—DATS, an active component in garlic oil—at 100 μM inhibited the proliferation of A375 human melanoma cells by downregulating the Akt and ERK pathways. Further treatment with the CSE substrate L-cysteine at 600 mg·kg·1 or 50 mg·kg·1 DATS significantly inhibited tumour growth in mice subcutaneously injected with B16-F10 cells by 67% compared with that in the control group [10]. A recent study also found that treatment of the A375 and SK-MEL-28 human melanoma cell lines with 2 mM NaHS, a donor to H2S gas, for 24 hours attenuated cell proliferation and migration and arrested the cell cycle but induced cell autophagy. Suppression of autophagy by ATG7 shRNA enhanced H2S-regulated cell apoptosis but had no synergistic effect on cell proliferation, migration, or division. Furthermore, NaHS treatment could decrease the protein expression of p-PI3K, p-Akt, and mTOR, while insulin-like growth factor-1 (IGF-1), an activator of the PI3K/AKT/mTOR pathway, could partly reverse the changes in cellular behaviour caused by NaHS, which suggested that the inhibition of human melanoma cell development by exogenous H2S donors might be correlated with suppression of the PI3K/AKT/mTOR pathway [9]. Moreover, 25 μM DATS inhibited the growth of both human melanoma cells and basal cell carcinoma cells by upregulating cytosolic Ca2+ mobilization and intracellular ROS production and decreasing the activities and protein expression of matrix metalloproteinase-2 (MMP-2) and MMP-9 without a significant effect on normal keratinocyte HaCaT cell growth [77].
Specifically, the inhibitory effect of DATS on invasion and metastasis in A375 cells was found to correlate with decreased levels of several integrin subunits and focal adhesion kinase (FAK) [78]. These results suggest that the antimetastatic potential of DATS for human melanoma cells might be due to disruption of the integrin/FAK signalling pathway.

Another H2S-releasing naproxen derivative, naproxen-4-hydroxybenzodithioate, at 10 and 30 μM was reported to induce caspase 3-mediated apoptosis and suppress human melanoma cell proliferation, migration, invasion, and colony formation in vitro [79].

Nevertheless, many studies have shown that in primary melanoma, the expression of CSE is usually increased, and the overexpression of CSE in cancer cells has a tumour-promoting effect; furthermore, blockade of CSE enzymatic activity reduced proliferation rates in human melanoma cells [80]. Therefore, to achieve anticancer efficacy, further research is needed to explore a reasonable strategy for H2S drug application, since different types of cancer cells exhibit distinct drug susceptibilities and physiological traits. Figure 4 shows the roles of H2S in skin cancers.

According to the abovementioned findings, the regulatory effects of different H2S donors on various skin cell types/tissues are summarized in Table 1.

**4. Therapeutic Potential of H2S in Skin Diseases**

In ancient times, our ancestors discovered the beneficial properties of bathing in thermal spring water, and this therapy remains a popular form of treatment for chronic skin and rheumatologic diseases today. The waters used to treat skin conditions have different physical and chemical compositions but are generally rich in sulfur, H2S, sulfates, and other ions [81, 82]. The activity of sulfur in the skin seems to be related mainly to its interaction with cysteine and its catabolites [83].

Bathing in sulfur-rich spring water can treat many immune-mediated skin diseases, such as psoriasis and AD. Due to the sulfur and H2S in thermal water, this therapy can decrease scales, pruritus, and inflammation in patients with psoriasis and exert beneficial anti-inflammatory, keratolytic, and antipruriginous effects [84]. The use of sulfur water has also been proposed to relieve AD, leg ulcers, acne, and hidradenitis suppurativa lesions because sulfur can interact with ROS in the deeper epidermis, producing sulfur and H2S, which may be transformed into pentathionic acid; this pentathionic acid may be the source of the antibacterial and antifungal properties of thermal springs [85–87]. Moreover, sulfur water is therapeutic in acne patients due to its keratolytic effect, which results in peeling [88]. Therefore, bathing in sulfur-containing hot springs acts as an important alternative dermatological therapy.

Multiple recent in vivo and in vitro experiments have shed light on the biological and pharmacological roles of H2S under a variety of physiological and pathological conditions. An increasing number of therapeutic applications of H2S in skin diseases have also been revealed. As mentioned above, sulfide salts, including NaHS and Na2S, are the most common class of H2S donors applied in biological studies, providing direct, instantaneous access to the physiologically relevant forms of sulfide (H2S and HS−) [89]. Diallyl disulfide (DADS) is the active compound from garlic, and GYY4137 is a water-soluble donor used as the “gold standard” H2S donor in a large number of experimental studies [90]. These H2S donors have been or are currently under evaluation in clinical trials. A few notable examples include the naproxen-based H2S donors ATB-346 and naproxen-HBTA, which have been reported to exert anti-inflammatory and anticancer effects [91]. Researchers reported that 100 μM ATB-346 and 30 μM naproxen-HBTA could inhibit human melanoma cell proliferation, migration, invasion, and colony formation, with the possible mechanisms including inhibition of prosurvival pathways associated with NF-κB and Akt activation.

Furthermore, polycaprolactone (PCL) containing jk1 was electrospun to prepare a pH-controlled H2S donor, generating a kind of nanofibre with a H2S-release function. PCL-jk1 could significantly promote wound repair and regeneration compared to that in a control group, which may have
been due to the release of H$_2$S, confirming the important role of H$_2$S function in physiological protection of wounds [92]. In addition, Lin et al. produced an H$_2$S-releasing depot formulation termed “NaHS@MPs” to treat diabetic wounds. Topical NaHS@MPs treatment of the wounds of diabetic db/db mice increased the proliferation and migration of epidermal keratinocytes, as well as angiogenesis, by inducing sustained phosphorylation of ERK1/2 and p38 and thus improved the healing of full-thickness wounds [93].

5. Conclusions

H$_2$S, the third kind of gaseous signalling molecule, plays important roles in physiological regulatory processes in the skin (Table 1) and joins NO and CO in the group of signalling agents termed “gasotransmitters.” CSE, CBS, and 3-MST are three key H$_2$S-producing enzymes that can be detected in the epidermis. Altered expression levels of these enzymes or H$_2$S levels are usually associated with various skin diseases, including psoriasis, vitiligo, fibrosis, delayed wound healing, and even melanoma. Thus, CSE, CBS, and 3-MST might be biomarkers and novel molecular targets for dermatological diagnostics and treatment.

It is simultaneously becoming increasingly obvious that oxidative stress alters a number of redox-sensitive signalling pathways in different skin types, contributing to skin ageing and numerous cutaneous diseases, including skin cancers [94]. H$_2$S, as an antioxidant, can protect cells from oxidative stress and act as a regulator of redox-sensitive signalling pathways.
damage by decreasing the production of intracellular ROS [95]. Thus, the application of H2S might serve as an effective and easy method to improve these skin conditions. In addition, remarkable progress has been made in the fields of H2S donor chemistry and biomaterials in a short period of time since the therapeutic potential of H2S was discovered. Therefore, filling the knowledge gaps regarding the precise metabolic mechanism behind the role of H2S in skin disorders and appropriate treatment with H2S are key issues to be addressed, which may facilitate promising strategies for the further clinical application of H2S in dermatology.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors’ Contributions

Qing Xiao organized, wrote, and prepared the manuscript. Lidan Xiong, Jie Tang, and Li Li contributed in writing and reviewing the major parts of the manuscript. All authors read and approved the final manuscript.

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