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Graphical Review

Hydrogen sulfide and its donors: Novel antitumor and antimetastatic therapies for triple-negative breast cancer

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ABSTRACT

Hydrogen sulfide (H_2S) is considered as a novel second-messenger molecule associated with the modulation of various physiological and pathological processes. In the field of antitumor research, endogenous H_2S induces angiogenesis, accelerates the cell cycle and inhibits apoptosis, which results in promoting oncogenesis eventually. Interestingly, high concentrations of exogenous H_2S liberated from donors suppress the growth of various tumors via inducing cellular acidification and modulating several signaling pathways involved in cell cycle regulation, proliferation, apoptosis and metastasis. The selective release of certain concentrations of H_2S from H_2S donors in the target has been considered as an alternative tumor therapy strategy. Triple-negative breast cancer (TNBC), an aggressive subtype with less than one year median survival time, is known to account for approximately 15–20% of all breast cancers. Due to the lack of approved targeted therapy, the clinical treatment of TNBC is still hindered by metastasis as well as recurrence. Significant efforts have been spent on developing novel treatments of TNBC, and remarkable progress in the control of TNBC by H_2S donors and their derivatives have been made in recent years. This review summarizes various pathways involved in antitumor and antimetastasis effects of H_2S donors and their derivatives on TNBC, which provides novel insights for TNBC treatment.

1. Introduction

H_2S has been discovered as a novel endogenous signaling gaseous transmitter along with nitric oxide (NO) and carbon monoxide (CO) [1,2] since Abe and Kimura revealed the endogenous production and intracellular signaling cascades of H_2S [3]. In general, taking L-cysteine as a substrate, endogenous H_2S liberation is mainly attributed to cystathionine-β-synthase (CBS), cystathionine-β-lyase (CSE) and 3-mercaptopyruvate sulfurtransferase (3-MST) (Fig. 1) [4]. The liberated H_2S participates in modulating physiological and pathological processes, including intestinal disorders [5], cardiovascular diseases [6–9], diseases caused by oxidative stress [10–12] and inflammation [13,14]. Sodium hydrosulfide (NaHS) and sodium sulfide (Na_2S) were generally used as the H_2S donors in early studies. Although sulphide inorganic salts exhibited cytotoxic effects on several tumor cells and therapeutic potential on the cardiovascular system [15–17], rapid oxidation of NaHS and Na_2S solution and uncontrolled release of H_2S lead to the discrepancies in curative effect [18]. Recently, some organic H_2S donors (ADT-OH, thiobenzamide, GYY4137, DADS and DATS, Fig. 2) are used for endogenous H_2S production in a sustained fashion [19–22]. Several H_2S donor-based therapeutics have entered Phase II clinical trials, such as ATB-346 and GIC-1001 (Fig. 2) [23,24]. Besides cardiovascular diseases and chronic diseases [25–32], H_2S donors show significantly different roles in neoplasia compared with endogenous H_2S. Endogenous H_2S and low levels of exogenous H_2S induce angiogenesis, accelerate cell cycle, inhibit apoptosis, and promote oncogenesis eventually [33,34], whereas H_2S donors trigger high concentrations of exogenous H_2S production to prevent tumor development. The donors

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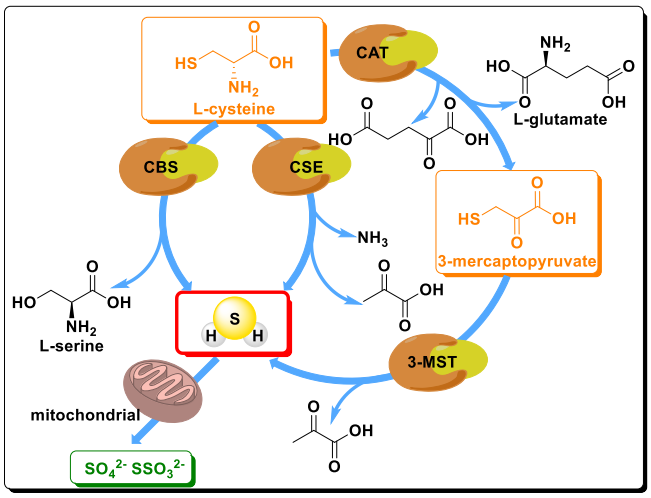

Fig. 1. Main mechanisms of endogenous H_2S production in mammalian cells. Endogenous H_2S can be produced mainly through three pathways. Among which, L-cysteine directly generates H_2S through the catalysis of CBS or CSE. H_2S is also biosynthesized by the synergistic effects of CAT and 3-MST. Ultimately, H_2S is metabolized in mitochondria in the form of thiosulfate or sulfate.

selectively inhibit progression of tumors by inducing intracellular acidification and inhibiting proliferation and metastasis of tumor cells through EGFR/ERK/MMP-2, PTEN/Akt, PI3K/Akt/mTOR and NF-κB pathways with no obvious adverse effects on animal health [35–42]. Thus, H_2S donors are instrumental for developing novel antitumor therapies with less side effects [43].

Rising mortality highly features cancer as a global health problem [44]. In terms of women's health, breast cancer has been prescribed as the most common cause of cancer death. Among them, around 15%–20% are diagnosed as TNBC, an aggressive subtype which is implicated in the lack of estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2) expression [45,46]. Patients can hardly ameliorate symptoms through endocrine therapy and no other treatments for TNBC have established except adjuvant chemotherapy or radiotherapy after surgery [47]. The chemotherapeutic drugs for advanced TNBC are mainly taxanes or anthracyclines. Although chemotherapy prolongs the survival of patients, the effects are relatively limited due to the poor prognosis, and high-intensity chemotherapy will impair the living quality of patients [48–50]. In contrast to other breast cancers, TNBC is frequently accompanied by the recurrence and higher probability of metastasis to the central nervous system as well as lungs [51,52]. The aggressive metastatic behaviors lead to the limited median survival which is less than one year for TNBC patients. Even if TNBC has been deeply studied in the past several decades and many targeted therapeutic agents including poly(ADP-ribose) polymerase (PARP) inhibitors [53], vascular endothelial growth factor (VEGF) inhibitors [54], epidermal growth factor receptor (EGFR) inhibitors [55] and tyrosine kinases (TKs) inhibitors [56] have been tried, none of them have completed all clinical trials. Elevated mortality raises the urgency of novel agents against TNBC, especially metastatic TNBC.

The progression of ER-negative breast cancer cells is related to the constitutively activated NF-κB [57–59]. Matrix metalloproteinases (MMPs), the key causes that account for the invasion and metastasis of tumor cells, could be regulated by the NF-κB signaling pathway and are over-expressed during breast cancer cells growth [60,61]. H_2S donors have been shown to inhibit NF-κB activation among other tumor cells [35]. They might have potential effects on metastatic tumors.

In terms of TNBC, H_2S donors exhibited potent therapeutic potential. As early as 2011, Chattopadhyay et al. verified the antitumor effect of HS-ASA (a novel H_2S donating aspirin, Fig. 2) on TNBC MDA-MB-231 cells *in vitro* and *in vivo*. HS-ASA was shown to inhibit proliferation accompanied by cell cycle arrest at G_0/G_1 phase in a dose-dependent manner. It markedly restrained the translocation of NF-κB (p65) into the nucleus via inhibiting the phosphorylation status of IKKα and IKKβ to decrease dissociation between NF-κB and IκB. Furthermore, after HS-ASA treatment, thioredoxin reductase-1 (TrxR) inhibition induced reactive oxygen species (ROS) accumulation also disrupted redox homeostasis in MDA-MB-231 cells. The subsequent decline of tumor mass and volume in mouse xenograft model indicated potent antitumor effects of HS-ASA on TNBC through inhibiting NF-κB pathway and TrxR activity, and elevating ROS levels [62].

Besides eliminating tumors, Liu et al. demonstrated that DATS (an extract of garlic) resulted in sharp attenuation of MDA-MB-231 cell migration, and metastasis phenotype inhibition was observed in zebrafish xenograft model. After the treatment with DATS, MDA-MB-231 cells with smooth surfaces and decreasing pseudopodia were observed, which indicated cell migration inhibitory effect. In addition, by blocking the NF-κB pathway, DATS significantly inhibited the mRNA levels, protein expression, and enzyme activity of MMP-2/9, the proteinases over-expressed during invasion, oncogenesis and metastasis, to degrade and reshape the dynamic balance of extracellular matrix. After DATS treatment, phosphorylation of ERK level was declined in a dose-dependent manner, which proved that the ERK/MAPK pathway was also associated with TNBC [63]. It has become a consensus that breast cancer stem cells play an important role in tumor proliferation and metastasis. As an important transcription regulator, the expression of FoxQ1 is related to the growth and metastasis of breast cancer. The down-regulation of FoxQ1 expression in DATS-treated SUM159 TNBC cells was discovered. As one of the markers of tumor stem cells, ALDH1 activity was completely inhibited after FoxQ1 knockdown and was further inhibited in SUM159 xenograft model. These studies showed that FoxQ1 might be a new target for TNBC treatment by DATS [64].

As a volatile extract of garlic oil, DADS also endowed with potent inhibitory effects on TNBC. Like DATS, Huang et al. confirmed the inhibitory effect of DADS on migration and invasion through wound-healing, transwell migration and invasion assays. The expression and activity of MMP-9 were significantly declined after the incubation with DADS. Besides, the potent antimetastatic effect of DADS was also revealed based on the observed reversal of the epithelial-mesenchymal transition (EMT). As an AU-rich RNA-binding protein, tristetraprolin (TTP) involves in the degradation of urokinase type plasminogen activator (uPA), an upstream gene of MMP-9, and inhibits tumor metastasis by mediating the expression of MMP-9. As reported by Xiong et al., decline of uPA and upregulation of TTP were detected after DADS treatment, which could be completely counteracted by TTP siRNA. Therefore, targeting TTP might be capable of exerting inhibitory effect on TNBC metastasis. By ameliorating aberrant activation of the β-catenin pathway, DADS improved the activity of caspase-3/9 and the expression of pro-apoptotic factor Bax, while it down-regulated anti-apoptotic factor Bcl-2 levels in MDA-MB-231 and BT-549 TNBC cell lines. These findings highlight the pro-apoptotic effect of DADS on TNBC cells. Consistent with the aforesaid *in vitro* results, the volume and weight of DADS-treated MDA-MB-231 xenograft tumors in mice were obviously declined [65,66].

ADT-OH, a commonly used H_2S donor that exhibited prominent cytoprotective properties [67], was conjugated with hyaluronic acid (HA) to improve the retention time and water solubility. Similarly, Dong et al. found that HA-ADT (Fig. 2) induced MDA-MB-231 cells apoptosis by elevating the ratio of Bad/Bcl-xl and Bax/Bcl-2 as well as the expression of cleaved caspase-3/9 and cleaved PARP. Further preliminary mechanism studies found PI3K/Akt/mTOR and Ras/Raf/MEK/ERK signaling pathways were suppressed in HA-ADT group compared with the control (PBS), NaHS and GYY4137 groups. The markedly shrunken xenograft tumors were also found in HA-ADT-treated nude mice, accompanied with reduced CD31 expression that

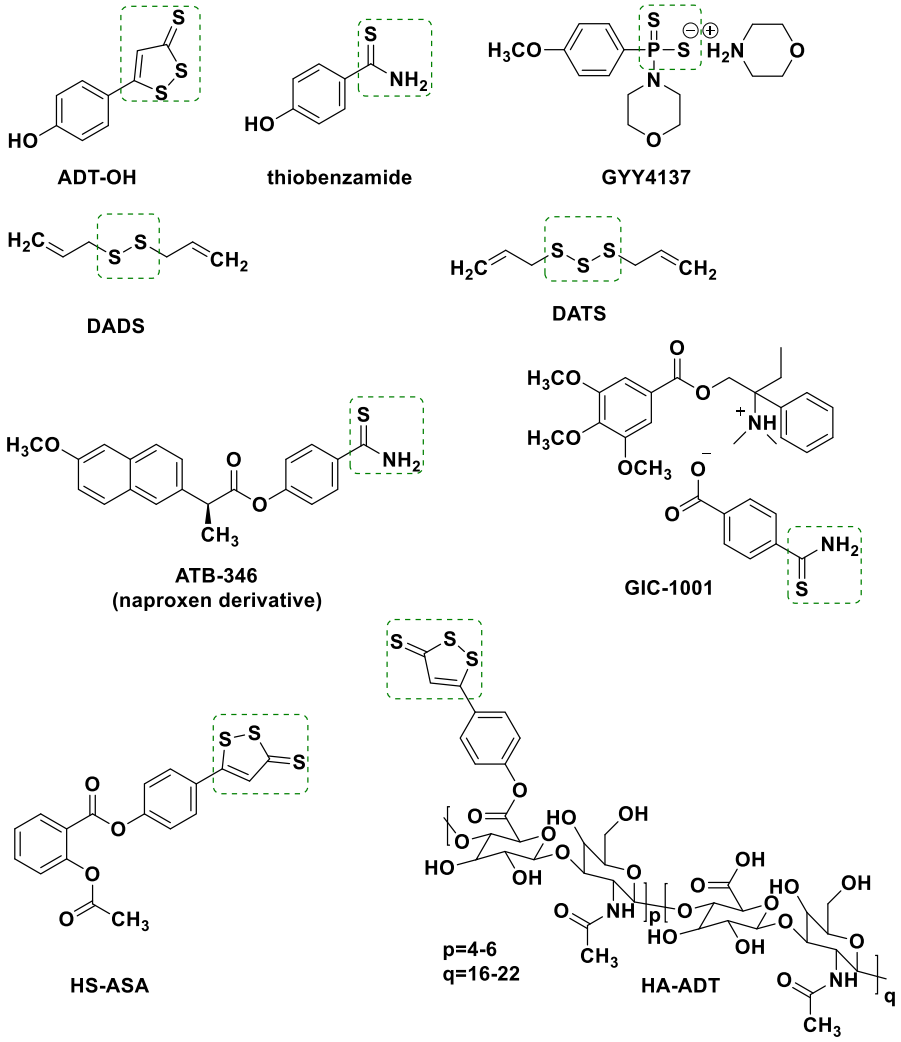

Fig. 2. Structural components of H_2S donors and H_2S generating drug candidates. Potential antitumor mechanism of H_2S donors against TNBC.

demonstrated angiogenesis inhibition [68].

In summary, on the one hand, H_2S donors and their derivatives effectively modulated the proliferation and apoptosis of TNBC cells by inhibiting the phosphorylation or expression of proteins associated with NF-κB, PI3K/Akt/mTOR and Ras/Raf/MEK/ERK signaling pathways. On the other hand, they also inhibited the expression of MMP-2/9 and EMT to resist TNBC metastasis by inhibiting aberrant activation of the β-catenin pathway. Other pathways that H_2S may be involved in TNBC prevention deserve further investigation. The mechanism of H_2S donors and their derivatives against TNBC is summarized in Fig. 3. As for sulfide salts, although NaHS administration alone exhibits little inhibitory effect on tumor growth in mice, it decreases O_2 consumption and increases O_2 delivery to alleviate tumor hypoxia, eventually radiosensitized MDA-MB-231 tumors. The results provided insights for H_2S donors in combination therapy [69].

2. Conclusions and perspectives

Since the current therapies for TNBC are mainly adjuvant chemotherapy or radiotherapy after surgery, patients can hardly bear side effects of long-term chemotherapy or radiotherapy, and they still face the risks of metastasis and relapse due to the lack of targeted drug molecules. Recently, H_2S donors and their derivatives have made attractive development in TNBC therapy. Although H_2S donors liberate high concentrations of H_2S, there is no research on actual impact of the H_2S itself in TNBC treatment, and it is unclear whether the remaining structural fragments after H_2S generation are related to the potent antitumor activity. The precise antitumor mechanism of H_2S deserves further study. Moreover, it is worth noting that the regulation mechanism of the expression and activity of CBS, CSE and 3-MST is remained ambiguous and argued. Given the evidence that inhibition of CBS induces apoptosis in several tumor cells (colon cancer, ovarian cancer, breast cancer, etc.), perhaps inhibition of H_2S biosynthesis through targeted inhibition of H_2S-producing enzymes exhibits comparable antitumor effects to H_2S donors. At present, investigations also elaborated on the connection between H_2S and NO which participated in modulating multiple physiological and pathological processes [70,71], such second messenger molecules provide novel insights for TNBC treatment. In light of the bell-shaped model effect of H_2S has been verified and widely accepted, the selective release of certain concentrations of H_2S from H_2S donors in the target to minimize the adverse effects of H_2S is essential. To cope with the special tumor microenvironment, H_2S donors that sensitive to definite pH, enzymes, NIR light or free radicals are being studied [72–75]. Nanosized delivery systems have also been tried for targeted delivery of exogenous H_2S and hope to endow it with improved antitumor effect through intratumoral conversion of nanostructures to microstructures [76,77]. These attempts may help researchers to study the precise mechanisms of H_2S in the therapy of cancers, especially TNBC. We hope that H_2S donating compounds can greatly improve the survival rate of TNBC patients in

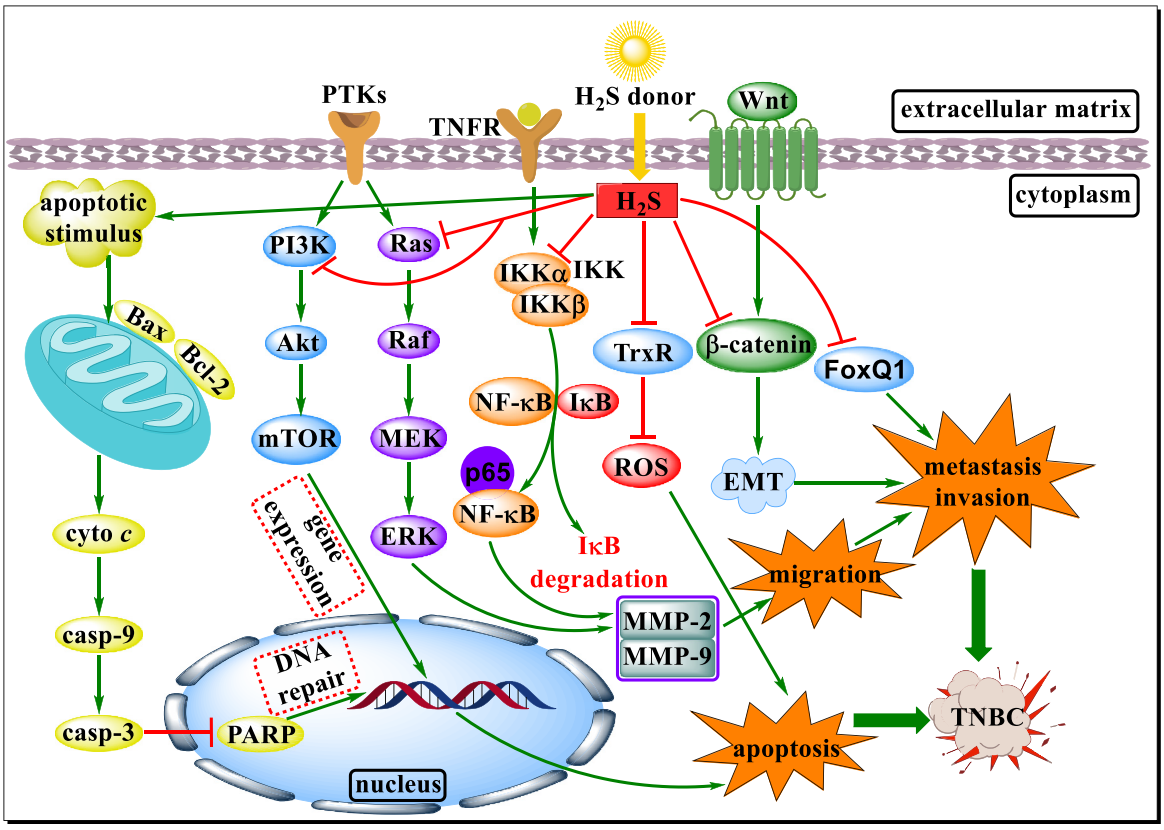

Fig. 3. Schematic diagram of partial action pathways of H_2S donors and their derivatives on TNBC. H_2S donors and their derivatives participate in the regulation of multiple pathways to induce apoptosis and block the invasion, proliferation and metastasis of TNBC cells by triggering the release of H_2S in response to specific stimuli. They not only promote TNBC cells apoptosis by activating mitochondrial apoptosis pathway and inhibiting phosphorylation or expression of related proteins involved in NF-κB, PI3K/Akt/mTOR, Ras/Raf/MEK/ERK signaling pathways, but also ameliorate aberrant activation of the β-catenin pathway, followed by MMP-2/9 activity inhibition and EMT reversal.

the future.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

[1] G.K. Kolluru, X. Shen, S. Yuan, C.G. Kevil, Gasotransmitter heterocellular signaling, Antioxidants Redox Signal. 26 (2017) 936–960.
[2] J.L. Wallace, R. Wang, Hydrogen sulfide-based therapeutics: exploiting a unique but ubiquitous gasotransmitter, Nat. Rev. Drug Discov. 14 (2015) 329–345.
[3] K. Abe, H. Kimura, The possible role of hydrogen sulfide as an endogenous neuromodulator, J. Neurosci. 16 (1996) 1066–1071.
[4] Z.J. Song, M.Y. Ng, Z.W. Lee, W. Dai, T. Hagen, P.K. Moore, D. Huang, L.W. Deng, C.H. Tan, Hydrogen sulfide donors in research and drug development, Med. Chem. Commun. 5 (2014) 557–570.
[5] E. Distrutti, L. Sediari, A. Mencarelli, B. Renga, S. Orlandi, E. Antonelli, F. Roviezzo, A. Morelli, G. Cirino, J.L. Wallace, S. Fiorucci, Evidence that hydrogen sulfide exerts antinociceptive effects in the gastrointestinal tract by activating KATP channels, J. Pharmacol. Exp. Therapeut. 316 (2006) 325–335.
[6] S. Mani, A. Untereiner, L. Wu, R. Wang, Hydrogen sulfide and the pathogenesis of atherosclerosis, Antioxid, Redox Signal 20 (2014) 805–817.
[7] D.D. Wu, J. Wang, H. Li, M.Z. Xue, A.L. Ji, Y.Z. Li, Role of hydrogen sulfide in ischemia-reperfusion injury, Oxid. Med. Cell. Longev. (2015) 1–16.
[8] B. Geng, J. Yang, Y. Qi, J. Zhao, Y. Pang, J. Du, C. Tang, H_2S generated by heart in rat and its effects on cardiac function, Biochem. Biophys. Res. Commun. 313 (2004) 362–368.
[9] A. Papapetropoulos, A. Pyriochou, Z. Altaany, G. Yang, A. Marazioti, Z. Zhou, M.G. Jeschke, L.K. Branski, D.N. Herndon, R. Wang, C. Szabo, Hydrogen sulfide is an endogenous stimulator of angiogenesis, Proc. Natl. Acad. Sci. U.S.A. 106 (2009) 21972–21977.
[10] S. Carballal, M. Trujillo, E. Cuevasanta, S. Bartesaghi, M.N. Moller, L.K. Folkes, M.A. Garcia-Bereguiain, C. Gutierrez-Merino, P. Wardman, A. Denicola, R. Radi, B. Alvarez, Reactivity of hydrogen sulfide with peroxynitrite and other oxidants of biological interest, Free Radical Biol. Med. 50 (2011) 196–205.
[11] C. Szabo, Hydrogen sulphide and its therapeutic potential, Nat. Rev. Drug Discov. 6 (2007) 917–935.
[12] R. Wang, Physiological implications of hydrogen sulfide: a whiff exploration that blossomed, Physiol. Rev. 92 (2012) 791–896.
[13] M. Bhatia, Hydrogen sulfide and substance P in inflammation, Antioxid, Redox Signal 12 (2010) 1191–1202.
[14] X.Y. Zhu, S.J. Liu, Y.J. Liu, S. Wang, X. Ni, Glucocorticoids suppress cystathionine gamma-lyase expression and H_2S production in lipopolysaccharide-treated macrophages, Cell. Mol. Life Sci. 67 (2010) 1119–1132.
[15] D. Wu, J. Li, Q. Zhang, W. Tian, P. Zhong, Z. Liu, H. Wang, H. Wang, A. Ji, Y. Li, Exogenous hydrogen sulfide regulates the growth of human thyroid carcinoma cells, Oxid. Med. Cell. Longev. (2019) 6927298 2019.
[16] A.Y. Xiao, M.R. Maynard, C.G. Piett, Z.D. Nagel, J.S. Alexander, C.G. Kevil, M.V. Berridge, C.B. Pattillo, L.R. Rosen, S. Miriyala, L. Harrison, Sodium sulfide selectively induces oxidative stress, DNA damage, and mitochondrial dysfunction and radiosensitizes glioblastoma (GBM) cells, Redox Biol. 26 (2019) 101220.
[17] T.S. Li, B. Zhao, C. Wang, H.Y. Wang, Z.W. Liu, W. Li, H.F. Jin, C.S. Tang, J.B. Du, Regulatory effects of hydrogen sulfide on IL-6, IL-8 and IL-10 levels in the plasma and pulmonary tissue of rats with acute lung injury, Exp. Biol. Med. 233 (2008) 1081–1087.
[18] Y. Zhao, H. Wang, M. Xian, Cysteine-activated hydrogen sulfide (H_2S) donors, J. Am. Chem. Soc. 133 (2011) 15–17.
[19] L. Li, M. Whiteman, Y.Y. Guan, K.L. Neo, Y. Cheng, S.W. Lee, Y. Zhao, R. Baskar, C.H. Tan, P.K. Moore, Characterization of a novel, water-soluble hydrogen sulfide-releasing molecule (GYY4137): new insights into the biology of hydrogen sulfide,

Circulation 117 (2008) 2351–2360.
[20] M. Busquet, S. Calsamiglia, A. Ferret, M.D. Carro, C. Kamel, Effect of garlic oil and four of its compounds on rumen microbial fermentation, J. Dairy Sci. 88 (2005) 4393–4404.
[21] K.C. Lai, S.C. Hsu, C.L. Kuo, J.S. Yang, C.Y. Ma, H.F. Lu, N.Y. Tang, T.C. Hsia, H.C. Ho, J.G. Chung, Diallyl sulfide, diallyl disulfide, and diallyl trisulfide inhibit migration and invasion in human colon cancer colo 205 cells through the inhibition of matrix metalloproteinase-2, -7, and -9 expressions, Environ. Toxicol. 28 (2013) 479–488.
[22] U. Hasegawa, A.J. van der Vlies, Design and synthesis of polymeric hydrogen sulfide donors, Bioconjugate Chem. 25 (2014) 1290–1300.
[23] J.L. Wallace, G. Caliendo, V. Santagada, G. Cirino, Markedly reduced toxicity of a hydrogen sulphide-releasing derivative of naproxen (ATB-346), Br. J. Pharmacol. 159 (2010) 1236–1246.
[24] N. Cenac, M. Castro, C. Desormeaux, P. Colin, M. Sie, M. Ranger, N. Vergnolle, A novel orally administered trimebutine compound (GIC-1001) is anti-nociceptive and features peripheral opioid agonistic activity and hydrogen sulphide-releasing capacity in mice, Eur. J. Pain 20 (2016) 723–730.
[25] B.V. Nagpure, J.S. Bian, Brain, learning, and memory: role of H_2S in neurodegenerative diseases, Handb. Exp. Pharmacol. 230 (2015) 193–215.
[26] C.M. Levinn, M.M. Cerda, M.D. Pluth, Activatable small molecule H_2S donors, Antioxidants Redox Signal. 32 (2020) 96–109.
[27] M. Lee, A. Sparatore, P. Del Soldato, E. McGeer, P.L. McGeer, Hydrogen sulfide-releasing NSAIDs attenuate neuroinflammation induced by microglial and astrocytic activation, Glia 58 (2010) 103–113.
[28] M. Lee, V. Tazzari, D. Giustarini, R. Rossi, A. Sparatore, P. Del Soldato, E. McGeer, P.L. McGeer, Effects of hydrogen sulfide-releasing L-DOPA derivatives on glial activation: potential for treating Parkinson disease, J. Biol. Chem. 285 (2010) 17318–17328.
[29] S.C. Kang, E.H. Sohn, S.R. Lee, Hydrogen sulfide as a potential alternative for the treatment of myocardial fibrosis, Oxid. Med. Cell. Longev. 2020 (2020) 4105382.
[30] W. Guo, Z. Cheng, Y. Zhu, Hydrogen sulfide and translational medicine, Acta Pharm. Sin. 34 (2013) 1284–1291.
[31] N. Yang, Y. Liu, T. Li, Q. Tuo, Role of hydrogen sulfide in chronic diseases, DNA Cell Biol. 39 (2020) 187–196.
[32] 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 (2007) 29–40.
[33] C. Szabo, C. Coletta, C. Chao, K. Módis, B. Szczesny, A. Papapetropoulos, M.R. Hellmich, Tumor-derived hydrogen sulfide, produced by cystathionine-β-synthase, stimulates bioenergetics, cell proliferation, and angiogenesis in colon cancer, Proc. Natl. Acad. Sci. U.S.A. 110 (2013) 12474–12479.
[34] D. Wu, W. Si, M. Wang, S. Lv, A. Ji, Y. Li, Hydrogen sulfide in cancer: friend or foe? Nitric Oxide 50 (2015) 38–45.
[35] K. Kashfi, Anti-cancer activity of new designer hydrogen sulfide-donating hybrids, Antioxidants Redox Signal. 20 (2014) 831–846.
[36] A. Reis, A. Stern, H.P. Monteiro, *S*-nitrosothiols and H_2S donors: potential chemotherapeutic agents in cancer, Redox Biol. 27 (2019) 101190.
[37] M. Akbari, E. Sogutdelen, S. Juriasingani, A. Sener, Hydrogen sulfide: emerging role in bladder, kidney, and prostate malignancies, Oxid. Med. Cell. Longev. 2019 (2019) 2360945.
[38] M.R. Hellmich, C. Szabo, Hydrogen sulfide and cancer, Handb. Exp. Pharmacol. 230 (2015) 233–241.
[39] D. Wu, M. Li, W. Tian, S. Wang, L. Cui, H. Li, H. Wang, A. Ji, Y. Li, Hydrogen sulfide acts as a double-edged sword in human hepatocellular carcinoma cells through EGFR/ERK/MMP-2 and PTEN/AKT signaling pathways, Sci. Rep. 7 (2017) 5134.
[40] S.S. Wang, Y.H. Chen, N. Chen, L.J. Wang, D.X. Chen, H.L. Weng, S. Dooley, H.G. Ding, Hydrogen sulfide promotes autophagy of hepatocellular carcinoma cells through the PI3K/Akt/mTOR signaling pathway, Cell Death Dis. 8 (2017) e2688.
[41] V. Citi, E. Piragine, E. Pagnotta, L. Ugolini, L. Di Cesare Mannelli, L. Testai, C. Ghelardini, L. Lazzeri, V. Calderone, A. Martelli, Anticancer properties of erucin, an H_2S-releasing isothiocyanate, on human pancreatic adenocarcinoma cells (AsPC-1), Phytother Res. 33 (2019) 845–855.
[42] Q.H. Gong, Q. Wang, L.L. Pan, X.H. Liu, H. Xin, Y.Z. Zhu, S-propargyl-cysteine, a novel hydrogen sulfide-modulated agent, attenuates lipopolysaccharide-induced spatial learning and memory impairment: involvement of TNF signaling and NF-κB pathway in rats, Brain Behav. Immun. 25 (2011) 110–119.
[43] Z.W. Lee, L.W. Deng, Role of H_2S donors in cancer biology, Handb. Exp. Pharmacol. 230 (2015) 243–265.
[44] P. Boyle, The globalisation of cancer, Lancet 368 (2006) 629–630.
[45] P. Kumar, R. Aggarwal, An overview of triple-negative breast cancer, Arch. Gynecol. Obstet. 293 (2016) 247–269.
[46] C. Denkert, C. Liedtke, A. Tutt, G.V. Minckwitz, Molecular alterations in triple-negative breast cancer–the road to new treatment strategies, Lancet 389 (2017) 2430–2442.
[47] H. Yao, G.C. He, S.C. Yan, C. Chen, L.J. Song, T.J. Rosol, X.Y. Deng, Triple-negative breast cancer: is there a treatment on the horizon? Oncotarget 8 (2017) 1913–1924.
[48] W.D. Foulkes, I.E. Smith, J.S. Reis-Filho, Triple-negative breast cancer, N. Engl. J. Med. 363 (2010) 1938–1948.
[49] O. Fadare, F.A. Tavassoli, Clinical and pathologic aspects of basal-like breast cancers, Nat. Clin. Pract. Oncol. 5 (2008) 149–159.
[50] P. Schmid, S. Adams, H.S. Rugo, A. Schneeweiss, C.H. Barrios, H. Iwata, V. Dieras, R. Hegg, S.A. Im, G. Shaw Wright, V. Henschel, L. Molinero, S.Y. Chui, R. Funke, A. Husain, E.P. Winer, S. Loi, L.A. Emens, I.M.T. Investigators, Atezolizumab and nab-paclitaxel in advanced triple-negative breast cancer, N. Engl. J. Med. 379 (2018) 2108–2121.
[51] N.U. Lin, E. Claus, J. Sohl, A.R. Razzak, A. Arnaout, E.P. Winer, Sites of distant recurrence and clinical outcomes in patients with metastatic triple-negative breast cancer: high incidence of central nervous system metastases, Cancer 113 (2008) 2638–2645.
[52] H. Sihto, J. Lundin, M. Lundin, T. Lehtimaki, A. Ristimaki, K. Holli, L. Sailas, V. Kataja, T. Turpeenniemi-Hujanen, J. Isola, P. Heikkilä, H. Joensuu, Breast cancer biological subtypes and protein expression predict for the preferential distant metastasis sites: a nationwide cohort study, Breast Cancer Res. 13 (2011) R87.
[53] M.W. Audeh, Novel treatment strategies in triple-negative breast cancer: specific role of poly(adenosine diphosphate-ribose) polymerase inhibition, Pharmgeno. Pers. Med. 7 (2014) 307–316.
[54] D.W. Miles, V. Dieras, J. Cortes, A.A. Duenne, J. Yi, J. O'Shaughnessy, First-line bevacizumab in combination with chemotherapy for HER2-negative metastatic breast cancer: pooled and subgroup analyses of data from 2447 patients, Ann. Oncol. 24 (2013) 2773–2780.
[55] J.M. Nabholtz, N. Chalabi, N. Radosevic-Robin, M.M. Dauplat, M.A. Mouret-Reynier, I. Van Praagh, V. Servent, J.P. Jacquin, K.E. Benmammar, S. Kullab, M.R.K. Bahadoor, F. Kwiatkowski, A. Cayre, C. Abrial, X. Durando, Y.J. Bignon, P. Chollet, F. Penault-Llorca, Multicentric neoadjuvant pilot Phase II study of cetuximab combined with docetaxel in operable triple negative breast cancer, Int. J. Canc. 138 (2016) 2274–2280.
[56] B.S. Yadav, S.C. Sharma, P. Chanana, S. Jhamb, Systemic treatment strategies for triple-negative breast cancer, World J. Clin. Oncol. 5 (2014) 125–133.
[57] M.A. Sovak, R.E. Bellas, D.W. Kim, G.J. Zanieski, A.E. Rogers, A.M. Traish, G.E. Sonenshein, Aberrant nuclear factor-kappaB/Rel expression and the pathogenesis of breast cancer, J. Clin. Invest. 100 (1997) 2952–2960.
[58] D.K. Biswas, A.P. Cruz, E. Gansberger, A.B. Pardee, Epidermal growth factor-induced nuclear factor κB activation: a major pathway of cell-cycle progression in estrogen-receptor negative breast cancer cells, Proc. Natl. Acad. Sci. U.S.A. 97 (2000) 8542–8547.
[59] H. Nakshatri, P. Bhat-Nakshatri, D.A. Martin, R.J. Goulet Jr., G.W. Sledge Jr., Constitutive activation of NF-κB during progression of breast cancer to hormone-independent growth, Mol. Cell Biol. 17 (1997) 3629–3639.
[60] B. Su, J. Su, H. He, Y. Wu, H. Xia, X. Zeng, W. Dai, X. Ai, H. Ling, H. Jiang, Q. Su, Identification of potential targets for diallyl disulfide in human gastric cancer MGC-803 cells using proteomics approaches, Oncol. Rep. 33 (2015) 2484–2494.
[61] Y. Sun, X. Wang, Q. Zhou, Y. Lu, H. Zhang, Q. Chen, M. Zhao, S. Su, Inhibitory effect of emodin on migration, invasion and metastasis of human breast cancer MDA-MB-231 cells in vitro and in vivo, Oncol. Rep. 33 (2015) 338–346.
[62] M. Chattopadhyay, R. Kodela, N. Nath, A. Barsegian, D. Boring, K. Kashfi, Hydrogen sulfide-releasing aspirin suppresses NF-κB signaling in estrogen receptor negative breast cancer cells in vitro and in vivo, Biochem. Pharmacol. 83 (2012) 723–732.
[63] Y.P. Liu, P.T. Zhu, Y.Y. Wang, Z.H. Wei, T. Li, Z.J. Zhu, X.B. Sheng, S.L. Wang, J.S. Ruan, Z.G. Liu, Y.Z. Cao, Y.L. Shan, L.H. Sun, A.Y. Wang, W.X. Chen, Y. Lu, Antimetastatic therapies of the polysulfide diallyl trisulfide against triple-negative breast cancer (TNBC) via suppressing MMP2/9 by blocking NF-κB and ERK/MAPK signaling pathways, PloS One 10 (2015) e0123781.
[64] S.H. Kim, C.H. Kaschula, N. Priedigkeit, A.V. Lee, S.V. Singh, Forkhead Box Q1 is a novel target of breast cancer stem cell inhibition by diallyl trisulfide, J. Biol. Chem. 291 (2016) 13495–13508.
[65] J. Huang, B. Yang, T. Xiang, W. Peng, Z. Qiu, J. Wan, L. Zhang, H. Li, H. Li, G. Ren, Diallyl disulfide inhibits growth and metastatic potential of human triple-negative breast cancer cells through inactivation of the β-catenin signaling pathway, Mol. Nutr. Food Res. 59 (2015) 1063–1075.
[66] T. Xiong, X.W. Liu, X.L. Huang, X.F. Xu, W.Q. Xie, S.J. Zhang, J. Tu, Tristetraprolin, A novel target of diallyl disulfide that inhibits the progression of breast cancer, Oncol. Lett. 15 (2018) 7817–7827.
[67] U. Hasegawa, N. Tateishi, H. Uyama, A.J. van der Vlies, Hydrolysis-sensitive dithiolethione prodrug micelles, Macromol. Biosci. 15 (2015) 1512–1522.
[68] Q. Dong, B. Yang, J.G. Han, M.M. Zhang, W. Liu, X. Zhang, H.L. Yu, Z.G. Liu, S.H. Zhang, T. Li, D.D. Wu, X.Y. Ji, S.F. Duan, A novel hydrogen sulfide-releasing donor, HA-ADT, suppresses the growth of human breast cancer cells through inhibiting the PI3K/AKT/mTOR and Ras/Raf/MEK/ERK signaling pathways, Canc. Lett. 455 (2019) 60–72.
[69] G. De Preter, C. Deriemaeker, P. Danhier, L. Brisson, T.T. Cao Pham, V. Gregoire, B.F. Jordan, P. Sonveaux, B. Gallez, A fast hydrogen sulfide-releasing donor increases the tumor response to radiotherapy, Mol. Canc. Therapeut. 15 (2016) 154–161.
[70] R.A. Youness, R.A. Assal, A. Abdel Motaal, M.Z. Gad, A novel role of sONE/NOS3/NO signaling cascade in mediating hydrogen sulphide bilateral effects on triple negative breast cancer progression, Nitric Oxide 80 (2018) 12–23.
[71] N. Sen, Functional and molecular insights of hydrogen sulfide signaling and protein sulfhydration, J. Mol. Biol. 429 (2017) 543–561.
[72] W. Chen, M. Chen, Q. Zang, L. Wang, F. Tang, Y. Han, C. Yang, L. Deng, Y.N. Liu, NIR light controlled release of caged hydrogen sulfide based on upconversion nanoparticles, Chem. Commun. 51 (2015) 9193–9196.
[73] J. Kang, Z. Li, C.L. Organ, C.M. Park, C.T. Yang, A. Pacheco, D. Wang, D.J. Lefer, M. Xian, pH-controlled hydrogen sulfide release for myocardial ischemia-reperfusion injury, J. Am. Chem. Soc. 138 (2016) 6336–6339.
[74] C.R. Powell, K.M. Dillon, J.B. Matson, A review of hydrogen sulfide (H_2S) donors: chemistry and potential therapeutic applications, Biochem. Pharmacol. 149 (2018) 110–123.
[75] Y. Zhao, H.A. Henthorn, M.D. Pluth, Kinetic insights into hydrogen sulfide delivery from caged-carbonyl sulfide isomeric donor platforms, J. Am. Chem. Soc. 139 (2017) 16365–16376.
[76] K. Kaur, R.J. Carrazzone, J.B. Matson, The benefits of macromolecular/supramolecular approaches in hydrogen sulfide delivery: a review of polymeric and self-assembled hydrogen sulfide donors, Antioxidants Redox Signal. 32 (2020) 79–95.
[77] Y. Liu, F. Yang, C. Yuan, M. Li, T. Wang, B. Chen, J. Jin, P. Zhao, J. Tong, S. Luo, N. Gu, Magnetic nanoliposomes as in situ microbubble bombers for multimodality image-guided cancer theranostics, ACS Nano 11 (2017) 1509–1519.