Review article

S-nitrosothiolis and H₂S donors: Potential chemo-therapeutic agents in cancer

Adriana Karla Cardoso Amorim Reisa, Arnold Sternb,*, Hugo Pequeno Monteiroc,***

a Department of Chemistry, Institute of Environmental, Chemical and Pharmaceutical Sciences - Universidade Federal de São Paulo – Campus Diadema, São Paulo, Brazil
b New York University, School of Medicine, New York, NY, USA
c Department of Biochemistry, Center for Cellular and Molecular Therapy - Universidade Federal de São Paulo – Campus São Paulo, São Paulo, Brazil

A B S T R A C T

Nitric Oxide (NO) and Hydrogen Sulfide (H₂S) are components of an “interactome”, which is defined as a redox system involving the interactions of RSS, RNS and ROS. Chemical interaction by these species is common and is characterized by one and two electron oxidation, nitrosylation, nitration and sulfuration/polysulfidation reactions. NO and H₂S are gases that penetrate cell membranes, are synthesized by specific enzymes, are ubiquitous, regulate protein activities through post-translational modifications and participate in cell signaling. The two molecules at high concentrations compared to physiological concentrations may result in cellular damage particularly through their interaction with other reactive species. NO and H₂S can interact with each other and form a variety of molecular species which may have constructive or destructive behavior depending on the cell type, the cellular environment (ex. oxygen tension, pH, redox state), where the products are produced and in what concentrations. Cross talk exists between NO and H₂S, whereby they can influence the generation and signaling behavior of each other. Given the above mentioned properties of NO and H₂S and studies in cancer cells and animal models employing NO and H₂S donors that generate higher than physiological concentrations of NO and H₂S and are effective in killing cancer cells but not normal cells, lend credence to the possibility of the utility of these donors in an approach to the treatment of cancer.

1. Introduction

Nitric oxide (NO) is a gaseous, cell membrane permeable, free radical endowed with a wide range of biological activities. Within normal and tumor cells, NO is generated by the catalyzed oxidation of the amino acid L-arginine by two constitutive and one inducible isoform of the NO synthases (NOS). Most of NO-mediated functions occur through a c-GMP-dependent pathway which is important for vasodilation, neurotransmission, and smooth muscle cell relaxation. Cyclic-GMP-independent pathways involve the reactions of NO with O₂⁻, O₂⁻*, the transition metal zinc and thiols. Although less frequent, these reactions bear important consequences for cellular signaling [1].

The combination of NO with O₂⁻ or with thiols results in nitration and s-nitrosylation of proteins, respectively. S-nitrosylation, but not tyrosine nitration, of cysteine thiols is clearly associated with cell signaling [2–5]. Many intracellular proteins that function in the canonical signaling pathways, such as Ras, Src kinase, EGFR, the ERK1/2 MAP kinases, PI3K, and Akt, have their activities regulated by S-nitrosylation [1,6,7]. NO-mediated S-nitrosylation of canonical signaling pathways either stimulates or inhibits normal or tumor cell proliferation [1,6].

In the last three decades, a growing interest in the carcinogenic and anti-carcinogenic properties of NO has become evident. This dual character is directly related to the NO concentration. At concentrations equal to 200 nM or above, NO acts as an anti-carcinogenic agent; whereas below this threshold, survival and pro-carcinogenic signaling pathways are stimulated [8]. Physiological concentrations of NO such as those generated intracellularly by NOS are carcinogenic [9]. They may facilitate cancer cell proliferation by inhibiting apoptosis, stimulating angiogenesis, and promoting genomic instability [10–13].

Various classes of NO donors have been investigated regarding their anti-carcinogenic actions. These compounds can release NO within a wide range of concentrations and time release [14]. NO is freely diffusible and readily oxidized in the intracellular milieu, an aspect that limits its signaling capacity. A particular class of NO donors, the S-nitrosothiols (SNOs), can overcome this limitation by protecting the NO moiety from oxidation and extending its time of action [1]. The role of S-nitrosylation of signaling proteins and non-physiological concentrations of NO generated by NO donors in anti-carcinogenesis is worth exploring for therapeutic purposes [1,6].

The concept of a Redox Code based on oxidative modifications of specific cysteine residues on proteins (cysteine redox switches) allows for the characterization of other redox-based posttranslational modifications [15]. In addition to S-nitrosylation, sulphydrylation/persulfidation also target regulatory cysteine redox switches in proteins. These
modifications are mediated by hydrogen sulfide (H$_2$S) and its one-electron oxidation products, the reactive sulfur species (RSS).

H$_2$S is a colorless and smelling gas synthesized in normal and cancer cells by two pyridoxal-5-phosphate-dependent cysteine enzymes, cystathionine $\beta$-synthase (CBS) and cystathionine $\gamma$-S-lyase (CSE) [16]. A third enzyme, 3-Mercaptopropionate sulfur-transferase (3-MST), a pyridoxal-5-phosphate -independent enzyme, acts in combination with another enzyme, cysteine aminotransferase to produce H$_2$S from L-cysteine and $\alpha$-ketoglutarate. Both enzymes are localized in the cytosol and mitochondria [17]. The three enzymes are constitutively expressed in normal and cancer cells, but only CSE expression is induced by inflammatory mediators [18].

H$_2$S generated by H$_2$S-generating enzymes may play an important role in cancer development [19]. Elevated CSE expression is found in lung adenocarcinomas, various hematopoietic cell lines, melanomas, glioblastomas, astrocytomas, and renal carcinoma [20]. CBS levels are suppressed in gastric and colorectal cancer by specific methylation of the enzyme promoter [21]. Suppression of CSE expression is associated with the development and progression of human gliomas [22]. In contrast to CBS and CSE, 3-MST levels are unchanged in human colon cancer cells when compared to the levels measured in normal colon epithelial cells [23]. The expression of the three H$_2$S synthesizing enzymes described for different cancer cell types suggests that the expression of one of them suffices as an endogenous source of H$_2$S.

Like NO, H$_2$S is a gaseous transmitter that also has dual behavior regarding proliferation and cell death. This duality may be explained by the concentrations of H$_2$S and RSS to which normal and cancer cells are exposed. At low concentrations (micromolar range), H$_2$S is cytotoxic and stimulates cell proliferation. At high concentrations (millimolar levels), H$_2$S is cytotoxic, promoting apoptosis and cell death [24–26].

H$_2$S donors have been tested as potential therapeutic agents against hypertension; they provide protection against tissue damage promoted by ischemia-reperfusion and certain types of cancer [24,27]. The use of H$_2$S donors in combination with SNO compounds is effective in inducing vasorelaxation [28]. This synergism may be operative in other clinical settings, such as cancer chemotherapy.

This review article discusses the role of SNOs and H$_2$S donors as anti-carcinogenic agents either as cytotoxic agents themselves or acting in combination through potential synergistic actions in cancer chemotherapy.

2. S-nitrosothiols (SNOs) as anti-carcinogenic agents

A wide range of structurally diverse compounds known as NO donors, release NO and/or reactive nitrogen species at different rates and have been tested in cancer treatment [14].

Cancer cells treated with NO donors undergo apoptotic cell death, whereas normal cells are less affected [14]. This may occur by a number of mechanisms that include invasion suppression, HIF-1a interference and radio-sensitization [29], sensitization to tumor necrosis factor related apoptosis inducing ligand - TRAIL [30], decreasing membrane potential and ATP levels, generating ROS and lowering the mitochondrial permeability transition [31]. Certain NO donors can affect DNA methylation, histone de-acetylation and lysine de-methylation leading to p53 re-activation [32,33].

Among these various types of NO donors, the SNOs are of particular interest. SNOs are derived from the covalent attachment of NO to a sulfur moiety of an organic thiol [1]. They can promote protein and peptide S-nitrosylation through the transfer of a nitroso group from one SNO to a target cysteine thiol, referred to as transnitrosylation [34].

SNOs expand NO signaling capacities by limiting its diffusibility while extending its temporal and spatial actions. For instance, S-nitrosothiosthenone (GSNO) at physiological concentrations regulates the activation of Ras and its compartmentalization during the stimulation of cell proliferation [1,35].

Another important aspect of the SNOs chemical biology is their capacity to release NO. SNO ester derivatives of non-steroidal anti-inflammatory drugs, as demonstrated by infrared spectroscopic analysis and theoretical calculations, effectively release NO [36]. Analysis of the conformational and structural aspects of SNOs may provide important information on an NO/SNO-mediated anti-carcinogenic activity of these compounds [36].

The two SNOs that have had their anti-carcinogenic properties extensively explored are: GSNO, which is a physiologically relevant SNO [1], and S-nitroso-N-acetylpenicillamine (SNAP), which is an effective nitrosylating compound [37]. The anti-carcinogenic effects of GSNO have been determined in several experimental settings. Direct effects of supra-physiological concentrations of GSNO inhibit tumor cell proliferation and tumor growth [38–40]. GSNO treatment of MCF-7 breast cancer cells resistant to doxorubicin, reversed drug resistance in these cells [41]. GSNO potentiates the anti-carcinogenic effects of cisplatin and radiation in head and neck squamous cell carcinoma [42].

SNAP also has a dual behavior regarding proliferative as opposed to anti-proliferative effects. Exposure of endothelial cells to concentrations of SNAP that release physiological levels of NO stimulates the Ras-ERK1/2 MAP kinases signaling pathway and cell cycle progression [4,43]. SNAP at concentrations that generate physiological levels of NO maintain vascular tone [44]. A slow and sustained release of NO from SNAP, induces apoptosis in CHP212 neuroblastoma cells [45]. SNAP increases p53 protein levels and induces apoptosis in ovarian cancer cells resistant or not to cisplatin [46]. Radio sensitization promoted by SNAP is observed in a number of cancer cell lines, such as glioma, cervical cancer HeLa cells, and murine mammary adenocarcinoma EMT-6 cells [47].

SNAP is a relatively stable and fairly water soluble SNO-derivative of penicillamine [48]. This led us to synthesize and characterize a series of S-nitroso-aryl-butanamides, novel SNO derivatives of penicillamine [49]. S-nitroso-aryl-butanamides are produced by reacting 2-acetamide-3-methyl-3-mercaptop-N-aryl-butanamides in acetone and tert-butyl-nitrite [49]. Calculations of the S–N bond length for SNAP and for the S-nitroso-aryl-butanamides yield a value of 1.7 A which gives relative stability, and NO releasing capacity to the compounds [36] (Fig. 1). In vitro studies have revealed that the ortho- and meta chloro derivatives of the S-nitroso-aryl-butanamides are strongly cytotoxic against MCF-7 estrogen receptor positive human breast cancer cells. Human fibroblasts from normal breast tissue are less affected by these compounds [50]. This differential cytotoxicity might be related to the different capacities of normal and tumor cells to handle nitrosative stress conditions.

SNO donors act as anti-carcinogenics by promoting cell death through S-nitrosylation of specific protein targets [51]. S-nitrosylation of Glyceraldehyde-3-phosphate-dehydrogenase at Cys 145 located at the active site of the enzyme, promotes cell death [52]. Apoptosis is induced in human acute monocytic leukemia - THP1- cells through the activation of the Ras-ERK1/2 MAP kinases by supra-physiological concentrations of GSNO [38]. Treatment of HEK293 cells with supra-physiological concentrations of GSNO, results in s-nitrosylation of the X-linked inhibitor of apoptosis, and inhibition of its anticaspase-3 and anti-apoptotic functions [53]. S-nitrosylation of specific cysteine residues of the cell death receptors TNF-R1, CD95, TRAIL-R1, and Fas stimulates apoptotic cell death of HepG2, an hepatoblastoma cancer cell line, and SW480 colon cancer cells [54,55].

Extracellular GSH and Cys are potential targets to nitroso groups transferred from a SNO compound through transnitrosylation, generating GSNO and CysNO [1]. GSNO and CysNO may function as signal transducers in SNO-mediated signaling events [56]. Extracellular GSNO does not cross the plasma membrane but can transfer its nitroso group to Cys. CysNO utilizes the L-type amino acid transporter on the plasma membrane for cell uptake [57]. Inside the cell, CysNO transfers its nitroso group to cytoplasmic GSH generating increasing concentrations of GSNO; potentially creating nitrosative stress conditions [56].
GSNO reductase and Thioredoxin-1 (Trx-1) have been characterized as denitrosylases in normal and tumor cells [58]. Trx-1 denitrosylase activity is associated with the decomposition of GSNO yielding NO and \( O_2^- \), leading to the generation of the highly toxic oxidant peroxynitrite (ONOO-) [59,60]. Increasing expression levels of Trx-1 have been directly correlated with tumor progression [60].

Exposure of tumor cells to increasing concentrations of SNO donors might generate high intracellular levels of GSNO through transnitrosylation [56]. High GSNO levels associated with high expression levels of Trx-1 in tumor cells exposed to SNO donors sets up the condition for the establishment of nitrosative/nitrative stress. The high expression levels of Trx-1 in tumor cells may represent an important molecular target to be explored in chemotherapeutic regimens based on SNO donors.

3. H₂S donors as anti-carcinogenic agents

H₂S, like NO, has dual behavior regarding proliferation and cell death [25,61–63]. This duality may be explained by the concentration of the products of H₂S reactivity and the fact that cancer cells have physical and biochemical characteristics that differ from normal cells. Low concentrations of H₂S cause cancer cell proliferation, while high concentrations are cytotoxic [27]. Although many H₂S donors have been synthesized and have a variety of effects [27], few have been studied for their anti-carcinogenic effect, as compared to NO donors.

Three major events have been consistently associated with H₂S-mediated anti-carcinogenic effects: induction of uncontrolled intracellular acidification, induction of cell cycle arrest, and promotion of apoptosis [26].

The increased glucose uptake by cancer cells with the accumulation of lactate is known as the Warburg effect, and is directly associated with tumor growth and metastasis. Acidification derived from the excretion of lactate into the surrounding environment promotes angiogenesis, chemoresistance, and the suppression of the host immune system [64]. Uncontrolled intracellular acidification is stimulated by prolonged exposure of MCF-7 and HepG2 cells, breast and hepatic cancer cell lines respectively, to GYY4137, a slow-releasing H₂S donor [65]. A decrease in glycolysis and an increase in lactate production leading to cell death have been observed in a number of cancer cells treated with GYY4137 [66,67], which decreases tumor growth in a xenograph mouse model [66].

Cell cycle inhibition has been consistently observed in, hepatic [66], breast [67], gastric [68] and colon [69] cancer cells exposed to high concentrations of various H₂S donors. Various molecular targets have been described.

Apoptosis induced by an H₂S donor [70] and an H₂S releasing naproxen hybrid donor [71] in melanoma and other tumor cell lines is associated with suppression of NF-κB activity and inhibition of Akt and extracellular signal-regulated kinase pathways [70,71] and the naproxen hybrid decreases tumor development in a mouse melanoma model [71]. H₂S donors potentiate green tea polyphenol induced apoptosis in multiple myeloma cells [72]. The precise intermediate by which the H₂S donors influence cancer cell death is not fully appreciated.

The organosulfur compound diallyldisulfide (DADS); a natural H₂S donor which is present in the oil-soluble fraction of garlic extracts [73], has anti-carcinogenic activities. Like other H₂S donors, DADS anti-carcinogenic activities involve the induction of exacerbated intracellular acidification, cell cycle arrest and apoptosis. DADS-induced apoptosis is mediated by increasing ROS production in cells [74]. Ajoene, another organosulfur compound obtained from garlic extracts induces apoptosis mediated by ROS [75]. However, this is not a general anti-carcinogenic mechanism that can be attributed to other classes of H₂S donors [27].

4. Interactions between nitric oxide, reactive oxygen species and reactive sulfur species and redox homeostasis

Interactions between NO, ROS, and RSS and their use by the machinery of normal and cancer cells, is necessary for maintenance of a homeostatic condition characterized by the formation, utilization, and elimination of the reactive species and their by-products [76]. This
redox homeostasis is maintained by highly efficient detoxification systems, exemplified by the antioxidant enzymes superoxide dismutase (SOD), catalase (CAT), and GSH peroxidase, and by the redox systems, GSH, GSNO reductase, and Trx/Trxr reductase [76]. In tumor cells, intracellular sources of ROS include the mitochondrial respiratory chain and the enzymes collectively known as the NADPH oxidases (NOXs) [77].

ROS and RSS might have their intracellular levels regulated by the same set of antioxidant enzymes. This is supported by the findings that SOD catalyzes the oxidation of H2S mostly to H2S2, and that CAT eliminates the H2S2 and other polysulfides [78,79].

ROS and RSS may interact with each other in opposite ways, depending on the nature of the donor; RSS can either promote or inhibit ROS generation in cancer cells [61,74,75]. The RSS donor, DADS, induces apoptosis in human leukemia cell lines through activation of NADPH oxidase (NOX) and stimulation of ROS production [80]. The polysulfide Na2S4 inhibits cisplatin-induced NOX activity in non-small-cell-lung cancer cell lines [61].

The interactions between NO and ROS can be exemplified by the very efficient reaction between NO and O2 that generates the highly toxic and potent oxidant ONOO- [81]. Although the reaction is very efficient, production of NO and O2 generates NOON to have occurred at the same place, at the same time, and at the same rate [82]. Normal and cancer cells can avoid the generation of ONOO- by using specific means to prevent the process. SOD lowers the level of O2 through dismutation and generation of H2O2 which is metabolized by CAT. Minimizing NO levels is another way to avoid the reaction. Cancer cells express alternative splicing isoforms of the inducible isoform of NOS [83]. Alternative splicing isoforms form heterodimers with the full-length isoform, lowering the intracellular NO level [84]. Another strategy used by cancer cells to minimize NO levels is the overexpression of arginase [85].

NO interacts with H2S to form intermediates that may include nitrosothiols, nitrosopersulfides, nitrosyl, and nitrous oxide [86]. Effective means of control of this production of a plethora of reactive species arising from interactions between NO, ROS, and RSS are likely to be operative in cancer cells. The putative ways for maintaining intracellular redox homeostasis are summarized in Fig. 2.

5. Nitric oxide, S-Nitrosothiols and H2S donors: potential synergistic actions against cancer

The fact that NO and H2S can interact to form a variety of intermediate species [86] affecting each other’s biochemical behavior, suggests that the combined administration of donors with each of the gaseous transmitters or the sole administration of a single compound with capacity to generate H2S and NO might cause cancer cell apoptosis.

Isomers of NO, H2S-hybrids with acetylsalicylic acid that are capable of releasing NO and H2S, although the causative intermediate(s) have not been characterized nor the extent of release of NO and H2S, cause apoptosis in a number of cancer cell lines [87–89]. One of the compounds, NBS 1120, administered to athymic nude mice bearing a human colon cancer xenograph has significantly reduced the size of the tumor and has functioned as a chemo-preventive agent [90]. When an H2S and an NO-donor have been administered simultaneously as individual agents in treating human colon cancer cells no additive or synergistic behavior in anti-proliferative effects is observed [24].

Conflicts of interest

The authors declare no conflict of interest.

Acknowledgements

The authors wish to acknowledge the various students, post-docs,
Fig. 2. Biosynthesis of nitric oxide and hydrogen sulfide, generation of reactive oxygen species, and redox homeostasis. A. NO is produced by three nitric oxide synthase (NOS) isoforms: two constitutive isoforms, NOS-1 and NOS-3, and one inducible, NOS-2 catalyzes the oxidation of l-arginine to l-citrulline. NOS-2 is widely expressed in tumor cells and NOS-2 alternative splicing isoforms potentially regulate negatively intracellular NO levels in these cells. Negative regulation of NO production is also achieved through the upregulation of arginase. B. Reactive oxygen species (ROS) are produced through activation of the NADPH oxidase (NOX) enzymes or through leakage of the mitochondrial electron transport chain which releases O$_2^\cdot$. O$_2^\cdot$ is dismutated to H$_2$O$_2$ by Superoxide Dismutases (SOD) and H$_2$O$_2$ is reduced to H$_2$O by Catalase, maintaining intracellular optimal levels of the reactive species. C. H$_2$S is generated from oxidation of l-cysteine and other substrates, including 3-mercaptopyruvate. Two cytoplasmic enzymes cystathionine β-synthase (CBS) and cystathionine γ-lyase (CSE) and two mitochondrial enzymes 3-mercaptopyruvate sulfur-transferase (3-MST) and Cysteine aminotransferase (Cys-AT) are responsible for intracellular generation of H$_2$S. H$_2$S can be converted into polysulfide and other reactive sulfur species (RSS). SOD and Catalase may help in the maintenance of optimal intracellular levels of RSS.
Fig. 3. Proposed mechanism for nitrosative stress in tumor cells exposed to a combination of SNO donors and H₂S. The SNO donor SNO-Aryl-butanamide nitrosylates Cys generating CysNO. CysNO directly enters the cell through an amino-acid transporter (LAT). SNO-Aryl-butanamide reacts with H₂S generating HSNO which freely diffuses into the cell. CysNO and HSNO nitrosylate GSH and protein thiols promoting nitrosative stress and tumor cell apoptosis.

and collaborators whose published reports contributed importantly to this review article. The support from the Brazilian Funding Institutions, FAPESP (Grant Numbers: 2010/51784-3; 2012/10470-1; 2016/06539-7), CNpq (Grant Number: 481154/2013-2), and CAPES, is greatly acknowledged.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.redox.2019.101190.

References

[1] D.T. Hess, A. Matsumoto, S. Kim, H.E. Marshall, J.S. Stamler, Protein S-nitrosylation: purview and parameters, Nat. Rev. Mol. Cell Biol. 6 (2005) 150–166, https://doi.org/10.1038/nrm1569.
[2] H.P. Monteiro, Signal transduction by protein tyrosine nitration: competition or cooperation with tyrosine phosphorylation-dependent signaling events? Free Rad. Biol. Med. 33 (2002) 765–773.
[3] H.P. Monteiro, R.J. Arai, L.R. Travassos, Protein tyrosine phosphorylation and protein tyrosine nitration in redox signaling, The redox code, Antioxidants Redox Signal. 6 (2005) 150–166, https://doi.org/10.1089/ars.2005.007.
[4] C.H. Switzer, S.A. Glynn, R.Y. Cheng, J.E. Green, L.A. Ridnour, J.E. Green, S. Ambs, D.A. Wink, S-nitrosylation of EGFR and Src activates an oncogenic signaling network in human basal-like breast cancer, Mol. Canc. Res. 12 (2004) 1203–1216, https://doi.org/10.1158/1541-7786.MCR-12-0124.
[5] Z. Huang, J. Fu, Y. Zhang, Nitric oxide donor-based cancer Therapy: advances and prospects, J. Med. Chem. (2017) 7617–7635, https://doi.org/10.1021/acs.jmedchem.6b01672.
[6] D.P. Jones, H. Sies, The redox code, Antioxidants Redox Signal. 23 (2015) 734–746, https://doi.org/10.1089/ars.2015.6247.
[7] P. Kamoun, Endogenous Production of Hydrogen Sulfide in Mammals, Amino Acids, 2004, pp. 243–254, https://doi.org/10.1007/s00726-004-0072-x.
[8] K.R. Olson, Hydrogen sulfide as an oxygen sensor, Antioxidants Redox Signal. 22 (2015) 377–397, https://doi.org/10.1089/ars.2015.6390.
[9] B.D. Paul, S.H. Snyder, H₂S: a novel gasotransmitter that signals by sulfhydration, Trends Biochem. Sci. 40 (2015) 667–700, https://doi.org/10.1016/j.tibs.2015.06.007.
[10] D.A. Wink, Y.Li, A.Tsung, H.Huang, Q.Du, M.Yang, M.Deng, S.Xiong, X.Wang, D.D.Roberts, D.A. Wink, S-nitrosylation of EGFR and Src activates an oncogenic signaling network in human basal-like breast cancer, Mol. Canc. Res. 12 (2014) 1312–1332, https://doi.org/10.1158/1541-7786.MCR-13-0621.
[11] C.J.R. Oliveira, M.F. Cucurcius, M.S. Moraes, M. Tsujiia, L.R. Travassos, A. Stern, H.P. Monteiro, The low molecular weight S-nitrosithiol, S-nitroso-N-acetylpenicillamine, promotes cell cycle progression in rabbit aortic endothelial cells, Nitric Oxide 18 (2008) 241–255, https://doi.org/10.1016/j.niox.2008.02.001.
[12] H. Zhou, C.T. Stemberski, J.S. Stamler, Cross talk between S-nitrosylation and phosphorylation involving kinases and nitrosylases, Circ. Res. 3 (2018) 1485–1487, https://doi.org/10.1161/CIRCRESAHA.118.313109.
[13] H.P. Monteiro, P.E. Costa, A.R.C.A. Reis, A. Stern, Nitric oxide: protein tyrosine phosphorylation and protein S-nitrosylation in cancer, Biomed. J. 38 (2015) 380–388, https://doi.org/10.4103/2319-4170.158624.
A.K.C.A. Reis, et al.

W.L. Batista, F.T. Ogata, M.F. Curcio, R.B. Miguel, R.J. Arai, A.L. Matsuo, N. Hogg, The biochemistry and physiology of S-nitrosothiols, Annu. Rev. Biochem. 2013, 82, 561–581.

Z.W. Wang, Z. Wen, Z. Wang, M. Xian, J. Cheng, P.G. Wang, Equilibrium and kinetic studies of transmission between S-nitrosothiols and thiols, Bioorg. Med. Chem. Lett. 2011, 21, 433–436.

M. Tsuji, W.L. Batista, F.T. Ogata, A. Stern, H.P. Monteiro, R.J. Arai, Thioredoxin-1 promotes survival in cells exposed to S-nitrosothiol-mediated cell death, Antioxid. Redox Signal. 2015, 23, 1–12.

K. Wang, Z. Zhang, L. Li, H. Wang, A. Ji, Y. Li, Hydrogen sulfide acts as a double-edged sword in human hepatocellular carcinoma cells through ERG/ERK/MAP-2 and PTEK/ARK signaling pathways, Sci. Rep. 2017, 7, 1–14.

D. Wu, M. Li, W. Tian, S. Wang, L. Cui, H. Li, H. Wang, A. Ji, Y. Li, Hydrogen sulfide-induced apoptosis in cancer cells, Pigment Cell Melanoma Res. 2015, 28, 61–72.

J. Wei, S. Wang, Y. Sun, H. Wang, L. Cui, Y. Li, Hydrogen sulfide sensitizes cancer cells via JNK and p38 MAPK signaling pathways, Cancer Cell Int. 2015, 15, 1–20.

A.C. Lynskey, A.C. Kimmelman, Metabolic interactions in the tumor microenvironment, Trends Cell Biol. 2017, 27, 863–875.

C.J.R. Oliveira, F. Schindler, A.M. Ventura, M.S. Morais, R.J. Arai, E. Leung, M. Fraser, R.R. Fiscus, B.K. Tsang, cisplatin alters nitric oxide synthase levels in human ovarian cancer cells: involvement in p53 regulation and cell proliferation, Br. J. Pharmacol. 2011, 164, 1803–1809.

L. Leon-Bollotte, S. Subramaniam, O. Cauvard, S. Plenchette-Colas, C. Paul, T. Miró, J. Llop, M. Soria-Diez, J. Martínez, A. Serrablo-Requejo, G. Blanco-Fernández, et al., Regulation of cell death receptor S-nitrosylation and apoptotic signaling by S-nitrosation of the death receptor fas promotes fas ligand-mediated apoptosis in cancer cells, Gastroonocolgy 2015, 140, 2009–2018.

J. Bao, S. Mucanoe, H. Kamata, H. Tachibana, Hydrogen sulfide donors selectively potentiate a green tea polyphenol EGCG-induced apoptosis of multiple myeloma cells, Sci. Rep. 2017, 7, 1–9.

J.A. Milner, Preclinical perspectives on cancer and garlic, J. Nutr. 2006, 136, 8275–8315.

L. Yi, Q. Su, Molecular mechanisms for the anti-cancer effects of diallyl disulfide, Food Chem. Toxicol. 2011, 49, 362–370.

R. Doshi, T. Tahara, M. Tsurumaki, S. Adachi, T. Ishii, Hydrogen sulfide-elicited nitrosylation of thioredoxin-1 sensitizes cancer cells to cisplatin treatment, J. Biol. Chem. 2014, 289, 15651–15662.

J. Bao, S. Mucanoe, H. Kamata, H. Tachibana, Hydrogen sulfide donors selectively potentiate a green tea polyphenol EGCG-induced apoptosis of multiple myeloma cells, Sci. Rep. 2017, 7, 1–9.

J.A. Milner, Preclinical perspectives on cancer and garlic, J. Nutr. 2006, 136, 8275–8315.

L. Yi, Q. Su, Molecular mechanisms for the anti-cancer effects of diallyl disulfide, Food Chem. Toxicol. 2011, 49, 362–370.

R. Doshi, T. Tahara, M. Tsurumaki, S. Adachi, T. Ishii, Hydrogen sulfide-elicited nitrosylation of thioredoxin-1 sensitizes cancer cells to cisplatin treatment, J. Biol. Chem. 2014, 289, 15651–15662.

J. Bao, S. Mucanoe, H. Kamata, H. Tachibana, Hydrogen sulfide donors selectively potentiate a green tea polyphenol EGCG-induced apoptosis of multiple myeloma cells, Sci. Rep. 2017, 7, 1–9.

J.A. Milner, Preclinical perspectives on cancer and garlic, J. Nutr. 2006, 136, 8275–8315.

L. Yi, Q. Su, Molecular mechanisms for the anti-cancer effects of diallyl disulfide, Food Chem. Toxicol. 2011, 49, 362–370.

R. Doshi, T. Tahara, M. Tsurumaki, S. Adachi, T. Ishii, Hydrogen sulfide-elicited nitrosylation of thioredoxin-1 sensitizes cancer cells to cisplatin treatment, J. Biol. Chem. 2014, 289, 15651–15662.

J. Bao, S. Mucanoe, H. Kamata, H. Tachibana, Hydrogen sulfide donors selectively potentiate a green tea polyphenol EGCG-induced apoptosis of multiple myeloma cells, Sci. Rep. 2017, 7, 1–9.

J.A. Milner, Preclinical perspectives on cancer and garlic, J. Nutr. 2006, 136, 8275–8315.

L. Yi, Q. Su, Molecular mechanisms for the anti-cancer effects of diallyl disulfide, Food Chem. Toxicol. 2011, 49, 362–370.

R. Doshi, T. Tahara, M. Tsurumaki, S. Adachi, T. Ishii, Hydrogen sulfide-elicited nitrosylation of thioredoxin-1 sensitizes cancer cells to cisplatin treatment, J. Biol. Chem. 2014, 289, 15651–15662.

J. Bao, S. Mucanoe, H. Kamata, H. Tachibana, Hydrogen sulfide donors selectively potentiate a green tea polyphenol EGCG-induced apoptosis of multiple myeloma cells, Sci. Rep. 2017, 7, 1–9.

J.A. Milner, Preclinical perspectives on cancer and garlic, J. Nutr. 2006, 136, 8275–8315.

L. Yi, Q. Su, Molecular mechanisms for the anti-cancer effects of diallyl disulfide, Food Chem. Toxicol. 2011, 49, 362–370.

R. Doshi, T. Tahara, M. Tsurumaki, S. Adachi, T. Ishii, Hydrogen sulfide-elicited nitrosylation of thioredoxin-1 sensitizes cancer cells to cisplatin treatment, J. Biol. Chem. 2014, 289, 15651–15662.

J. Bao, S. Mucanoe, H. Kamata, H. Tachibana, Hydrogen sulfide donors selectively potentiate a green tea polyphenol EGCG-induced apoptosis of multiple myeloma cells, Sci. Rep. 2017, 7, 1–9.

J.A. Milner, Preclinical perspectives on cancer and garlic, J. Nutr. 2006, 136, 8275–8315.

L. Yi, Q. Su, Molecular mechanisms for the anti-cancer effects of diallyl disulfide, Food Chem. Toxicol. 2011, 49, 362–370.
opportunities for redox metabolomics and personalized medicine, Antioxidants Redox Signal. 27 (2017) 678–712, https://doi.org/10.1089/ars.2017.7083.

[77] I.I.C. Chio, D.A. Tuveson, ROS in cancer: the burning question, Trends Mol. Med. 23 (2017) 411–429, https://doi.org/10.1016/j.molmed.2017.03.004.

[78] K.R. Olson, Y. Gao, F. Arif, N. Arora, S. Patel, E.R. DeLeon, T.R. Sutton, M. Feelisch, M.M. Cortese-Krott, K.D. Straub, Metabolism of hydrogen sulfide (H2S) and production of reactive sulfur species (RSS) by superoxide dismutase, Redox Biol. 15 (2018) 74–85, https://doi.org/10.1016/j.redox.2017.11.009.

[84] M.S. Sousa, F.R. Latini, H.P. Monteiro, J.M. Cerutti, Arginase 2 and nitric oxide

[83] N.T. Eissa, A.J. Strauss, C.M. Haggerty, E.K. Choo, S.C. Chu, J. Moss, Alternative splicing of human inducible nitric-oxide synthase mRNA: tissue-specific regulation and induction by cytokines, J. Biol. Chem. 271 (1996) 27184–27187.

[85] L. Yi, X.X. Ji, H. Tan, M. Lin, Y. Tang, L. Wen, Y.H. Ma, Q. Su, Role of of Ras-related C3 botulinum toxin substrate 2 (Rac 2), NADPH oxidase and reactive oxygen species in dithiyl ditosphide-induced apoptosis of human leukemia HL-60 cells, Clin. Exp. Pharmacol. Physiol. 37 (2010) 1147–1153.

[81] C. Szabó, H. Ischiropoulos, R. Radi, Peroxynitrite: biochemistry, pathophysiology and development of therapeutics, Nat. Rev. Drug Discov. 6 (2007) 662–680.

[82] D. Jourd'heul, F.L. Jourd'heul, P.S. Kutchukian, R.A. Musah, D.A. Wink, M.B. Grismal, Reaction of superoxide and nitric oxide with peroxynitrite im-
plications for peroxynitrite-mediated oxidation reactions in vivo, J. Biol. Chem. 276 (2001) 28799–28805.

[80] M.M. Cortese-Krott, B.O. Fernandez, M. Kelm, A.R. Butler, M. Feelisch, On the smallest S-nitrosothiol, HSNO; cellular cross-talk of H2S and S-nitrosothiols, J. Am. Chem. Soc. 134 (2012) 12016–12027, https://doi.org/10.1021/ja209699r.

[89] M. Chattopadhyay, R. Kodela, P.L. Duvalsaint, K. Kashfi, Gastrointestinal safety, complications for peroxynitrite-mediated oxidation reactions in vivo, J. Biol. Chem. 271 (1996) 27184–27187.

[88] R. Kodela, M. Chattopadhyay, K.D. Straub, Catalase as a sulde-sulfur oxido-reductase: an ancient (and modern?) regulator of reactive sulfur species (RSS), Redox Biol. 12 (2017) 325–339, https://doi.org/10.1016/j.redox.2017.02.021.

[87] R. Kodela, M. Chattopadhyay, K. Kashfi, NOSH-aspirin: a novel nitric oxide −

[86] M.M. Cortese-Krott, B.O. Fernandez, M. Kelm, A.R. Butler, M. Feelisch, On the smallest S-nitrosothiol, HSNO; cellular cross-talk of H2S and S-nitrosothiols, J. Am. Chem. Soc. 134 (2012) 12016–12027, https://doi.org/10.1021/ja209699r.

[85] L. Yi, X.X. Ji, H. Tan, M. Lin, Y. Tang, L. Wen, Y.H. Ma, Q. Su, Role of of Ras-related C3 botulinum toxin substrate 2 (Rac 2), NADPH oxidase and reactive oxygen species in dithiyl ditosphide-induced apoptosis of human leukemia HL-60 cells, Clin. Exp. Pharmacol. Physiol. 37 (2010) 1147–1153.

[81] C. Szabó, H. Ischiropoulos, R. Radi, Peroxynitrite: biochemistry, pathophysiology and development of therapeutics, Nat. Rev. Drug Discov. 6 (2007) 662–680.

[82] D. Jourd'heul, F.L. Jourd'heul, P.S. Kutchukian, R.A. Musah, D.A. Wink, M.B. Grismal, Reaction of superoxide and nitric oxide with peroxynitrite im-
plications for peroxynitrite-mediated oxidation reactions in vivo, J. Biol. Chem. 276 (2001) 28799–28805.

[80] M.M. Cortese-Krott, B.O. Fernandez, M. Kelm, A.R. Butler, M. Feelisch, On the smallest S-nitrosothiol, HSNO; cellular cross-talk of H2S and S-nitrosothiols, J. Am. Chem. Soc. 134 (2012) 12016–12027, https://doi.org/10.1021/ja209699r.

[89] M. Chattopadhyay, R. Kodela, P.L. Duvalsaint, K. Kashfi, Gastrointestinal safety, complications for peroxynitrite-mediated oxidation reactions in vivo, J. Biol. Chem. 271 (1996) 27184–27187.

[88] R. Kodela, M. Chattopadhyay, K.D. Straub, Catalase as a sulde-sulfur oxido-reductase: an ancient (and modern?) regulator of reactive sulfur species (RSS), Redox Biol. 12 (2017) 325–339, https://doi.org/10.1016/j.redox.2017.02.021.

[87] R. Kodela, M. Chattopadhyay, K. Kashfi, NOSH-aspirin: a novel nitric oxide −

[86] M.M. Cortese-Krott, B.O. Fernandez, M. Kelm, A.R. Butler, M. Feelisch, On the smallest S-nitrosothiol, HSNO; cellular cross-talk of H2S and S-nitrosothiols, J. Am. Chem. Soc. 134 (2012) 12016–12027, https://doi.org/10.1021/ja209699r.

[85] L. Yi, X.X. Ji, H. Tan, M. Lin, Y. Tang, L. Wen, Y.H. Ma, Q. Su, Role of of Ras-related C3 botulinum toxin substrate 2 (Rac 2), NADPH oxidase and reactive oxygen species in dithiyl ditosphide-induced apoptosis of human leukemia HL-60 cells, Clin. Exp. Pharmacol. Physiol. 37 (2010) 1147–1153.

[81] C. Szabó, H. Ischiropoulos, R. Radi, Peroxynitrite: biochemistry, pathophysiology and development of therapeutics, Nat. Rev. Drug Discov. 6 (2007) 662–680.

[82] D. Jourd'heul, F.L. Jourd'heul, P.S. Kutchukian, R.A. Musah, D.A. Wink, M.B. Grismal, Reaction of superoxide and nitric oxide with peroxynitrite im-
plications for peroxynitrite-mediated oxidation reactions in vivo, J. Biol. Chem. 276 (2001) 28799–28805.