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Hydrogen Sulfide: An Emerging Molecular Mediator in Cancer Progression

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Abstract

Hydrogen sulfide (H_2S) has emerged as a key endogenous gasotransmitter involved in the regulation of numerous physiological and pathological processes. Similar to nitric oxide and carbon monoxide, H_2S functions as an important signaling molecule that maintains cellular homeostasis. Increasing evidence implicates dysregulated H_2S metabolism in cancer initiation, progression, and metastasis. Through modulation of cellular proliferation, apoptosis, angiogenesis, mitochondrial bioenergetics, and redox homeostasis, H_2S exerts diverse and context-dependent effects on tumor biology. These actions are primarily mediated by the enzymes cystathionine β-synthase (CBS), cystathionine γ-lyase (CSE), and 3-mercaptopyruvate sulfur transferase (3-MST). Notably, H_2S exhibits a dual role in cancer, promoting tumor growth at physiological concentrations while exerting antitumor effects at higher levels through apoptosis induction, metastasis suppression, and inhibition of oncogenic signaling. Recent studies have further highlighted its involvement in ferroptosis, protein sulfhydration, and DNA repair mechanisms. Collectively, H_2S represents a promising therapeutic target and a novel avenue for cancer intervention.

Keywords: Sulfide, Cancer, Signalling Pathway, Neoangiogenesis, Tumour

Introduction

Hydrogen sulfide (H2S) is a gasotransmitter that is present in mammalian tissues, just like carbon monoxide (CO) and nitrogen oxide (NO). It is the third most prevalent naturally occurring gas, after NO and CO[1]. The myriad biochemical, physiological, and pathological processes that occur in living systems are mediated in

large part by H_2S[2]. A wide range of disorders are thought to be influenced by H_2S during their development and progression ranging from benign to malignant[3]. H_2S has been shown to play a significant role in the development of oral diseases, respiratory diseases, cardiovascular diseases and commonly kidney diseases in addition to its carcinogenic roles, which involve both the inhibition and advancement of cancer[3]. The mammalian system's operation is thus greatly influenced and regulated by these substances[1]. H_2S has a significant impact on the body's enzymatic synthesis and control.

Due to its distinct chemistry, molecular reactivity mechanisms, ability to alter proteins, and active involvement in a variety of redox processes with metal, H_2S has come to be recognized as a crucial signalling molecule in cancer biology. H_2S has been connected to a range of physiological mechanisms involved to the cell cycle and the development of tumours, including angiogenesis, growth tumours, biogenesis of cells and mitochondria, neoangiogenesis, invasion, metastasis, sulfhydration of proteins, epithelial-mesenchymal transition, DNA mending and resistance to chemotherapy[4]. The synthesis, metabolism, measurement and modulation of H_2S as a novel treatment in cancer[5].

The current review highlights developments in understanding of H_2S in cancer management by emphasizing its functional participation in crucial cellular processes as ferroptosis, DNA repair, programmed cell death, immunomodulatory responses and downstream processes, effects on cellular functions, acting as a mediator in cancer and playing a role in signalling. The therapeutic potential of H_2S donors, either alone or in combination, is also highlighted in this perspective. along with other therapies. While many biological functions are typified by H_2S, physiological processes in mammalian systems are fully comprehensible and expounded upon.

Physiological and pathological function of H_2S:

A vast array of physiological and pathological conditions, including arterial relaxation, neural activity, angiogenesis, glucose metabolism, energy production, atherosclerosis, vasodilatation, anti-inflammatory reaction, anti-cancer and cardiovascular system shielding are the role of H_2S in cancer as well as in normal being[6]. However, there are differing perspective in expansion as well as development of carcinogenesis. Several investigations from the past few years have advised that there may be two distinct functions that endogenous or exogenous H_2S production can play in the formation of carcinogenic cells[7]. Human CSE profligacy is present in a number of reactions that use homocysteine and cysteine to create H_2S. It can also be produced through platelet-rich plasma (PRP)-independent 3 alpha ketoglutarate cysteine aminotransferase (CAT) or mercapto-pyruvate sulphate transferase (3-MST)[8]. Free H_2S in mitochondria can be oxidized by sulfhydryl reductase (SQR) and methylated in the cytoplasm by sulfhydryl-S-methyl transferase. Furthermore, when biological liquids combine molecules with metal and meth-haemoglobin, free H_2S is released[9]. H_2S generation increases in vivo in the presence of phosphodiesterase inhibitors, inorganic sulfide salts and organic H_2S donors[10]. Hydrosulfide sodium and p-4morpholinodithiophosphoric acid (GYY4137) and p-4-methoxyphenyl are two typical H_2S donors, NOSH-aspirin, SG-1002 and ACS67 (a latanoprost mixed compound) releasing moiety, as well as L-cysteine, which functions as a substrate for the endogenous formation of H_2S.

The normal range of H_2S in changed cells and the processes that cause its variation in tumour cells are not well established. Existing investigations suggests that even a little quantity of H_2S is needed to sustain cellular activity and that any variation in its concentration,

whether it be rising or falling, has a major effect on cellular activity that modulates cancer.

Endogenous production of H_2S:

All mammals, including humans, produce H_2S enzymatically, according to recent experimental studies. Two pyridoxal-5-phosphates (PLP), CSE and CBS, are the components often seen in enzymatic process. Additionally, 3-MST, another enzyme, is independent of PLP, working with CAT and with ketoglutarate to convert L-cysteine into H_2S. The cytosol and mitochondria both contain both enzymes in co-localization. Additionally, research has demonstrated that D-amino acid oxidase can catalyse D-cysteine to create 3-mercaptopyruvate, an achiral ketoacid that is subsequently converted into H_2S in the kidneys and brain by 3-MST.

Mammalian cells hold the generated H_2S until it is either released immediately, changed into bound sulfane sulfur or transformed into acid-labile sulfur. Haemoglobin-mediated scavenging, excretion from the kidneys or lungs, thiolmethyl transferase and rhodanese-mediated methylation to produce dimethyl sulfide and methanethiol, and mitochondrial oxidation to sulfate and thiosulfate are all possible ways that H_2S might be catabolized. The fluid component of the cytoplasm contains CBS and CSE, which are also referred to as cytosolic enzymes with specific tissue distributions. Mainly found in the central nervous system (CNS), CBS can also be found in the kidney, liver, uterus, placenta, pancreatic islets, and ileum. Otherwise CSE can be produced in the heart, kidney, uterus, ileum, vascular smooth muscle, liver. In cardio vascular system CSE is the main enzyme that produce H_2S. CBS and CSE primarily found in cytosol whereas 3MST can be detected in mitochondria mainly. In acid-labile sulfur, H_2S can be immediately released, stored, or bound via the cells enzymatic mechanism. Furthermore, enzymatic or non-enzymatic mechanisms can create H_2S endogenously. Garlic's organic and inorganic polysulfides, glucose, elemental sulfur, and glutathione are the sources of the body's endogenous, non-enzymatic H_2S production. Alternative non-enzymatic methods of producing H_2S from glucose include glycolysis (>90%) and phospho-gluconate production via nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (<10%). Methanethiol and H_2S are gasotransmitter compounds that are produced when glucose reacts with homocysteine, cysteine, or methionine.H_2S is also produced through the direct reduction of elemental sulfur and glutathione. By decreasing analogue of the glucose oxidation pathway like NADH or NADPH, elemental sulfur is converted to H2S. Moreover, garlic and garlic-derived organic polysulfides, such as diallyl trisulfide (DATS), diallyl disulfide (DADS), S-allyl cysteine (SAC), and diallyl sulfide (DAS), may have a thiol-dependent effect on the production of H2S. Similarly, two pyridoxal-5-phosphate dependent enzymes, such as CBS and CSE, create L-cysteine, and when 3-MST and CAT work together, H2S is produced [Fig-1].

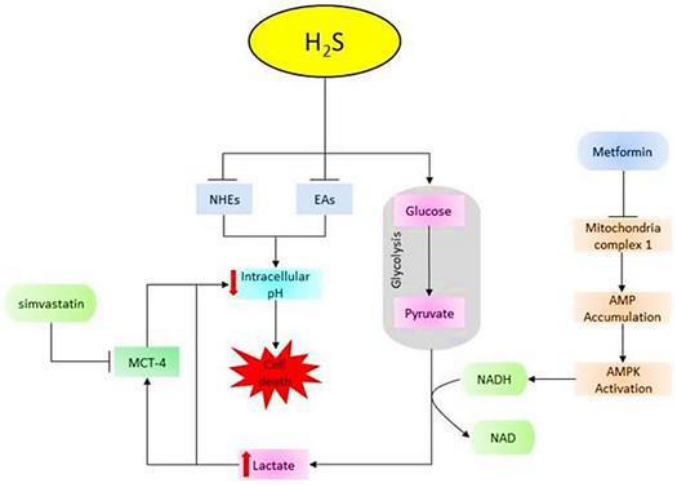

Figure 1: Regulation of cancer cell metabolism by Hydrogen sulfide (H_2S)

Mammals produce H_2S primarily through the production of cysteine, which is a crucial process. The cytosolic enzymes CSE and CBS are dependent on pyridoxal-5-phosphate. In order to catalyse the formation of H_2S and cystathionine from homocysteine through cysteine declination and degradation, CBS is primarily expressed in the central nervous system. In addition to producing cysteine, ammonia, and ketobutyrate from cystathionine and H_2S from cysteine metabolism, CSE is most widely expressed in the cardiovascular system. 3-MST and CAT, which are primarily found in the cytosol and mitochondria of various organs like neuroglia cells, kidneys, hearts, and liver, make up the third route. CAT catalyses the conversion of cysteine to 3-MST in the presence of ketoglutarate, which can result in the breakdown and generation of H_2S and pyruvate from 3-MP. Two primary processes contribute to the synthesis and biogenesis of H_2S in the human body: specific endogenous enzymes and microbial metabolic pathways within the gut microbiota, particularly in sulfate-reducing bacteria. Microbiota prevalence has been specifically linked to elevated amounts of free H_2S in plasma as well as the colon and cecum (intestinal tracts). The three primary human enzymes that have been researched to make H_2S endogenously are CBS, CSE, and 3-MST. Persulfides and polysulfides are also thought to be secondary sources of H_2S, which can be formed or produced endogenously or via dietary consumption.

Binary role of H_2S in cancer:

The role of H2S in cancer is dependent on the concentration, type and replenishment of the donor.

1. The Cancer-Promoting Effect of H2S:

Since H_2S is a bioenergetic stimulator at low concentrations, mammalian cells are thought to react to it. Sulfides, even at low concentrations, are an appropriate energy substrate because of their strong affinity for mammalian mitochondria. Due to this, the mitochondrial enzyme SQOR serves as an electron donor for a variety of cellular bioenergetic processes, self-regulating in tandem with coenzyme Q and complexes I and II. On the other hand, 3MP can improve it. Therefore, the growth of cancer can only be aided by H2S-mediated mitochondrial respiration when there is enough oxygen present. In addition, H_2S raises intramitochondrial cAMP levels and causes mitochondrial ATP synthase and lactate dehydrogenase to persulfidate. H_2S is a substrate for mitochondrial respiration. Glibenclamide prevents endothelial cell migration and p38 phosphorylation in response to H2S exposure, suggesting that p38 plays a role in the proangiogenic process that H2S induces. Mustafa et al. showed that H_2S mediates persulfidation by activating the KATP channel and affecting downstream effects. H_2S upregulates HIF-1a expression in many tests to facilitate ischemia-induced angiogenesis.

While the evidence for the concept that H_2S plays a role in hypoxia-induced angiogenesis during the development of cancer is not very strong, it is highly conceivable. It wasn't until the late 2000s that the pro-angiogenic action of H_2S was identified. The pharmacological or genetic deletion-induced suppression of CSE, which limits VEGF-induced angiogenesis, suggests that H_2S functions as a physiological angiogenic agent. It has been demonstrated that the proangiogenic effects of H_2S are mediated by the PI3K/AKT pathway, mitogen-activated protein kinase (MAPK), and ATP-sensitive potassium (KATP) channels. In endothelial malignancies, H_2S has also been demonstrated to stimulate angiogenesis. NaHS is found to accelerate the migration of endothelial cells isolated from breast carcinomas by Puppo et al. using a well-established model of tumour angiogenesis. When VEGF is not present, CSE suppression prevents B-TEC

migration, indicating that H_2S plays a critical role in external and endogenous breast cancer angiogenesis. By encouraging angiogenesis and supplying oxygen and nutrients to cancer cells, H_2S can accelerate the growth of tumours. In the field of cancer biology, it is imperative to acknowledge that elevated levels or quantities of NaHS have the potential to inhibit angiogenesis. This suggests that the pro-angiogenic trend might only be observed at low or endogenous H_2S concentrations. In addition to acting as a barrier against apoptotic stimuli, H_2S exhibits anti-apoptotic properties. Furthermore, hepatocellular carcinoma, neuroblastoma, and colon cancer cells have all been shown to exhibit anti-apoptotic activity. Possible underlying mechanisms have been identified by additional research. These include the activation of the MEK1-ERK pathway, which is mediated by H_2S-linked persulfidation, the activation of the keap1 transcription factor NF-E2-related nuclear factor 2 (Nrf2), and the activation of the nuclear factor kappa-light-chain enhancer in activated B cells. The cell cycle, which attests to the high loyalty of the genetic transcript, is a sequence of extremely well-defined events that regulate the change from cellular quiescence to proliferation. This shift is known to be caused by H_2S. The four phases of the cell cycle are gap phase 1 (G1), DNA mammal cells, which are thought to react to H_2S as the bioenergetics synthesis phase (S phase), and gap phase 2 (G2), which is the cell's preparation for division and the mitotic phase (M phase). Cell division and distinct chromosomal separation take place during the M process. Normal cell cycle regulation breaking down is a typical characteristic of human cancer.

Cancer cells can multiply endlessly by eluding cell cycle arrest. Based on recent research, various cell types such as cardiomyocytes, cancer cells, and endothelial cells can experience an extension or acceleration of the cell cycle due to H_2S. Exogenous H_2S enhances proliferating nuclear antigens and cyclin-dependent kinase 4 while suppressing the expression of cell cycle regulatory genes. The effect of H_2S on the acceleration of the cell cycle in hepatoma and colon cancer cells was studied. As it has been demonstrated that blocking ERK or AKT phosphorylation dramatically inhibits the cell cycle, this basic signalling mechanism may be connected to the activation of the ERK and AKT pathways. This would accelerate the effect of H_2S on squamous cell carcinomas and colon cancer cell lines. The persulfidation of MEK1 illustrates the basic mechanisms of H_2S-induced ERK activation, even though it isn't stated explicitly. It is yet unknown, though, what molecular processes underlie AKT's crucial function in the growth of human cancer. There would be a big impact if this were explained and made clear.

2. Anti-Cancer Effect of H2S:

In contrast to normal fibroblasts, cancer cells will eventually die from continuous exposure to high H_2S concentrations. The potential processes behind H_2S inhibition of cancer growth Depends on the type of cell, dysregulation in endogenous H_2S levels is linked to the initiation and spread of cancer. H_2S regulation controls the proper operation of the cells. Scientific investigations have revealed elevated levels of H_2S-synthesizing enzymes in a number of human cancers, such as thyroid, ovarian, colon, prostate, and breast cancers; additionally, a poorer prognosis is associated with these tumour advancement.

One of the three key enzymes that plays a substantial role in the creation of H_2S; its expression reverses acquired resistance to 5-FU in colon cancer cell lines, thereby healing the malignancy[3]. This highly suggested and much anticipated study was recently unraveled by two new Chinese studies that examined the possible effects of H_2S

donation and inhibition on cancer cells, respectively, and were published in a cancer letter3. 5 -(4-hydroxyphenyl)-3H-1, 2dithiol-3-thione (ADT-OH) is a frequently employed H2S donor for breast cancer cells, according to exposure studies. By blocking the PI3K/AKT/mTOR and RAS/RAF/MEK/ERK signalling pathways, HA-ADT inhibits the development of human breast cancer cells. The physiological mechanisms of H_2S in cancer cells are now better understood thanks to these two studies, which also set a baseline that may affect future research on the possibility of using H_2S levels in the human body to target cancer cells. According to the results of increased expression of Bcl-2 and Bax, which mediate apoptosis-related cancer cell death and the disruption of signaling pathways upon exposure of H_2S donors, as demonstrated in11, co-treatment with DATS (dially thiosulfate, an H_2S donor) and Dex (dexamethasone) has been found to significantly inhibit sphere formation and colony formation and the proliferation of multiple myeloma cells by inducing apoptosis in these recent experiments.

Treatment also reduced the PI3K, p-AKT, and p-mTOR pathways and increased the expression of miR-127-3p12. H_2S has been identified as a potential contributor to anti-metastatic mechanisms against cancer. This is demonstrated by a novel study on the pharmacological inhibition of H_2S-producing enzymes, which suggests that inducing significant changes in gene and protein expression may pharmacologically induce the mesenchymal-to-epithelial transition (MET) and disrupt the EMT/MET balance in colon cancer[13]. On the other hand, a novel CSE inhibitor has been shown in a recent study to reduce human TNBC growth and metastasis by downregulating several signaling pathways. Further research on has clarified that ADT-OH inhibits IBA degradation, which lowers NF-B activity and, in turn, downregulates the anti-apoptotic proteins XIAP and Bcl-2. More importantly, it inhibits the ubiquitin-induced degradation of FADD by blocking the synthesis of MKRN1, a FADD E3 ubiquitin ligase[14]. Within cancer cells, the metabolic process of glycolysis occurs, and it is intended to boost glucose synthesis and turn lactate into energy. Inflammation and cell stress can result from lactate buildup. From intracellular acid production, cancer cells may be more susceptible to angiogenesis and metastasis in an acidic microenvironment[15]. Therefore, focusing on intracellular pH regulators is a viable cancer treatment approach. By cumulatively absorbing glucose, GYY4137 (200–1000 nM) boosted glycolysis in cancer cells. By interfering with anion exchangers (AE) and sodium/proton exchangers (NHS), it momentarily prevents intracellular acids from being exported[16]. One should not completely give up on H_2S catabolism to H2SO4, since this may result in intracellular acidification later on. Therefore, in a panel of cancer cell lines, uncontrollably high intracellular acidification takes place, culminating in cell death$_{16}$. GYY4137's behaviour was only caused by H_2S since it did not exhibit any similar impact when tested with ZYJ1122, a sulfur-free control molecule[17].

Cancer has been shown to progress due to dysregulation of the cell cycle. In order to effectively treat cancer cells, cell cycle arrest induction is used. The H_2S-suppressive effect on the cell cycle switch has been documented in numerous studies. To induce G1/S phase cell cycle arrest and subsequent apoptosis in vitro and in vivo in the gastric cancer cell line SGC-7901, sproargyl-cysteine (SPRC) functions as an H_2S donor[18]. Using NaHS (0.4 to 1 mM), colon cancer cell lines (HT-29, SW116, and HCT116) experience cell cycle arrest at G1/S. This is probably caused by upregulating the cyclin-dependent kinase inhibitor p21Cip1[19]. Moreover, it has been proposed that GYY4137 has an inductive effect on cell

cycle arrest in a variety of cancer types[17,20]. For instance, GYY4137 was found by Lu et al. to suppress cyclin D1, which in turn suppressed the G1/S cell cycle transition and, as a result, tumour growth in the subcutaneous HepG2 xenograft model[21]. In a breast cancer cell line (MCF7), GYY4137 caused a partial arrest of G2/M, however, the underlying mechanism is uncertain[17]. Since neither GYY4137 nor NaHS caused cell cycle arrest in normal fibroblast cells in the aforementioned studies, H_2S causes cell cycle arrest in cancer cells.

H_2S has been shown to stimulate E-cadherin, which has anti-metastatic properties and to block histone deacetylase, which causes tumour suppressor genes to become epigenetically reactivated. Given how many biological processes H_2S affects, the molecular targets causing its pleiotropic impacts on these systems are yet unknown. Pro-survival pathways are triggered in cancer cells that continue to proliferate, upsetting the delicate balance between apoptosis and survival[22]. Breast cancer, prostate cancer, and non-small cell lung cancer are among the cancers that have been linked to the activation of the signaling pathway NF-B. Moreover, H2S has been demonstrated to prevent TNF and LPS from activating NF-B, in addition to triggering it through persulfidating the p65 subunit. Consequently, it is not unexpected that long-term exposure to donated hybrids or H2S results in negative side effects such apoptosis and NF-B suppression[23].

However, more investigation is required to fully comprehend the chemical mechanism via which H_2S inhibits NF-B activity, as this is a topic that requires more research. By suppressing STAT3 activators and downregulating B cell lymphoma 2 through STAT3, for example, GYY4137 causes apoptosis in hepatocellular cancer cell lines[20]. Chronic exposure to H_2S also induces apoptosis in oral cancer cells, most likely as a result of pleckstrin homology-like Domain-A1, an apoptotic suppressor presents in this kind of cancer, being downregulated[24]. Going forward, it will be crucial to identify and explain the H_2S-target proteins implicated in the processes leading to cell survival.

H_2S as a signaling molecule and role in signaling pathways:

As a signaling molecule and its function in signaling routes in many different tissues and structures, such as the circulatory system, neurological system, and organs, H_2S functions as a signal molecule[25]. The utilization of H_2S by inflammatory cells is influenced by endothelial cells, smooth muscle cells, mitochondria, endoplasmic reticulum, and transcription factors. H_2S production is essential for the bioenergetics, proliferation, and migration of cancer cells, and CBS enhanced it in colorectal and ovarian malignancies. In vitro human colon cancer cells have the potential to contribute to SIRT1 overexpression. In colorectal and ovarian tumors, CBS enhanced the synthesis of H_2S, which is essential for the bioenergetics, migration, and proliferation of cancer.

Since H_2S increases the activity of the NF-κB pathway, it has been suggested that H_2S acts as an endogenous mediator of inflammation. By blocking the NFκB pathway, CSE inhibition can also limit the growth of melanoma cells. Nevertheless, in an inflammatory state, exogenous H_2S can inhibit the NF-κB pathway's activity. Signaling pathways like PI3K/AKT and PI3K/SGK1/GSK3 may use this mechanism as a checkpoint[26]. When marked by extreme oxidative stress, excessive autophagy may be a factor in the vascular endothelial dysfunction linked to diabetes [Fig-2].

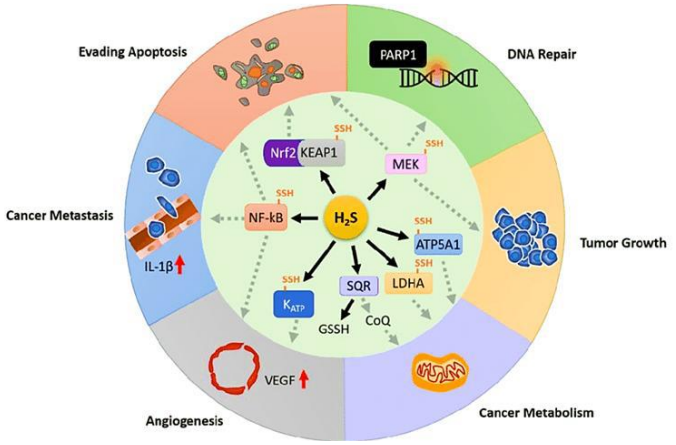

Figure 2: Multifactorial role of H_2S in cancer progression and cellular signaling

Protein sulfhydration and cancer:

When a sulfur atom is added to a reactive protein cysteine, a post-translational protein modification known as protein sulfhydration occurs. This creates a persulfide group, or a-SSH. When an oxidized cysteine derivative reacts with a sulfide or sulfide oxidation product, cysteine persulfide is produced. Protein sulfhydration generally inhibits, and the majority of activating events are triggered by a negative regulator's inhibition brought on by persulfidation[27]. A few well-studied self-hydrated proteins linked to cancer will be examined in this section. Likewise, polysulfides are thought to be important mediators of the various oncogenesis routes. According to a recent study, a poor prognosis is indicated by high levels of CSE and CBS expression. Utilizing surface-enhanced Raman spectroscopy, stage III or IV ovarian tumors were studied. The results showed that increased CSE expression was linked to increased tumor polysulfides, cisplatin resistance, and a poor prognosis. Furthermore, in ovarian carcinoma cell lines with high expression of CSE, increased polysulfide synthesis increased cisplatin resistance. By lowering polysulfides and raising histone H2AX phosphorylation, CSE suppression increased ovarian tumor cells' susceptibility to cisplatin. When the quantity of sulfur atoms in each hydrogen polysulfide increased, there was a slight increase in the amount of DNA damage caused by cisplatin in vitro[28]. By incorporating sulfate sulfur into the cysteine's active site and lowering PTEN phosphatase activity, polysulfides inactivate PTEN, a tumour suppressor gene product. This process, along with numerous others linked to polysulfides, is probably going to have a major role in the cancer.

H_2S and DNA repair:

ATR kinase suppression decreased cellular H_2S levels, suggesting that H_2S plays a role in DNA repair; low cellular H_2S levels increased ATR kinase activity as measured by CHK1 phosphorylation; high levels of H2S, however, inhibited the hallmark of ATR kinase activity, ATRser-435 phosphorylation[29]. ATRCHK1pathway activation is elevated in a variety of tumour types. Moreover, a poor prognosis for bladder, ovarian, and breast malignancies is linked to higher expression of ATR protein, phospho-ATR, and phospho-CHK1. Elevations in ATR and CHK1 may lead to an increase in H_2S generation since the ATR kinase regulates H_2S concentrations. Additionally, tailored ATR inhibition is being researched for use in cancer therapy[30]. Perhaps some H_2S generation could be somewhat suppressed by this cancer treatment approach. It is important to look into these possible cancer-related incidents.

H_2S and immunomodulation in cancer:

In both pathologic and normal circumstances, H_2S has strong and complex effects on the immune system regulation; at both low and high H_2S concentrations, reduced functionality is typically reported. A substantial body of research indicates that immunological regulation produced by H_2S may play a part in cancer[31]. As previously mentioned, CBS is present at the cancer cell membrane in breast cancer, where its-derived H_2S shields the cancer cells from reactive oxygen species (ROS)

produced by activated macrophages. Additionally, mice that were bred to develop melanoma were injected with either a vehicle or a vehicle + DATS, and the development of melanoma, splenic myeloid-derived suppressor cells (MDSCs), dendritic cells, and T cells were evaluated. By preventing tumour-specific T cells from proliferating, MDSCs aid in the development of cancer. Injection of DATS inhibited the growth of melanoma and reduced the quantity of MDSCs in the spleen, blood, and tumour microenvironment, while increasing CD8 T-cells and dendritic cells. It is possible that H2S donation regulates the immune system to control tumour formation because DATS delivery significantly decreased the immuno-suppressive activity of the MDSCs, restoring T cell function and T cell-mediated tumour growth suppression[32]. These results imply that H_2S can both drive and inhibit the growth of tumors by modifying the immune system.

H_2S and ferroptosis:

The physiological function and pathological state of an organism are closely linked to cell death, which is essential for mammalian growth and homeostasis. The timing and/or spatial organization of cell death is critical for the development of many human diseases. Most types of cell death in the body can be categorized into four types: necrosis, autophagy, pyroptosis, and apoptosis[33]. In 2012, "ferroptosis", a unique non-apoptotic cell death process mediated through an iron-dependent lipid peroxidation damage was coined. Ferroptosis is a form of cell death brought on by damage to the cell membrane through failure of the enzyme glutathione peroxidase (GPX) and intracellular lipid peroxide. This process is followed by the generation of reactive oxygen species (ROS) that is dependent on iron[34].

Ferroptosis is characterized by decreased mitochondrial volume, increased bilayer membrane density, and diminished or absent mitochondrial cristae in cells; nuclear concentration and chromatin marginalization are absent. Lung cancer has been connected to the mitochondrion, which generally controls the production of reactive oxygen species (ROS), ferroptosis, and the cell cycle. Moreover, in order for mitochondria to survive in a hostile environment, radiation and hypoxia activate their pathways. Because of their higher metabolic rate than normal cells, tumour cells take up more iron and ROS. Thus, in tumour cells, the alterations mentioned above prevent ferroptosis. By raising GSH concentration and decreasing ROS, H_2S has an antioxidative impact. Moreover, GPX4 activity is suppressed while the Xc system is maintained stable in order to lessen ferroptosis. One crucial aspect of ferroptosis is GSH depletion. GSH is an intracellular antioxidant that is produced by the homocysteine/methionine cycle. Significant H_2S production also occurs from L-cysteine, a precursor of GSH. A growing body of research indicates that H_2S reduces oxidative damage by increasing GSH production. Numerous studies indicate that H_2S promotes the synthesis of GSH to lessen oxidative damage. By increasing GSH levels and promoting its redistribution to the mitochondria, mitochondrial H_2S production in a neurocyte shields the cell from oxidative stress[35]. In order to improve poor glucose homeostasis, H_2S promotes GSH synthesis in a myotube. Treatment with H_2S donor NaHS increases GSH production, which delays cell senescence and lowers oxidative stress. The results showed that exogenous H_2S production (NaHS injection) significantly restored GSH loss in response to HHP. Thus, GSH reduction mediated by H_2S downregulation may represent a distinct mechanism of ferroptosis in HHP[36].

Recent studies have provided evidence of the positive benefits of H_2S on ferroptosis reduction. H_2S prevents

ferroptosis by inhibiting ALOX12 acetylation and managing the stability of the xCT (the functional submit of the Xc system). Treatment with H_2S donor GYY4137 decreases ferroptosis, which lessens the risk of acute lung injury[37]. Inhibiting H_2S production with the CBS inhibitor CH004 supplement exacerbates ferroptosis in hepatocellular cancer [106]. These studies suggest that H_2S may prevent ferroptosis and offer protection. The results of the investigation showed that the H_2S donor NaHS improved GPX4 expression and corrected high hydrostatic-induced ferroptosis by reducing ROS production and lipid peroxidation. Overall, ferroptosis has a major impact on the onset and management of cancer.

Conclusion

As a key endogenous gasotransmitter implicated in many physiological and pathological processes, including the development of cancer, hydrogen sulfide has drawn a lot of interest. Evidence suggests that H_2S regulates cellular processes such as proliferation, apoptosis, angiogenesis, redox balance, immunological regulation, and mitochondrial bioenergetics, hence playing a complicated role in tumour biology. H_2S greatly affects tumour growth and progression by mechanisms such as protein sulfhydration and modulation of several signalling pathways, including PI3K/AKT, MAPK, and NF-κB. Interestingly, H_2S plays dual roles in cancer that are depending on concentration. Higher quantities or pharmaceutical H_2S donors can have anticancer effects by triggering apoptosis, limiting metastasis, and causing cell cycle arrest, while low physiological levels may enhance tumour survival and angiogenesis. A number of cancers have also been linked to dysregulation of important H_2S-producing enzymes, including cystathionine β-synthase, cystathionine γ-lyase, and 3-mercaptopyruvate sulfur transferase.

In cancer biology, H_2S is an all-around promising molecular target. To better characterize its therapeutic potential and provide safe, focused approaches that use sulfide signalling for efficient cancer treatment, more mechanistic and clinical research is required.

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