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The Molecular Mechanism of Hydrogen Sulfide Regulation on Nasopharyngeal Carcinoma Cell Growth

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Abstract: Hydrogen sulfide (H_2S), as a critical gasotransmitter, plays a dual role in regulating tumor growth depending on its concentration and tumor type. In nasopharyngeal carcinoma (NPC), systematic reviews have demonstrated the involvement of H_2S in multiple cellular processes, including cell proliferation, apoptosis, and metastasis. This study systematically explores the molecular mechanisms of H_2S in NPC, focusing on its role in modulating signaling pathways, for example, PI3K/AKT, Wnt/β-catenin, and ROS-mediated pathways. The findings indicate that H_2S exerts its effects by regulating the expression of oncogenes and tumor suppressor genes, altering the tumor microenvironment, and influencing mitochondrial function. These insights provide a foundation for novel therapeutic strategies targeting H_2S metabolism in NPC.

Keywords: hydrogen sulfide, nasopharyngeal carcinoma, molecular mechanism, signal transduction, therapeutic target

1. Introduction

H_2S is a significant gas signaling molecule in organisms. The biosynthesis of H_2S in mammalian cells involves three principal enzymes, with two requiring pyridoxal-5'-phosphate (PLP) as a cofactor. Cystathionine-gamma-lyase (CSE) and cystathionine-β-synthase (CBS) can catalyze L-cysteine (L-Cysteine, L-cys) or homocysteine to generate H_2S; 3-mercaptopyruvate transferase (3-MST) is a non-PLP-dependent enzyme. Under the influence of alpha-ketoglutaric acid, 3-MST can cooperate with cysteine aminotransferase to catalyze L-cys to produce H_2S [1]. Additionally, 3-MST and D-amino acid oxidase catalyze D-cysteine to form H_2S in the brain and kidney [2].

NPC is a malignant tumor of the head and neck that originates from nasopharyngeal epithelial cells. Its pathological types encompass undifferentiated carcinoma, keratinized squamous cell carcinoma, and non-keratinized squamous cell carcinoma. Epidemiological data indicate that NPC exhibits significant regional clustering, with a high incidence in southern China, Southeast Asia, and North Africa. The clinical manifestations include a nasopharyngeal mass resulting in nasal sounds, hearing loss, trismus, and other symptoms, which seriously threaten the quality of life of patients. EBV infection, genetic susceptibility, and environmental factors (such as salt fish intake) are currently regarded as the main inducers of NPC, yet the molecular mechanism underlying its recurrence and metastasis remains poorly understood.

Although clinical management of nasopharyngeal carcinoma (NPC) has witnessed revolutionary advancements in both detection modalities and therapeutic strategies, challenges in managing both regional reappearance and distal metastatic deposits remain the principal causes of treatment failure

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for NPC [3][4]. Hence, there is an acute necessity to identify novel tumor markers and therapeutic targets in order to enhance the efficacy of nasopharyngeal cancer treatment. Studies have indicated that endogenous H_2S can facilitate tumor growth, such as in colon cancer, breast cancer, liver cancer, prostate cancer, etc. [1]. Despite the fact that H_2S has been demonstrated to have tumor-promoting effects in other cancers, its specific function in NPC has not been systematically clarified.

2. Biological function of H_2S

About two-thirds of the H2S in mammals is present at physiological pH as H+ and HS-, which can be broken down into H+ and S2- [2]. CSE, CBS, and 3-MST are the main catalyzers of endogenous H2S in mammals [5][6]. Notably, these enzymes act on certain molecular targets to control the function of nasopharyngeal cells and are significantly expressed in NPC cells, with human NPC cells exhibiting higher levels of CSE than normal ones [7]. It is still unclear exactly what molecular mechanism underlies the regulatory function.

To maintain homeostasis, biological systems dynamically regulate H_2S through dual pathways: immediate enzymatic catabolism via sulfide: quinone oxidoreductase (SQR) or stabilization as acid-labile sulfur pools (LSP) and sulfane sulfur (SS) reservoirs. SQR and persulfur dioxygenase (ETHE1) are two metabolic enzymes that are primarily responsible for its metabolism. These enzymes produce sulfate, which is subsequently expelled through respiration or urine [1]. In addition to its activity as a gas transmitter, the metabolism of H2S in mammals is linked to REDOX processes, binding to heme-coordinated metalloproteins, or post-translational modifications of proteins [1].

3. Molecular mechanism of H_2S regulation of NPC cell growth

Currently, H_2S is widely acknowledged as a third endogenous gas transmitter sharing similar pathophysiological features with carbon monoxide (CO) and nitric oxide (NO). As a lipid-soluble gas transmitter, H_2S freely crosses membranes to regulate cellular functions such as redox homeostasis and antioxidant response, angiogenesis, vasodilation, regulation of synaptic transmission, inflammatory response, glucose metabolism, ATP production, as well as apoptosis and cell proliferation. H2S can regulate angiogenesis by participating in ion channels, regulating miRNA, and modulating other angiogenic components. According to a recent study, human umbilical vein endothelial cells (HUVEC) that had CSE inhibited expressed more glycoproteins, FSS-like tyrosine kinases, and soluble anti-angiogenic indicators, which resulted in mitochondrial malfunction [8]. Supplementing with H2S can reverse this mitochondrial dysfunction and increase reactive oxygen species (ROS) and cellular bioenergy [8].

Under hypoxic conditions, an elevated H_2S level can be preserved through cellular redox homeostasis by upregulating anaerobic metabolic pathways such as glycolysis and other pathways related to cell protection. Moreover, a higher H_2S level can also trigger tissue vascular smooth muscle relaxation (vasodilation), endothelial cell proliferation and migration (angiogenesis) to facilitate the recovery of tissue oxygen supply. The H_2S-producing enzyme cystathione gamma-lyase (CTH) promotes prostate cancer progression and metastasis via the IL-1β/NF-κB signaling pathway [9].

3.1. H_2Sulfide regulates cell proliferation through PI3K/AKT/mTOR pathway

Studies have demonstrated that the expression of p-PI3K, p-AKT, and p-mTOR augmented following CSE overexpression, and declined upon CSE silencing. Hence, CSE can regulate cell apoptosis via the MAPK signaling pathway and cell proliferation through the PI3K and AKT/mTOR signaling pathway. CSE can modulate the growth of NPC cells through a ROS-mediated cascade of MAPK and PI3K/AKT/mTOR [7]. Endogenous H_2S promotes the proliferation of cancer cells by activating the PI3K/AKT signaling pathway, while suppressing the expression of tumor suppressor factors.

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3.2. H_2Sulfide regulates apoptosis through ROS/MAPK pathway

According to research, cell death, p53 activation (which is essential for controlling DNA damage and apoptosis), and p21 activation (which may establish the p23-dependent G1 cell cycle checkpoint) are all linked to the suppression of endogenous H2S. The Bax/Bcl-2 ratio rises in tandem with this (anti-apoptotic Bcl-2 shields cells from multifarious cytotoxic damage and usually prevents apoptosis, whereas Bax oligomerization is the primary molecular event that initiates intrinsic apoptosis cascade) [10]. According to experimental results from Wang et al., endogenous H2S inhibition may increase the ratio of Bax/Bcl-2 and Bad/Bcl-xl, along with the protein levels of cleaved caspase-3 and cleaved PARP, causing human NPC cells to undergo apoptosis [11].

Through the ROS/MAPK pathway, recent research has shown that inhibiting endogenous H2S can cause apoptosis and limit the development of human NPC cells [11]. The main members of the MAPK family in mammalian cells are ERK, p38, and JNK. While the activation of p38/JNK is an apoptotic signal, the activation of ERK is usually a survival signal. In order to improve immune function and suppress cancer cells, endogenous H2S stimulates apoptosis by activating the JNK/JunB/TNFSF14 and HO-1 signaling pathways and controls IDO1 and Foxp3 through the PRRX2/IL-6/STAT3 and NF-κB signaling networks [10].

Zhang et al.'s study on hepatocellular carcinoma (HCC) found that low levels of NaHS could promote the growth and migration of cancer cells, inhibit PTEN expression, and activate the EFGR/ERK/MPP signaling pathway. Furthermore, by suppressing the PI3K/Akt/mTOR signaling pathway, upregulating the expression of the LC-II and Atg5 proteins, and boosting autophagy, high concentrations of NaHS were able to prevent HCC [10].

3.3. H_2S regulates cell migration and invasion through Signaling Pathways

Researches have demonstrated that the invasion ability of cancer cells is conspicuously reduced upon inhibition of endogenous H_2S. EMT is regarded as a crucial mechanism of tumor invasion and metastasis in solid tumors, including pancreatic cancer, and an essential determinant of tumor progression. EMT is characterized by the loss of intercellular adhesion, enhanced cellular plasticity, and the development of mesenchymal phenotypes. Cancer cells can invade lymphatic vessels and blood vessels after local diffusion through EMT and accomplish metastasis. According to Wang's experimental outcomes, the reduction of endogenous H_2S levels within cancer cells is concomitant with a decline in the epithelial mesenchymal transformation (EMT) capacity of cancer cells. Studies have demonstrated that CSE/H_2S facilitates the migration and invasion of colorectal cancer cells, and the Wnt/β-catenin pathway regulates the expression of CSE genes at the transcriptional level, exerting an influence on the EMT process.

Remodeling of the extracellular matrix (ECM) constitutes another process exploited by tumor cells. Tumor cells are capable of facilitating the degradation of ECM by up-regulating matrix metalloproteinase (MMP). Tumor cells can invade and eventually metastasize through ECM by means of upregulating matrix metalloproteinase. Elevated levels of various matrix metalloproteinases are observed in numerous different tumor types[12].

Endogenous H_2S can promote cancer cell morphogenesis and migration by activating the p38 MAPK signaling pathway [10]. Dan Yang et al. demonstrated an inverse correlation between CSE expression levels and the expression of the immunosuppressive enzyme indoleamine 2, 3-dioxygenase 1 (IDO1), and this negative correlation seemed to be universal [13]. Thus, the H_2S/CSE axis potentially modulates p38 MAPK upstream kinases to regulate tumor aggressiveness. CBS can also inhibit the IL-6/STAT3 signaling pathway by down-regulating the IL-6 transcription factor PRRX2, thereby increasing the expression of Foxp3 gene in $CD4^+/CD25^+$ Tregs, thereby inhibiting Tregs invasion in tumors[10]. In addition, studies by Mustafa et al. have shown that endogenous H_2S

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mediates persulfidation reactive thiol groups in many proteins, including glyceraldehyde-3-phosphate dehydrogenase (GAPDH) and actin, inducing thiol-disulfide exchange (cysteine-SH group to the -SSH group). H_2S enhances GAPDH activity through the sulfurization of cysteine residues, which also happens to be the target of NO nitrosylation. NO inhibits GAPDH activity, suggesting that some targets may modulate apoptosis through competitive nitrosylation and sulfurization of the same cysteine residues [14]. Exogenous H_2S can also inhibit the growth of cancer cells by inhibiting STAT3 and the downstream proteins VEGF, HIF-1α and cyclin D1 [10].

3.4. Effects of H_2S on tumor immunity

Evading the host's immune response constitutes one of the prominent characteristics of tumors [15]. In vitro experiments, supra-physiological levels of NaHS inhibit lymphocyte proliferation and induce lymphocyte necrosis rather than apoptosis via the loss of mitochondrial membrane potential[16]. H_2S also exerts a diverse effect on macrophages, which can either enhance the immune response against tumors or play an immunosuppressive role, enabling tumor cells to evade immune surveillance. In a mouse tooth movement model induced by mechanical load, H_2S has a pro-inflammatory effect, and exogenous administration of H_2S elevates M1 macrophage levels, while CBS inhibitors reduce M1 macrophage levels. The pro-M1 macrophage polarization effect of H_2S is attributed to the activation of the STAT1 signaling pathway [17]. It was discovered that CBS is situated on the cell membrane of breast cancer cells, and the H_2S generated by CBS safeguards tumor cells from the damage inflicted by ROS produced by activated macrophages [18]. The molecular mechanism underlying the H_2S-mediated hypoxia-related inflammatory response remains incompletely understood and is likely associated with the oversulfidation of two transcription factors, namely NF-κB and hypoxia-inducible factor-1α (HIF1α) [19]. NF-κB is a crucial regulator of immune response, inflammation, and tumor. In quiescent cells, NF-κB is inhibited by the IκB protein and resides in the cytoplasm. In the state of infection and inflammation, the IκB kinase complex (IKK) is activated, leading to the inactivation of phosphorylated IκB suppressor proteins, followed by the translocation of NF-κB to the nucleus, initiating the transcription of related genes [20]. HIF1 is a heterodimer composed of oxygen-regulated HIF1α and constitutionally expressed HiF1β subunits. HIF1α rapidly degrades under normal oxygen conditions, but stably exists under hypoxia conditions and forms dimer with HIF1β. Both NF-κB and HIF1α control the expression of many downstream genes, which can be regulated by H_2S through post-translational modifications to enhance anti-tumor immune responses [20].

4. The Potential of H_2S as a Therapeutic Target

In tumor, H_2S has a bell-shaped effect of "low promotion and high inhibition", which provides two different strategies for tumor treatment, namely adding exogenous H_2S donors or inhibiting endogenous H_2S production. Endogenous H_2S can promote cancer by inducing angiogenesis, regulating mitochondrial bioenergy, accelerating cell cycle process and anti-apoptotic mechanism. Therefore, suppressing the production of H2S in cancer cells might constitute a novel therapeutic strategy for cancer. In contrast to the cancer-promoting role of H2S, relatively high concentrations of exogenous H2S can inhibit the growth of cancer cells through inducing unregulated intracellular acidification, causing cell cycle arrest, and facilitating apoptosis. [16].

Chemotherapy is a common cancer treatment, but its damage to normal tissue has been criticized. Untereiner et al found that CBS and 3-MST are upregulated and endogenous H_2S production is enhanced in 5' -fluorouracil resistant cells [21]. However, Stokes et al. found that DOX would lead to the decrease of H_2S content in cells, and after restoring H_2S level through exogenous donors, it was found that the efflux of doxorubicin slowed down, which could achieve a more effective chemotherapy[22].

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Pharoah et al. reported that hydropersulfide can reduce the ROS surge induced by adriamycin, enhance endogenous antioxidant defense, activate major regulators of mitochondrial function, and reduce caspase-3 activity, thereby reducing the potential cardiotoxicity induced by adriamycin. In addition, hydropersulfide may push cancer cells from REDOX equilibrium to reductive stress, thereby enhancing the anti-cancer effects of adriamycin in three different cancer cell lines [23]. In summary, H_2S has the potential to improve the shortcomings of chemical drugs on normal tissue damage and cell resistance. Dithiophosphate (GYY4137) is a synthetic water-soluble, hydrolysis-dependent H_2S sustained-release donor, which has vasodilatation, antihypertensive and anti-inflammatory effects. GYY4137 exhibits potent antitumor effects by inducing cell cycle arrest and promoting cell apoptosis. For example, GYY4137 significantly induced liver cancer cell death in HepG2 by decreasing glycolysis and reducing lactic acid overproduction, but the effect was not significant in non-tumor cells [24]. Lu et al. [25] found that GYY4137 inhibited STAT3 signaling pathway in HepG2 cells by reducing the phosphorylation level of STAT3 (Y705 site), and changed the expression of downstream STAT3 protein. Including cyclin D1, VEGF, HIF-1α and Caspase-3, they induce cell apoptosis and ultimately inhibit the proliferation, invasion and metastasis of tumor cells.

5. The Effect of Different Concentrations of H_2S on Tumors

The role of H_2S in tumor showed a bidirectional regulation mode of "low promoting and high suppressing", that is, low concentration of H_2S promoted tumor growth, while high concentration of H_2S inhibited tumor progression. Low concentration of hydrogen sulfide can promote tumor growth by inducing angiogenesis, accelerating cell cycle and inhibiting apoptosis. High concentration of H_2S can inhibit the proliferation and metastasis of tumor cells by inducing apoptosis and inhibiting key signaling pathways (such as NF-κB, PI3K/AKT/mTOR, etc.).

Table 1: The effect of different concentrations of H2S on tumors.

H_2S Concentration	Effect	Mechanism	Related research conclusions
Low Concentration	Cancer promotor	- Induces angiogenesis - Accelerates cell cycle - Inhibits apoptosis	- In colorectal cancer, selective expression of CBS (cystathione-β-synthase) is elevated, promoting tumor proliferation and invasion [26]
High Concentration	cancer suppressor	- Induce phosphorylation of multiple pathways, inhibit tumor progression - Up-regulate apoptotic markers (e.g. caspase-3/9, PARP) - Inhibit NF-κB, PI3K/AKT/mTOR, Ras/Raf/MEK/ERK signals	- In triple-negative breast cancer (TNBC), high concentration of H_2S inhibits tumor invasion and metastasis by inhibiting NF-κB, PI3K/AKT/mTOR and Ras/Raf/MEK/ERK signaling pathways [27] - In pancreatic cancer, high concentration of H_2S donor Erucin induces apoptosis by decreasing ERK1/2 phosphorylation [28]

6. Conclusion

In summary, H_2S readily permeates lipid bilayers, functioning as a versatile redox-active signaling molecule in biological systems, and it exerts anti-apoptotic effects in cancer cells through multiple mechanisms. First, at low concentrations, H_2S, through its inherently reducing properties, increases

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intracellular GSH levels and clears ROS by activating cysteine/cystine transporters. H_2S can directly induce the opening of ATP-sensitive potassium (KATP) channels, induce relaxation of vascular smooth muscle, and promote local blood supply of tumor. Mustafa et al. reported that H_2S can activate glyceraldehyde 3-phosphate dehydrogenase (GAPDH) involved in glucose metabolism through S-sulfhydrylation under hypoxia conditions, and improve the enzyme activity of GAPDH. Promotes anaerobic metabolism[14]. Beyond its role as a gaseous signaling molecule, H_2S modulates cancer cell apoptosis through site-specific S-sulfhydration of cysteine residues in key apoptotic regulators, such as ERK, JNK, and p3 controlling many pathophysical processes, ERK controlling cell growth and differentiation, and JNK and p38 playing significant roles in inflammation and apoptosis. The PI3K/Akt signaling cascade is another important intracellular signaling pathway that is closely linked to tumorigenesis, malignant progression, and drug resistance [29]. Additionally, it reacts to both extracellular and intracellular cues to support angiogenesis, growth, metabolism, proliferation, and cell survival [30]. Phosphatase and tensin homologue genes and PI3K-α are the two most often altered genes in the PI3K/Akt pathway, which is frequently seen in human malignancies. This mechanism can inactivate pro-apoptotic factor Bad and pro-apoptotic caspase 9, and decrease the expression of death ligand FasL[31]. H2S directly inhibits cell growth and triggers cell death by acting on NF-κB and Keap1, which are upstream and downstream of the p53 regulatory network. In addition to directly controlling numerous intracellular signaling pathways, H2S also has a role in controlling the tumor microenvironment [20][32].

By identifying the mechanism of H_2S in the process of apoptosis of cancer cells, H_2S can be applied to cancer therapy. Different concentrations of H_2S play a key role in tumor initiation and progression, providing two pathways for tumor treatment: adding exogenous H_2S donors or inhibiting endogenous H_2S synthesis. Therefore, improving the tumor specificity and biosafety of H_2S synthase inhibitors, as well as designing and developing sustained-release H_2S donors or H_2S-releasing mixed drugs as novel anti-tumor drugs will be future research hotspots, and may provide great value for the clinical diagnosis and treatment of tumors. In addition, most of the current mechanism studies are based on in vitro experiments and need to be further verified in animal models.

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