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Review

Hydrogen sulfide in cancer: Friend or foe?

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ABSTRACT

Hydrogen sulfide (H_2S) is the third gaseous signaling molecule that plays important roles in cancer biological processes. Recent studies indicate that H_2S has both pro-cancer and anti-cancer effects. Endogenous H_2S can exert pro-cancer functions through induction of angiogenesis regulation of mitochondrial bioenergetics, acceleration of cell cycle progression, and anti-apoptosis mechanisms. Thus, the inhibition of the production of H_2S in cancer cells may be a new cancer treatment strategy. In contrast to the pro-cancer effect of H_2S, relatively high concentrations of exogenous H_2S could suppress the growth of cancer cells by inducing uncontrolled intracellular acidification, inducing cell cycle arrest, and promoting apoptosis. Therefore, H_2S donors and H_2S-releasing hybrids could be designed and developed as novel anti-cancer drugs. In this review, the production and metabolism of H_2S in cancer cells are summarized and the role and mechanism of H_2S in cancer development and progression are further discussed.

Contents

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1. Introduction

Hydrogen sulfide (H_2S) was known only as an environmental pollutant for several centuries but is now widely considered an important biological and pharmacological mediator. In mammals, endogenous H_2S mainly comes from the metabolism of L-cysteine and homocysteine by the catalysis of two pyridoxal-5′-phosphate (PLP)-dependent enzymes, termed cystathionine γ-lyase (CSE) and cystathionine β-synthase (CBS). Both CSE and CBS are cytosolic enzymes [1–3]. 3-Mercaptopyruvate sulfurtransferase (3-MST), a PLP-independent enzyme, acts in combination with cysteine aminotransferase (CAT) to produce H_2S from L-cysteine in the presence of α-ketoglutarate [4]. CAT and 3-MST are localized in both the cytosol and mitochondria [1,5]. Once formed, H_2S can be immediately released or stored as bound and acid-labile sulfur in the cells [6].

H_2S has been recognized as the third endogenous gasotransmitter in mammals, along with nitric oxide and carbon monoxide [7–9]. A number of studies have shown that H_2S is involved in many physiological and pathophysiological functions [1,2,5,8–12]. Nevertheless, there has been some controversy on the role of H_2S in cancer development and progression. In multicellular organisms, normal cellular homeostasis is maintained through a balance between the processes of cell proliferation and cell death. Aberrations in cell survival could disrupt the normal cell cycle regulation and initiate tumor formation and metastasis [13–15]. In recent years, an increasing amount of evidence suggests that exogenously administered and/or endogenously produced H_2S could exhibit two obviously opposite functions on the growth of cancer cells [16–19]. Therefore, it is urgent and essential to illuminate the effect and mechanism of H_2S on the growth and proliferation of cancer cells.

In this review, we highlight recent studies that provide new insight into the production and metabolism of H_2S in cancer cells, as well as further discuss the role and mechanism of H_2S in cancer development and progression.

2. The production of H_2S in cancer

2.1. CSE

Accumulating evidence indicates that CSE plays important roles in many different types of cancer cells. For example, knockdown of CSE by shRNA or its inhibition by DL-propargylglycine inhibits the proliferation and migration of SW480 human colon cancer cells [20]. Similarly, CSE expression can be detected at both the mRNA and protein levels in human colon cancer HCT116 cells [8,21]. Marked CSE expression is also observed in WiRd, another colon cancer cell line [22]. These results suggest that CSE/H_2S may play a role in the progression of human colonic cancers. In hepatoma cells, endogenous H_2S production is connected with the regulated CSE expression, and the H_2S/CSE system is critical for maintaining cell proliferation [23,24]. The expression level and functional activity of CSE in C6 glioma cells have also been directly measured and confirmed [25]. S-propargyl-cysteine (SPRC), a structural analog of S-allycysteine, can significantly increase the protein expression and activity of CSE in human gastric carcinoma SGC-7901 cells [26]. Another study suggests that the expression of CSE mainly contributes to the endogenously produced H_2S in PC-3 prostate cancer cells [27]. Taken together, these results indicate that CSE may play an important role in cancer development and progression, and the underlying molecular mechanisms need to be intensively studied. The identification and development of specific CSE inhibitors may provide opportunities for cancer prevention and treatment.

2.2. CBS

CBS can also be detected in several types of cancer cells. For instance, there is little or no CBS in the normal prostatic peripheral zone epithelial cell line RWPE-1, while the androgen-dependent prostate cancer cell LNCaP has significant expression of CBS [28]. Similarly, compared with the nonmalignant colonic mucosa cells, colon cancer-derived epithelial cell lines exhibit selective CBS up-regulation and increased H_2S production [8,29]. In ovarian cancer cells, CBS expression is significantly high both at the protein and mRNA levels [30]. Moreover, human breast adenocarcinoma MDA-MB-468, MCF-7, and Hs578T cells exhibit significantly increased levels of CBS when compared with normal breast cells [31]. Recent studies have shown that the transcription factor Sp1 can be activated by estrogen-related receptor α1 (ERRα1) and plays an important role in regulating the expression of CBS in different cell types [32–36]. Whether ERRα1 could play a role in the expression of CBS in cancer cells needs to be further investigated. The expression level of CBS mRNA is low in hepatocellular carcinoma (HCC), but hypoxic conditions and irradiation could significantly enhance the protein level of CBS in the human HCC cell line HepG2 [37,38]. In gastric and colorectal cancers, CBS is suppressed by promoter methylation, and the methylation-mediated silencing of CBS could be reversed by genetic or pharmacologic demethylation [39]. Furthermore, decreased CBS expression could promote the development and progression of human gliomas [40]. Interestingly, the expression of CBS is not detected in leukemia cells, which suggests that CBS may exist primarily in solid cancers [41]. Therefore, it can be concluded that the expression of CBS changes markedly in different types of human cancers, and it has been shown to have cancer-specific characteristics. Further studies are needed to elucidate the precise mechanism of action of CBS in cancer cell proliferation, invasion and metastasis.

2.3. 3-MST

3-MST expression has also been observed in many cancer cells. The expression of the 3-MST gene is low in normal human epidermal melanocytes, whereas significantly higher expression of the 3-MST gene has been detected in a panel of human melanoma cell lines [42,43]. However, there is no obvious change in 3-MST protein expression between non-tumorigenic human colonic epithelial cells and colon carcinoma-derived cell lines [8,44]. Conversely, the activity of 3-MST in the human astrocytoma U373 cell line is lower than that in murine cortical astrocytes [45,46]. In human neuroblastoma SH-SY5Y cells, 3-MST expression at both the mRNA and protein levels has been confirmed [43,47]. 3-MST protein expression is also detected in the mitochondria of the murine hepatoma cell line Hepa1c1c7, suggesting that 3-MST-derived H_2S may serve as an inorganic source of energy and the electron donor to support adenosine 5′-triphosphate (ATP) generation and mitochondrial electron transport in mammalian cells [48,49].

3. The catabolism of H_2S in cancer

H_2S can be metabolized through several enzymatic and nonenzymatic processes in normal mammalian cells [50,51]. The main pathway of H_2S catabolism occurs in mitochondria [52]. H_2S could be converted into thiosulfate through several enzymes including quinone oxidoreductase, S-dioxygenase, and S-transferase. Thiosulfate is further metabolized to sulfate via the actions of thiosulfate reductase and sulfite oxidase [50,51]. H_2S can also be methylated by thiol S-methyltransferase to form methanethiol and dimethylsulfide in the cytosol [53]. The third pathway involves the interaction between H_2S and methemoglobin that leads to