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Hydrogen sulfide and cancer

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Abstract

Recent studies revealed increased expression of various hydrogen sulfide (H_2S) producing enzymes in cancer cells of various tissue types, and new roles of H_2S in the pathophysiology of cancer have emerged. This is particularly evident in cancers of the colon and ovaries, where the malignant cells both overexpress cystathionine-β-synthase (CBS) and produce increased amounts of H_2S, which enhances tumor growth and spread by (a) stimulating cellular bioenergetics, (b) activating proliferative, migratory, and invasive signaling pathways, and (c) enhancing tumor angiogenesis. Importantly, in preclinical models of these cancers, either pharmacological inhibition or genetic silencing of CBS was shown to be sufficient to suppress cancer cell bioenergetics *in vitro*, inhibit tumor growth and metastasis *in vivo*, and enhance the antitumor efficacy of front-line chemotherapeutic agents, providing a strong rationale for the development of CBS-targeted inhibitors as anticancer therapies. However, the observation that inhibition of H_2S biosynthesis exerts anticancer effects is contradicted by other studies showing that increasing H_2S with exogenous donors also exert antitumor actions. Herein, we present a brief review of the scientific literature documenting the function of H_2S, H_2S donors, and transsulfuration enzymes in cancers from various tissue types, and propose that the paradoxical actions of H_2S can be resolved by considering the bell-shaped pharmacology of H_2S, whereby lower (endogenous) H_2S production tend to promote, while higher (generated from exogenously added H_2S donors) tend to inhibit cancer cell proliferation. Finally, we suggest areas for future investigations to expand our knowledge of this nascent field.

Keywords

Cancer; hydrogen sulfide; mitochondria; bioenergetics; angiogenesis; proliferation; signaling

1. Biological roles of H_2S: a brief overview

Work over the last decade recognized the importance of endogenously produced H_2S in a variety of biological functions in the nervous, cardiovascular and immune system, in health and disease (reviewed in: Szabo, 2007; Kimura, 2011; Whiteman et al. 2011; Wang, 2012). The three principal enzymes involved in the physiological production of H_2S are CBS, CSE

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and 3-mercaptopyruvate sulfurtransferase (3-MST). For the purposes of the current article, we focus on the biological effects of H_2S that are relevant for cancer biology; these include the regulation of vascular function (physiologically: vasorelaxation and stimulation of angiogenesis) (reviewed in: Wang et al. 2010; Szabo and Papapetropoulos, 2011), regulation of cellular bioenergetics (physiologically: stimulation of mitochondrial electron transport and maintenance of cellular energetics (reviewed in: Szabo et al. 2014; Módis et al., 2014) and the regulation of intracellular signaling and cell death (physiologically, acting as a direct and indirect antioxidant and inhibiting oxidative damage and cell death in response to diverse stimuli) (reviewed in: Wang, 2012; Kolluru et al. 2013). Appreciating the complexities of H_2S biology requires familiarity with its pharmacology, including the fact that it is a labile, diffusible gas, and that it has a bell-shaped (or biphasic) dose-response curve, whereby lower concentrations (or lower rates of production) can exert markedly different (often, opposing) effects compared to the effects of H_2S seen at higher concentrations (or higher rates of production) (reviewed in: Szabo et al. 2014).

2. Role of endogenous H_2S production in colon cancer

In 2013 we have compared human colon cancer specimens with patient-matched normal mucosa tissue, and discovered that there is a selective upregulation of CBS in the cancer tissue, while the non-cancerous peritumor tissue has low CBS expression levels. The expression of the other two H_2S-producing enzymes, CSE and 3-MST did not show an upregulation in the tumor tissue. When subsequently checking several colon adenocarcinoma-derived cell lines (HCT-116, HT-29, LoVo), we have also observed a selective upregulation of CBS, as compared to the non-malignant colonic epithelial cell line NCM356. We have also conducted cell fractionation studies to test the localization of CBS in colon cancer cells. While CBS is traditionally viewed as a cytosolic enzyme, it can also be translocated to the mitochondria (Teng et al. 2013; Szabo et al. 2014). Our results revealed that CBS in the HCT116 cancer cells is present both in the cytosol, and in the mitochondria. As expected, homogenates of the patient-derived colon tumor specimens, as well as homogenates of the colon cancer-derived cell lines showed increased rates of H_2S production, and this response was inhibited by the prototypical CBS inhibitor compound aminooxyacetic acid (AOAA) (Szabo et al. 2013)

Next, we have studied the functional role of CBS-derived H_2S in the control of colon cancer cell proliferation, migration, and invasion *in vitro*, by a combination of genetic (shRNA-mediated stable silencing of CBS in HCT116 cells, or adenoviral overexpression of CBS in NCM356 cells) and pharmacologic (CBS inhibition by AOAA) approaches. Genetic silencing or pharmacological inhibition of CBS suppressed HCT116 cell proliferation, migration and invasion (Szabo et al. 2013). We have subsequently also used S-adenosyl-L-methionine (SAM), an allosteric activator of CBS; this compound, at low concentrations, increased HCT116 cell proliferation (Módis et al. 2014).

Part of the proliferative and pro-migratory effects of CBS-derived H_2S, are likely to be due to stimulation of Akt/PI3K signaling, as prior studies have demonstrated that exogenous H_2S donors stimulate HCT116 cell migration via activation of these pathways (Szabo and Hellmich, 2013). In addition, part of the effect of CBS-derived H_2S is due to mitochondrial,

bioenergetic stimulatory effects. We have observed that both the silencing of CBS and the inhibition of CBS with AOAA suppressed HCT116 bioenergetic functions (including basal electron transport and a bioenergetic parameter known as 'respiratory reserve capacity', which is quantified as the increase in mitochondrial oxygen consumption in response to a mitochondrial uncoupling agent.) (Szabo et al. 2013) CBS inhibition not only suppressed mitochondrial function, but also glycolytic function in HCT116 cells (Szabo et al. 2013), an effect, that may be attributable to the known stimulatory role of H_2S on the activity of GAPDH (Mustafa et al. 2009), an essential enzyme in the glycolytic pathway. Similar to the effects of the allosteric CBS activator SAM on proliferation, SAM, at low concentrations, increased HCT116 cell bioenergetic functions (Módis et al. 2014).

Subsequent studies in nude mice bearing xenografts of either HCT116 cells or patient-derived tumor tissue (PDTX) extended the findings into *in vivo* models. Silencing of CBS expression and/or pharmacological inhibition of CBS with AOAA significantly reduced the growth rate of the tumor xenografts. While we conclude that part of the effects of CBS inhibition seen *in vivo* are likely related to intratumoral mechanisms (i.e. inhibition of cancer cell metabolism and signaling), part of the effect may also involve paracrine mechanisms in the tumor microenvironment, because CBS silencing or CBS inhibition suppressed the density and complexity of CD31-positive blood vessels within the tumor tissue (indicative of reduced tumor angiogenesis). Furthermore, in line with the role of H_2S as a local vasodilator, direct injection of AOAA into the tumor parenchyma reduced peritumor blood flow (Szabo et al, 2013). In addition to reducing primary tumor growth, inhibition of CBS with AOAA decreased the metastatic spread of HCT116 cell from the cecum to the liver (i.e., decrease the number of metastatic lesions per area) in an orthotopic xenograft model in nude mice and, AOAA synergizes with the anti-metastasis effects of oxaliplatin in the same model (Bohanon et al. 2014).

In HCT116 cells, silencing or pharmacological inhibition of CSE did not exert any effects on HCT116 proliferation, migration or tumor growth *in vitro* or *in vivo* (Szabo et al, 2013). In contrast, in another human colon cancer cell line (SW480), high expression levels of CSE were observed; these levels were further increased by activation of the Wnt pathway in these cells. Moreover, pharmacological inhibition of CSE (with propargylglycine [PAG]) or genetic silencing of CSE attenuated cell proliferation *in vitro*. In addition, SW480 cells with CSE silencing tended to reduce tumor growth (significant reduction in tumor volume, but not in tumor weight) when injected into tumor-bearing nude mice (Fan et al. 2014).

The above findings are consistent with the conclusion that increased H_2S production (from CBS, but in other cell lines also from CSE) plays an essential role in colon cancer cell proliferation.

3. Role of endogenous H_2S production in ovarian cancer

Similar to colon cancer cells, CBS has been found to be overexpressed in primary epithelial ovarian cancer tissues, as well as in multiple ovarian cancer cell lines. When examining a collection of more than 200 patients' tissue microarrays constructed from primary epithelial ovarian cancers, Bhattacharyya and colleagues we found high expression of CBS in primary

ovarian tumors, particularly in serous carcinoma, the most common histologic variant. Tumors that had serous histology and higher grade cancers tended to contain higher levels of CBS. CBS expression was already strong in most of the early stage (FIGO stages I and II) ovarian cancers studied (Bhattacharyya et al. 2013). In additional studies, quantitative RT-PCR and immunoblotting were used to compare the expression of CBS mRNA and protein levels in a variety of ovarian cancer cell lines, when compared to a control, non-malignant ovarian surface epithelial cell line (OSE). Most ovarian cancer cell lines studied showed high CBS expression (both at protein and mRNA level). CSE was not found to be overexpressed in ovarian cancers, but it was found in the normal ovarian epithelial cell line. Similar to the colon cancer study (see above), CBS exhibited significant mitochondrial localization in A2780 cells (Bhattacharyya et al. 2013).

Next, Bhattacharyya and colleagues studied the functional role of CBS-derived H_2S in the control of ovarian cancer cell proliferation, migration, and invasion *in vitro*, by a combination of genetic (siRNA-mediated stable silencing of CBS in A2780, A2780/CP-70, OV202 and SKOV3 cells cells) and pharmacologic (CBS inhibition by AOAA) approaches. Downregulation or inhibition of CBS was found to inhibit cell proliferation *in vitro*, and AOAA treatment (especially at higher concentrations) also reduced cell viability. When studying the intracellular mechanisms responsible for these actions, Bhattacharyya and colleagues found that downregulation or inhibition of CBS reduces the intracellular content of the key antioxidant glutathione (GSH+GSSG), and triggers apoptotic cascades. This latter effect may well the consequence of the intracellular antioxidant depletion after CBS inhibition/silencing. Another important consequence of the CBS silencing or CBS inhibition was an increase in cellular reactive oxygen species levels; this effect may well be secondary to antioxidant depletion (see above) or it may also be related to changes in mitochondrial function (see below). Finally, silencing CBS in A2780 cells also affected intracellular signaling pathways: Bhattacharyya and colleagues found that CBS silencing increases the expression of p53, while the expression of the RelA/ p65 subunit of NF-κB was decreased (Bhattacharyya et al. 2013).

Similar to the study in colon cancer cells, H_2S in ovarian cancer cells supports mitochondrial function and cellular bioenergetics. Bhattacharyya and colleagues found that silencing of CBS reduced mitochondrial oxygen consumption, and similar effects were seen when ovarian cancer cell lines were treated with the CBS inhibitor AOAA. Additional consequences of CBS silencing and/or CBS inhibition were (a) an increase in mitochondrial ROS production, (b) a decrease in intracellular NAD/NADH ratio, (c) a reduction in ATP synthesis and an increase in ADP/ATP ratio (Bhattacharyya et al. 2013).

Subsequent studies in nude mice transplanted with A2780/CP-20 xenografts extended the findings into *in vivo* models. Silencing of CBS resulted in a significant, approximately 40% reduction in tumor weight and an even more marked (approximately 70%) decrease in the number of tumor nodules. The reduction by CBS silencing of the proliferative capacity of the cancer cells was confirmed with Ki-67 staining. In addition (and similar to the colon cancer study discussed above), CBS silencing resulted in an inhibition of peritumor angiogenesis, as evidenced by a reduction of CD31 staining (Bhattacharyya et al. 2013).

Last, but not least, Bhattacharyya and colleagues also demonstrated that inhibition of CBS sensitizes the cancer cells to concomitant chemotherapy *in vitro* and *in vivo*. *In vitro*, CBS silencing of A2780 cells shifted the IC_{50} of cisplatin from 13.1 mM to 7.9 mM. *In vivo*, the combination therapy of CBS siRNA and cisplatin produced a dramatic reduction in tumor weight and number of tumor nodules (both effects approximately 80-90%), when compared to the group that received cisplatin alone (Bhattacharyya et al. 2013).

4. Lack of functional role of endogenous H_2S production in melanoma

In contrast to colon cancer cells and ovarian cancer cells, Panza and colleagues found that CBS is not overexpressed in human nevi (compound, junctional or dysplastic forms). Likewise, in samples of human primitive melanoma, CBS and 3-MST displayed a variable, but always very low level of expression. Furthermore, four distinct human melanoma cell lines (A375, Sk-Mel-5, Sk-Mel-28 and PES 43), when compared in normal human epidermal melanocytes (NHEM) showed no increase in CBS expression. In contrast, another H_2S-producing enzyme, CSE exhibited significantly higher expression in all of the nevi, melanoma samples and melanoma cell lines studied (Panza et al. 2014).

In order to evaluate whether the various H_2S-producing enzymes had a functional effect on the proliferation of human melanoma cell line, A375 cells were transiently transfected with siRNAs for either CBS, CSE or 3-MST. Silencing of these enzymes did not affect melanoma cell proliferation (Panza et al. 2014). These data indicate that in melanoma (as opposed to colon cancer and ovarian cancer), the expression of H_2S-producing enzymes does not have an endogenous stimulatory role on cell proliferation.

5. CBS silencing accelerates the development of glioma

To assess the role of CBS in glioma tumorigenesis, Takano and colleagues established a subclone of U87-MG glioma cells with stable silencing of CBS. When subcutaneously or orthotopically injected into the flank of SCID mice, the subclone with CSE silencing exhibited a shorter latency period for tumor growth, as well as a more pronounced overall tumor growth rate. In addition to greater tumor volume, the CBS silenced tumors exhibited increased depth of invasion, vascular density, cell proliferation, and more apoptosis (Takano et al. 2014). These findings unveil a role of CBS in glioma that is markedly different from its role in colon cancer or ovarian cancer. As far as the mechanisms responsible for the observed effects, in vitro studies by Takano and colleagues showed that glioma cells respond to CBS silencing with increased VEGF and ANGPTL4 levels, higher HIF2a expression and increased anchorage-independent cell growth (Takano et al. 2014).

6. Changes in H_2S-producing enzymes in other forms of cancer

A limited number of studies are available that detect significant changes in various H_2S-producing enzymes in other forms of cancer. Perhaps the most detailed study was conducted by Guo and colleagues in human prostatic tissues and prostate cancer tissues. In normal prostatic tissue, CBS and CSE were both detected in the prostatic epithelium, while the periacinar stroma cells contained CSE, but not CBS. LNCaP (an androgen-dependent prostate cancer cell line) exhibited marked CBS and CSE expression; this is in marked

contrast with the low expression of CBS and CSE in RWPE-1 (a normal prostatic peripheral zone epithelial cell line). A lesser degree of CBS and CSE expression was seen in several other prostatic cancer lines. Both CBS and CSE were identified primarily cytoplasmic. Guo and colleagues did not investigate the effect of silencing or pharmacological modulation of CBS or CSE on the proliferation rate of LNCaP cells. However, they have tested dihydrotestosterone (DHT) on the expression of CBS and CSE and found that it increased the expression of both CBS and CSE in LNCaP cells (Guo et al. 2012). Other cancer cell types where the expression of CBS has been demonstrated include myeloma (De Vos et al. 2002), biliary track carcinoma (Hansel et al. 2003), and a significant portion of the cells contained in the NCI60 collection; with most consistent/highest increases seen in most breast cancers and most renal cancers present in the collection (Zhang et al., 2005). None of these studies have investigated the functional effect of modulation of H_2S synthesis in these cancer cell lines.

7. H_2S donors and cancer

There is an apparent paradox in the literature, since many reports (discussed in the previous sections) show that inhibition of H_2S biosynthesis exerts anticancer effects, while many studies show that H_2S donors of various types exert anticancer actions *in vitro* and *in vivo* (overviewed in: Hellmich et al. 2014). In addition, treatment of the recipients with high doses of the CBS/CSE substrate L-cysteine has been shown to increase the growth of melanoma (Panza et al. 2014). This paradox can be resolved by considering the bell-shaped pharmacology of H_2S, whereby lower (endogenous) H_2S production tend to promote, while higher (generated from exogenously added H_2S donors) tend to inhibit cancer cell proliferation (see for review: Hellmich et al. 2014).

8. Conclusions and future directions

Although limited in terms of quantity and mechanistic detail, there is a reasonable body of evidence suggesting that endogenous H_2S production is important for the growth and proliferation of at least two types of cancer: colon cancer and ovarian cancer. The data show that melanoma does not rely on endogenous H_2S production for its growth and proliferation, while in glioma, CBS silencing, in fact, accelerates tumor proliferation. It is reasonable to hypothesize that different types of cancer utilize different H_2S-associated pathways, and that the linking of these pathways to proliferative and cell survival/cell death mechanisms is tumor-cell-type dependent. The field of H_2S in cancer is a young one, where, (as overviewed in Hellmich et al. 2014), additional work is necessary in many areas, including **(a)** studies to further delineate the mechanism of upregulation of H_2S-producing enzymes in cancer cells; **(b)** studies aimed to 'place' the H_2S-related energetic mechanisms into the overall scheme of tumor cell bioenergetics; **(c)** additional work on clinical samples, including biomarkers of H_2S production in patients with cancer; **(d)** studies aimed at 'connecting' the H_2S pathway in cancer cells to various known pathways of cell proliferation and death/survival signaling; **(e)** further studies focusing on the interaction of tumor cell-derived H_2S with its microenvironment including cancer stem cells; **(f)** investigations not only into changes in the expression/activity of H_2S-producing enzymes, but also enzymes involved in its metabolism and degradation; **(g)** studies exploring potential interactions of the H_2S system with other

gaseous mediators in cancer, such as nitric oxide and carbon monoxide; and **(h)** pharmacological and drug discovery studies into improved CBS inhibitors for the therapy of cancer, in forms of cancer where the preclinical data warrant such expansion.

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