H2S and DNA Repair

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Hydrogen sulfide (H2S) is a gasotransmitter that exerts numerous physiologic and pathophysiologic effects. Recently, a role for H2S in DNA repair has been identified, where H2S modulates cell cycle checkpoint responses, the DNA damage response (DDR), and mitochondrial and nuclear genomic stability.

H2S | hydrogen sulfide | DNA repair | cystathionine β-synthase | ATR | MEK1

1. Introduction

The maintenance of genomic stability is essential for life, and cells have evolved complex and intricate molecular machinery to ensure DNA stability and accurate DNA replication [1][2][3][4]. Eukaryotic cells carry two separate genomes with different evolutionary origins [4][5]. The nuclear genome is diploid, linear, and in humans contains roughly 3.3 billion base pairs encoding over 20,000 genes [4][5]. Conversely, the mitochondrial genome is circular, contains 37 genes in 16,569 base pairs, and occurs in multiple copies at 100–1000/cell [4][5]. The two genomes extensively interact, with the nuclear genome encoding roughly 1500 mitochondrial proteins, including those involved in mitochondrial DNA repair, while mitochondrial genomic damage can initiate apoptotic cell death via cytochrome c release and can also activate the innate immune response [4][5][6][7]. Hydrogen sulfide (H_2S) is a gasotransmitter that, along with nitric oxide and carbon monoxide, functions in a vast number of different physiologic and pathophysiologic processes [8][9]. Specifically, H_2S has many physiologic regulatory roles, including in the renal, cardiovascular, central nervous, and digestive systems, and is also dysregulated in many different pathologic processes including cancer, cardiovascular diseases, and neurodegeneration [10][11][12][13][14][15][16][17]. Recently, H_2S has been found to regulate mitochondrial and nuclear DNA stability and repair [11][12][13].

2. Life’s Origin and H_2S

2.1. Life’s Origin and H_2S

Biochemical, fossil, and molecular clock dating methods indicate that life first appeared 3.7 to 4.2 billion years ago in a reducing, ferruginous, and euxinic environment probably at hydrothermal vents rich in NH_3, N_2, CO_2, CO, CH_4, H_2, H_2S, and dissolved metals, especially Fe^{2+} and Mn^{2+} [18][19][20][21][22][23]. Due to the fact of its ubiquity on the early Earth and versatile chemistry, H_2S likely played an essential role in prebiotic chemistry and the emergence of life [20][22][23]. Support for this comes from analyses demonstrating that reactive oxygen and reactive sulfur species detoxifying mechanisms have been present since the origin of life, some four billion years ago, and have continued to the present in the biochemistry of the Archaea, Bacteria, and Eukarya [18][19][20][21][22][23][24]. Since genomic

stability maintenance is an ancient and absolute requirement for life, and H_2S biochemistry is similarly ancient and ubiquitous, it is very likely that H_2S functioned in the earliest biochemical pathways including in those regulating genomic stability [1][2][3][11][12][13][17][20][21][22][23][24][25][26].

2.2. H_2S and the DNA Damage Response

The DNA damage response (DDR) comprises a complex network of cellular pathways that cooperatively detect DNA damage, signals its presence, and promotes DNA repair, maintaining genomic stability [1][2][3]. Phylogenomic analyses indicate that many elements of the Eukaryotic DDR are ancient, appearing in the first Metazoa and subsequently undergoing evolutionary diversification [27].

Extensive evidence indicates that H_2S affects cell DNA stability, impinging on the DDR and cell viability. For example, when the nuclei from Chinese hamster ovary cells were treated 2 h with 1 µM Na_2S, they exhibited significant DNA damage that was attenuated by treatment with the antioxidant butyl-hydroxyanisole [28]. Treatment of two glioblastoma cell lines with a high amount of Na_2S (476 µM) for 4 h, increased DNA damage, oxidative stress levels, and increased γ-H2AX foci formation [29]. Additionally, treatment of human intestinal epithelial cells with very high (1–2 mM) Na_2S induced DNA breaks as measured by the comet assay [30]. Similarly, human lung fibroblasts treated 12 h with 10 µM NaHS showed micronuclei formation, increased p21, p53, Bax, cytochrome c, Ku-70 and Ku-80 expression, and a G_1 checkpoint response [31]. These studies implicate H_2S in the DDR as; (1) broken DNA activates the DDR, (2) γ-H2AX foci formation requires the activities of the DDR proteins ATM, ATR, and DNA-PK, (3) the Ku70/Ku80 heterodimer associates with DNA-PK to promote DNA repair, and (4) the ATM kinase is required for the oxidative stress-induced G_1 checkpoint response and rapid p53 induction [1][2][3][32].

Other studies have shown that H_2S can increase/preserve DNA stability. For example, in a murine model, a unilateral nephrectomy with contralateral ureteral obstruction suppressed H_2S kidney levels and caused more DNA damage in CSE deficient mice compared to wild-type mice, indicating that CSE expression plays a role in maintaining DNA stability upon ischemia/reperfusion injury [33]. Additionally, daily injection of the H_2S donor diallyl sulfide intraperitoneally into female rats at 50 mg/kg induced p53, Gadd45a, PCNA, and DNA polymerase δ in their breast tissue, suggesting that H_2S enhances breast tissue DNA repair capacity [34]. Interestingly, exogenous H_2S also affects the mitochondrial genome. For example, CSE deficient murine smooth muscle and aortic tissue showed reduced mitochondrial DNA copy numbers, mitochondrial content, mitochondrial-specific mRNAs (*MT-CO1*, *CytB*, and *Atp 6*), and mitochondrial transcription factor A (TFAM) mRNA and protein expression, and it elevated DNA methyltransferase 3A (Dnmt3a) expression, accompanied by increased global DNA methylation with increased TFAM promoter methylation [35]. Treatment with 30 and 60 µM NaSH for 48 h reversed these effects, with increased mitochondrial marker expression (mitochondrial DNA copy numbers, mRNAs, and mitochondrial content) and decreased Dnmt3a and TFAM promoter methylation, increasing TFAM expression [35]. This study indicates that CSE-derived H_2S plays an important role in the maintenance of mitochondrial function and genomic stability. Lastly, 30–100 nM concentrations of AP39, a mitochondria-targeted H_2S donor, increased endothelial cell H_2S levels and stimulated mitochondrial electron transport and bioenergetic functions. Treatment of the endothelial cells with oxidative stress increased reactive oxygen species (ROS), reduced cell viability, suppressed cellular

bioenergetics, and increased mitochondrial DNA damage, events reversed by 100 nM AP39 treatment [36]. Taken together, these studies indicate that under different conditions H_2S can increase DNA damage or suppress it and also impinges on the DDR. A caveat to keep in mind is that many experimental procedures in these studies used high concentrations of H_2S donors that are likely non-physiologic [29][30]. Additionally, many studies of H_2S biology use H_2S synthesis inhibitors that have low specificity, complicating experimental result interpretation (reviewed in [37]).

3. H_2S and Mitochondrial DNA Repair

The mitochondria are the major cellular site for ROS generation, and the mitochondrial genome is subject to significant DNA, protein, and lipid oxidative damage [38]. Mitochondrial DNA repair is distinct from and, in general, less complex than the nuclear DNA repair systems. For example, base-excision repair (BER) predominates, while nucleotide excision repair (NER) is absent [5][39]. Moreover, mitochondrial genomes with double-stranded DNA (dsDNA) breaks are usually rapidly degraded, leading to a drop in genome copy number, which are replaced through non-cleaved genome replication, often leading to a shift in heteroplasmy [5]. A role for H_2S in mitochondrial function is well established with, for example, the mitochondrial H_2S donor AP39 promoting mitochondrial bioenergetics and genomic stability and in the face of exogenous oxidants [36]. Additionally, in ovarian cancer cell lines, CBS expression maintains mitofusin-2 expression, with CBS knockdown lowering mitofusin-2 expression, causing mitochondrial fragmentation with a fused spherical morphology and increased unbranched mitochondria [40]. Mitofusin-2 exerts anti-apoptotic effects, and its ablation is lethal in mice [41]. Interestingly, its expression is lower in obesity, diabetes, and in animal models prone to atherosclerosis, and is increased by weight loss and exercise [41].

The apyrimidinic/apurinic endonuclease 1 (APE1), exonuclease G (EXOG), DNA Ligase III (LIG3), and DNA polymerase gamma (Pol γ) play central roles in mitochondrial BER [4][11][42][43][44]. Loss of these proteins has severe often lethal effects. For example, EXOG depletion induces persistent single-stranded DNA breaks leading to apoptosis, while APE1 ablation is embryonic lethal, and its removal by Cre expression causes apoptotic cell death within 24 h [42][43]. In the A549 lung adenocarcinoma cell line, siRNA knockdown of CBS, CSE, or 3-MST or treatment with the CSE-specific inhibitor D, L-propargylglycine (PAG) combined with exogenous oxidative stress significantly increased mitochondrial DNA damage [11]. Interestingly, the interactions of EXOG with APE1, LIG3, and POL were all attenuated with CBS, CSE, or 3-MST knockdown or pharmacologic CBS inhibition by aminooxyacetic acid (AOAA) [11]. The interactions of EXOG with APE1 or LIG3 following AOAA treatment were restored and mitochondrial DNA damage was reduced with AP39 co-treatment, demonstrating that mitochondrial H_2S restored these interactions and increased mitochondrial genomic stability [11]. Mass spectrometric analysis revealed that EXOG Cys 76 was sulfhydrated, with the H_2S donor NaHS increasing EXOC and APE1 interactions. Mutation of EXOG Cys 76 to alanine lowered its interactions with APE1 and made the interaction insensitive to NaHS treatment [11]. Thus, this elegant study demonstrated that mitochondrial H_2S plays a central role in mitochondrial genomic stability and DNA repair.

4. H_2S and Nuclear DNA Repair: ATR and MEK1

4.1. ATR

Nuclear DNA repair and the DDR involve at least five major pathways comprising BER, NER, mismatch excision repair, homologous recombination, and non-homologous end joining [1][2][3]. The *ataxia-telangiectasia mutated,* and RAD3-related serine/threonine protein kinase (ATR) plays a central role in the DDR, where it stabilizes single-stranded DNA (ssDNA) at stalled replication forks, lowers replication stress, initiates cell cycle checkpoints, and promotes faithful anaphase chromosomal segregation [1][2][3][12]. Interestingly, increased ATR/phospho-ATR expression is a poor prognostic factor in breast, bladder, and ovarian cancers [45][46][47]. Analysis of a colon adenocarcinoma cell lines with wild-type and biallelic knock-in hypomorphic ATR Seckel syndrome 1 genes revealed lower cellular H_2S levels in the mutant cells compared to the wild type [12]. ATR inhibition with the pharmacologic ATR inhibitor NU6027 also significantly lowered cellular H_2S levels in the wild-type but not the mutant cells [12]. Treatment of both cell lines with the CBS/CSE inhibitor β-cyano-L-alanine suppressed H_2S levels in both cell types, demonstrating that cellular H_2S levels are regulated by CBS/CSE and ATR, which form separate regulatory foci [12].

Interestingly, ATR activation correlates with serine 435 phosphorylation, an event also required for ATR-XPA dimer formation and subsequent NER [12][48]. Treatment of the colon adenocarcinoma cell lines with β-cyano-L-alanine increased this phosphorylation, while treatment with the H_2S donor diallyl trisulfide significantly suppressed it in the wild-type but not mutant cells. UV light and oxidative stress treatments similarly induced this phosphorylation in the wild-type but not mutant cells [12]. Activated ATR phosphorylates the CHK1 kinase serine 345, leading to its activation [1][2][3][12]. When the cells lines were pretreated with β-cyano-L-alanine, followed by a low concentration of oxidative stress, oxidative stress-induced CHK1 phosphorylation increased with H_2S synthesis inhibition, an event again not seen in the mutant cells [12]. Lastly, to examine the effects of these events on genomic stability, oxidative stress-induced dsDNA breaks were quantified in both cell types with and without H_2S synthesis inhibition by β-cyano-L-alanine treatment. H_2S synthesis inhibition caused low levels of oxidative stress to significantly induce dsDNA breaks, where otherwise they were not increased [12]. The mutant cells also showed increased breaks compare to the wild-type cells [12]. Taken together, these finding indicate that ATR regulates cellular H_2S levels and H_2S, in turn, regulates ATR phosphorylation, ATR kinase activity, and nuclear genomic stability [12].

4.2. MEK1

An important initial and required step in the DDR is carried out by poly (ADP-ribose) polymerases (PARPS) that transfer ADP-ribose from NAD^+ to glutamic acid residues on a protein acceptor, creating ADP-ribose polymers at sights of DNA damage [1][2][3][49]. These chains function in the recruitment of factors involved in DNA repair such as polymerase β, XRCC1, and ligase IIIα [1][2][3][50]. PARP activation is tightly regulated by a cascade of kinases including the MEK/ERK signaling pathway [1][2][3][50][51][52]. In an interesting study, treatment of human endothelial cells for 2 h with 10 μM NaHS increased MEK1 Cys 341 S-sulfhydration. This event resulted in ERK1/2

phosphorylation and its subsequent translocation into the nucleus, where it activated PARP-1 through a direct interaction [13]. Mutation of MEK1 Cys 341 to Gly blocked these events.

Next HEK293 cells were treated with methyl methanesulfonate (MMS), which induces ssDNA and dsDNA breaks and activates PARP-1 activity, with PARP-1 then recruiting XRCC1 and DNA ligase III to initiate DNA repair [13][51][52][53]. MMS treatment of the HEK293 cells resulted in MEK1 Cys 341 S-sulfhydration, but not in cells carrying the Gly 341 mutated MEK1 [13]. This S-sulfhydration increased in CSE over-expressing HEK293 cells. Lastly, application of MMS to human endothelial cells, with and without co-treatment with 0.1–10 μM NaHS, increased PARP-1 activity in a dose-dependent manner, with PARP-1 activation detectable at 5 min with NaHS treatment and only at 30 min without NaHS treatment [13]. NaHS treatment also reduced the amount of HEK293 cell DNA damage and increased the amounts of XRCC1 and DNA ligase III recruited [13]. This study indicates that CSE-generated H_2S acts as a DNA damage protectant, S-sulfhydrating MEK1 Cys 341, activating ERK1/2 and PARP-1 to repair DNA damage [13].

These studies on the roles of ATR and MEK1 in nuclear DNA repair demonstrate that H_2S plays an important and, as yet, poorly defined role in nuclear DNA repair regulation [12][13]. Interestingly, low cellular H_2S concentrations activate ATR, as measured by its kinase activity towards CHK1 [12]. Conversely, MEK1 activity in DNA repair is increased with increased H_2S concentrations, as supplied either by exogenous NaHS or increased CSE expression [13]. Thus, these studies imply that nuclear DNA repair is likely modulated by both increased and decreased cellular H_2S concentrations [12][13]. Additionally, CBS and CSE knockdown both attenuated the mitochondrial interactions of EXOG with APE1, LIG3, and POL γ, implying that ATR may also indirectly regulate mitochondrial BER [11][12].

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