Review

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A potential role of hydrogen sulfide (H_2S) in regulation of the Ras-ERK signaling-dependent transcription of DNA methyltransferases

T. A. Nikitina

Oles Honchar Dnipropetrovsk National University
72, Gagarin Av., Dnipropetrovs'k, Ukraine, 49050
tatyana-dudkova@mail.ru

The Ras-ERK cell signaling regulates transcription of DNA methyl-transferases (DNMTs). A role of H_2S in regulation of the Ras-ERK signaling activity and DNMTs expression has also been shown. Here we propose a hypothesis that H_2S regulates the Ras-ERK signaling-dependent DNMTs transcription. Oxidative stress, lipid metabolism, protein sulfhydration, nitrosylation and nitration are the main targets of regulation by H_2S. These cell processes are important for the post-translational modifications (PTMs) of the Ras-ERK signaling pathway enzymes. We provide evidence for the dependence of DNMTs transcription on the PTMs of the enzymes of the Ras-ERK signaling pathway regulated by H_2S.

Keywords: Ras-ERK cell signaling, DNA methyltransferases, H_2S

Introduction

DNMTs are the group of enzymes that catalyze methylation of cytosine nucleic acids in CpG dinucleotide sequences of DNA. The product of this reaction is 5-methylcytosine (Fig. 1) [1, 2]. The main substrate of DNMTs is

S-adenosinemethionine (SAM) converted to S-adenosinehomocysteine (SAH) as a result of the reaction. SAH is a DNMTs concurrent inhibitor that is why SAH utilization is important for the DNMTs activity [3]. The methionine cycle is a cascade of reactions which provides the SAM biosynthesis and SAH utilization [3, 4].

In the last decade more attention has been paid to the metabolite of the methionine cycle hydrogen sulfide (H_2S). H_2S is biosynthesized by many organisms, including humans. There are three basic routes of H_2S biosynthesis in humans: 1) enzymatic condensation of two homocysteine molecules (30 % of total H_2S production); 2) enzymatic condensation of

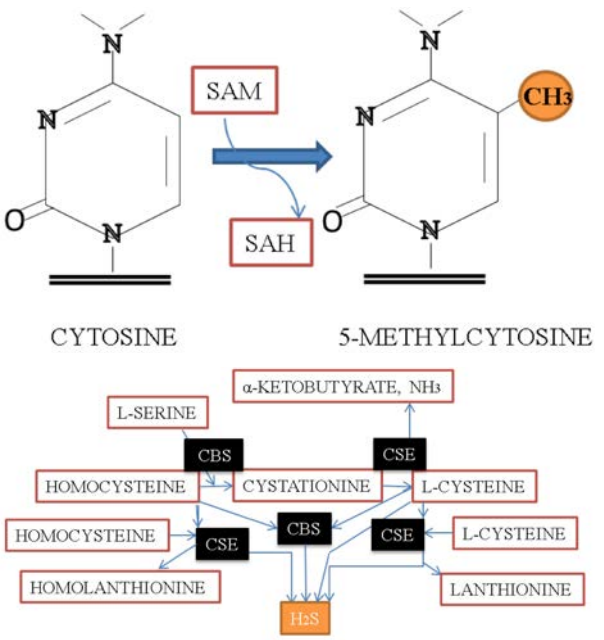

Fig. 1. *A* – Schematic representation of the conversion of cytosine to 5-methylcytosine (the author). *B* – Schematic representation of the main enzymatic routes of H_2S biosynthesis in humans (the author).

cysteine and homocysteine (25–70 % of total H_2S production); 3) enzymatic cysteine conversion to H_2S, pyruvate and NH4+. The second reaction is catalyzed by Cystationine-beta-Synthase (CBS) others are catalyzed by Cystathionine-gamma-Lyase (CSE) [5, 6].It is now known that H_2S is a substrate for post-translational modification of a protein, called sulfhydration [7]. Furthermore, H_2S is an important element of the antioxidant system [8], as well as a regulator of the lipid [9–12] and NO metabolism [13–16].

We hypothesized an important role of H_2S in the Ras-ERK signaling pathway regulation of the DNMTs transcription through above-mentioned mechanisms. Indeed, there are a lot of studies on the Ras-ERK signaling and DNMTs transcription regulation by H_2S upon the oxidative stress conditions [17–19]. We also pointed out to the proteine sulfhydration and nitrosylation as well as lipid metabolism as new potential regulation targets of H_2S important for the Ras-ERK dependent DNMTs transcription.

General characterization of the DNMTs expression regulation

There are three active DNMTs in humans – DNMT1, DNMT3a, DNMT3b. DNMT1 catalyzes methylation per sample, saving methylation pattern during cell division. DNMT3a/3b are de novo methyltransferases. Two isoforms, DNMT2 and DNMT3L, show a very weak activity [20, 21]. The main function of DNA methylation is down-regulation of the gene expression. It is important for X-chromosome inactivation, gene imprinting, and cell-specific gene expression [22–24].

The regulation of DNMTs is performed at the transcriptional and post-transcriptional levels. There is an evidence of Sp1 and Sp3 transcriptional regulation of DNMT1, DNMT3a, DNMT3b [25, 26], DNMT3b down-regulation by FOXO3a and DNMT3a down-regulation by p53 [27, 28]. Most of the studies are dedicated to the DNMT1 regulation. It is well known that the transcription of DNMT1 is regulated by Ras/AP-1 and RB/E2F signaling [29–31]. It is also possible to observe phosphorylation by kinases C, α, βI, βII, δ, γ, η, ζ μ and acetylation by Tip60, HAUSP, UHRF1, HDAC1, PCNA as the main PTMs of DNMT1 [32–33].

So, DNMTs are under a tight control of cell signaling at the transcriptional and protein biosynthesis levels. That is why the great prospects are opened for researches to affect DNA methylation through cell signaling pathways. Thus, the researches have a great potential to affect DNA methylation through cell signaling pathways.

General description of the DNMTs transcription regulation by the Ras-ERK signaling

ERK ½ (extracellular signal-regulated kinase), also known as p42⁄p44MAPK or MAPK1 and MAPK3, are isoforms of MAPK (mitogen-activated protein-kinases) belonging to the family of proteins-transduced signals from the plasma membrane to the nucleus. The activation of plasma membrane receptors results in induction of the Ras-Raf-MEK-ERK phosphorylation cascade, which leads to ERK nucleus translocation and transcription initiation. However, besides their action in the nucleus, ERK are also impotent cytoplasmic signaling proteins [34].

There is a line of *in vitro* studies on the role of the Ras-ERK signaling regulation of the DNMTs transcription [35–39]. The first studies were carried out with the human adrenocortical cancer and mouse embryonal teratocarcinoma cell lines [35, 36]. In the experiment with adrenocortical cell line bearing amplified *ras* gene, the authors demonstrated the Ras dependent DNMT1 expression at the transcriptional level [35]. The experiments with mouse embryonal teratocarcinoma showed similar results [36]. Both studies highlighted the AP-1 transcriptional regulation of the *dnmt1* gene promoter. It was shown that the gene promoter of *dnmt1* bears AP-1 transcriptional sites [37].

Besides the *dnmt1* expression regulation through AP-1 transcriptional sites by ERK, there are two *in vitro* issues dwelling on the role of ERK in the transcriptional regulation of DNMT 3a and DNMT3b employing unknown mechanisms [38, 39]. The ex-

periments with TGF-b1 treatment of the prostate cancer cell line demonstrated the dependence of the ERK nuclear localization on DNMT1, DNMT3a, DNMT3b mRNA and protein expression [38]. The studies on the colon cancer cell line demonstrated no correlation between DNMT3a and DNMT3b expression levels regarding ERK and MEK activity and protein level, but showed such correlation for the DNMT1activity and the protein level [39].

Consequently, there is an evidence of strong dependence of DNMT1 expression on the Ras-ERK signaling. Moreover, the mechanism of the DNMT1 transcription regulation by ERK-AP-1 pathway is well described [29, 30, 38]. There are controversial data about [31, 32]. The data on DNMT3a and DNMT3b transcription by the Ras-ERK signaling are controversial, which gives room for further research in the field.

H_2S-dependent routes of the DNMTs transcription regulation by the Ras-ERK signaling

Regulation of the Ras-ERK signaling-dependent DNMTs transcription by sulfhydration

H_2S is a substrate of the cysteine residue sulfhydration reaction, PTM of proteins. There is a growing number of studies on the role of protein sulfhydration in the cell signaling [7]. Some of them are dedicated to the Ras-ERK signaling dependence on the sulfhydration, the level of H_2S concentration and the activity of H_2S producing enzymes [41–43]. It is well-known that the ERK proteins dissociate from binding partner MEK and undergo activation-based phosphorylation to perform their function [35]. There are *in vitro* experiments that show the H_2S dependent ERK phosphorylation. For example, the treatment of mouse cardiomyocytes with H_2S donor (NaHS) induces ERK phosphorylation, while inhibition of the endogenous production of the gas has an opposite effect [41]. The identical treatment conditions for the mouse embryonal cortical neuron culture led to similar results [42]. Moreover, the authors use different inhibitors to show that the NaHS regulation of ERK phosphorylation depends on the MEK1 activity.

The mechanism of such H_2S-dependent effect on ERK phosphorylation was later discovered by K. Zhao and his colleagues. This research group showed MEK1 sulfhydration at cysteine 341 in experiments with the human endothelial cells, fibroblasts and CSE knockout mice. In these experiments MEK1 sulfhydration induced ERK phosphorylation and nucleus translocation [43].

In the light of the above-mentioned mechanism of DNMT1 transcription through AP-1 sites, H_2S donors and CBS or CSE inhibitors can affect MEK1 sulfhydration and subsequent ERK activation and DNMT1 transcription. This field of research is open and may represent interest for further studies in molecular biology.

Regulation of the Ras-ERK dependent DNMTs transcription by redox activity of H_2S

Several studies demonstrate the role of oxidative stress and ROS in the regulation of general DNMTs expression. For example, in vivo study demonstrates DNMT1, DNMT3b, but not DNMT3a upregulation and subsequent DNA hypermathylation as a result of neonatal hypoxia [44]. S.O. Lim and his colleagues detected *in vitro* ROS dependent Snail protein overexpression, that regulates the HDAC1 and DNMT1 immobilization on gene promoters. In this experiment, the authors also identified the hypermethylation of E-cadherin gene promoter [45]. An interesting study on the ROS regulation of the methylation protein machinery localization was carried out with the human embryonal carcinoma cell line [46]. A treatment of the cell culture with hydrogen peroxide (H_2O_2) results in the increase of SIRT1 and DNMT1 chromatin binding force as well as the methylation protein complex consisting of DNMT1, DNMT3B, SIRT1, EZH2 and γ-H2AX translocation to the transcriptional active genes, such as MYC, ACTB, TIMP3 and MLH1. [47].H_2O_2 treatment induced the catalase gene promoter hypermethylation and downregulation of the gene expression, as described in the study using hepatocellular carcinoma

cell line. A pre-treatment with antioxidant, N-acetylcysteine, or DNMTs inhibitor 5-aza-deoxocytidine prevented the effect of H_2O_2 on the gene promoter methylation status and gene transcription [48].

Such sensitivity of DNMTs expression during oxidative stress could be referred to as a result of a well-known effect of oxidative stress on different cell signaling pathways, particularly the Ras-ERK signaling. Indeed, there are several PTMs of Ras and Raf by ROS. Ras is oxidized on cysteine 118; Raf cysteine-rich domain is also oxidized by ROS. Such events result in the Raf membrane immobilization and its subsequent activation [49–51]. There are also a few studies carried out with melanoma cell lines, which demonstrate ROS induction of the Ras-ERK dependent DNMT1 overexpression and DNA hypermethylation [52]. These data can prove our assumption of an important role played by oxidative stress and thereby antioxidants in the Ras-ERK dependent DNMTs expression.

There are a lot of studies on the role of antioxidant properties of H_2S, such as ROS scavenging, SOD2, eNOS induction, *etc.* [8, 13]. Consequently, we hypothesized that the ROS formation prevention by H_2S could affect the Ras-ERK signaling and result in the methylation pattern modulation during oxidative stress. Indeed, there are some studies on the role of H_2S in the Ras-ERK signaling regulation during oxidative stress [17, 18]. For example, $CoCl_2$ (the hypoxia mimetic) treatment of the myoblastic cell line could stimulate ROS formation and subsequent ERK activation. A pre-treatment with H_2S donor, NaHS, and *N*-acetyl-l-cysteine could downregulate the ROS level and ERK activity [17]. Similar experiments with the pheochromocytoma cell line demonstrated the same results. The authors also discovered hypoxia-inducible factor-1 alpha (HIF-1α) down-regulated CBS expression. The pre-treatment with NaHS can compensate an effect of endogenous H_2S and downregulate ERK activity in the oxidative stress conditions [18]. There is also one study, which shows that down-regulation of DNMT1, DNMT3a, DNMT3b expression levels after homocysteine treatment of endothelial cells was blocked by NaHS. The authors proved that H_2S donors could regulate NADP+/NADPH balance and induce SOD2 expression, after which DNMTs expression is down-regulated [19].

Thus, as it was mentioned above, there are several studies on the role of H_2S in the regulation of DNMTs expression and the Ras-ERK signaling during oxidative stress. However, there are no direct studies on the role of H_2S in the regulation of Ras-ERK-dependent DNMTs transcription in the oxidative stress conditions. It is very important to explore or to research the exact role H_2S donors and inhibitors play in the regulation of Ras-ERK-dependent methylation pattern under oxidative stress.

H_2S regulation of the Ras-ERK signaling dependent DNMTs transcription through NO

Nitric oxide (NO) is also an endogenously produced gas regulating cell signaling along with H_2S. A rate-limiting enzyme of NO biosynthesis is nitric oxide synthase (NOS) in humans. NO is a substrate of protein nitrosylation and nitration. These PTMs are important for the enzymatic function of proteins [53]. The results of a series of experiments showed that H_2S regulated the NOS expression and NO production [19, 13–16]. It was demonstrated that H_2S donors up-regulated the endothelial NOS expression and NO production by mouse aortic vascular smooth cells and the subsequent protein nitrosylation *in vivo* [13]. GSNO, an NO carrier, releases NO in the presence of H_2S [14, 15]**.** The chemical reaction of H_2S with NO results in the formation of bioactive nitrosothiols, which release NO in the presence of Cu^{2+}. H_2S and nitrite produce HSNO in the presence of endothelial cells or Fe^{3+}-porphyrin. HSNO generates NO or HNO by the subsequent reaction with H_2S [16]. Another study demonstrates the inhibition of NOS and block of NO production by endothelial cells of the mouse brain *in vitro* [11]. Such property of H_2S as NO induction could be important for the DNMTs expression regulation, because a number of studies highlighted the role of NO in the regulation of DNA methylation. The first data appeared during the research of Duchenne

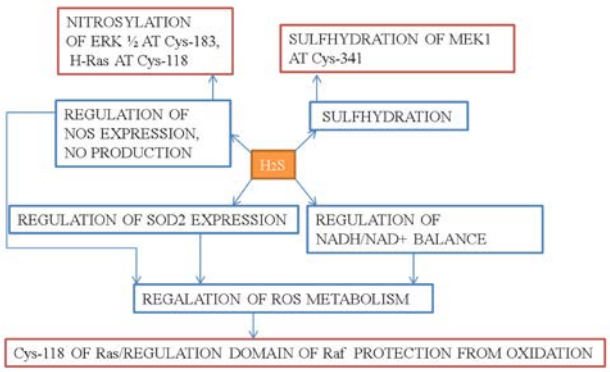

Fig. 2. Schematic representation of H_2S-regulated PTMs of the Ras-ERK pathway enzymes (the author).

muscular dystrophy. The authors identified NO-dependent global DNA methylation [53]. The research of the causes of gastritis demonstrated H. Pylori bacteria infection stimulation of the macrophage NOS expression induced the NO-dependent DNA methylation in gastric mucosa [54, 55]. It is known that the gene promoter methylation causes the inhibition of transcription and there is evidence in the literature on the NO-dependent global gene silencing in endothelial cells [56].

Hypothesizing the regulation of Ras-ERK-dependent DNMTs expression, we assume that nitrosylation of the Ras-ERK pathway enzymes could represent the NO-dependent mechanisms of DNA methylation regulation. Indeed, Cys118 of Ras and Cys 183 of ERK are S-nitrosylated [57, 58]; transcriptional factor targets of the Ras-ERK signaling pathways c-Fos and c-Jun (the elements of the AP-1 transcriptional complex important for DNMTs transcription) are also nitrosylated on cysteine residues with subsequent block of AP-1 complex formation [59, 60]. On the other hand, NO could demonstrate an opposite effect on AP-1 complex elements stimulating c-Fos neurotrophin-dependent expression [61].

In other words, the hypothesis of H_2S-dependent nitrosylation regulation of the Ras-ERK dependent DNMTs transcription is supported by appropriate literature. However, this hypothesis requires additional scientific research to be proved completely.

The role of H_2S in the cholesterol-dependent regulation of the Ras-ERK signaling mediated DNMTs transcription

Cholesterol is an important metabolite in humans at both body and cell level. Consequently, not a surprise that cholesterol metabolism affects epigenetics, particularly DNA methylation pattern. It turned out that several studies had proved the effect of mevalonate pathway inhibitors – statins – on DNMTs expression; however, they provide no evidence of a direct role of the Ras-ERK signaling [62–64].

The first study showed that the treatment of breast cancer, prostate cancer and osteosarcoma cells with physiologically relevant concentrations of simvastatin induced down-regulation on DNMT1 expression at the mRNA and protein levels [62]. The second one showed that the lovastatin treatment of colorectal cancer cells reduced the DNMTs level and BMP gene expression as a result of the gene promoter demethylation [63]. There is another study which demonstrated that the acute myeloid leukemia cells treatment with simvastatin had exerted a dose-dependent down-regulation effect on the DNMT1 and DNMT1 level [64].

The above-mentioned effect of cholesterol depletion could be explained by the Ras-ERK signaling modulation by this molecule. It is well known, that the plasms membrane (PM) structure is important for cell signaling. PM contains the so-called “lipid rafts”, which are composed of cholesterol and sphingolipids [65]. The lipid rafts harbor a lot of cell receptors and signaling proteins [66, 67]. The Ras proteins belong to PM proteins, activated in lipid rafts. It is discovered that a depletion of cholesterol level in PM can block the Ras-ERK signaling [67]. The Ras proteins are also farnasylated at Cys-185 and Cys-186 by the products of mevalonate pathway of cholesterol biosynthesis, which is done to achieve activity. At the same time, the block of mevalonate pathway can inhibit the Ras-ERK signaling [68]. There is a need for additional studies to clarify a direct role of the Ras-ERK signaling modulation by cholesterol in the DNMTs transcription regulation.

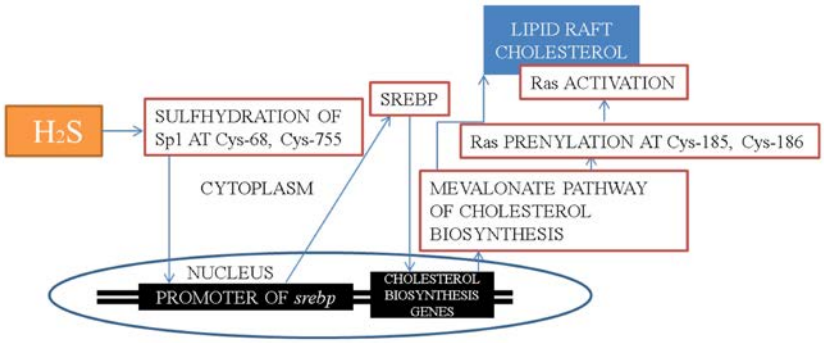

Fig. 3. Schematic representation of H_2S-mediated regulation of Ras proteins by SREBP (the author).

All in all, what is a potential role of H_2S in the cholesterol-dependent Ras-ERK signaling mediated the DNMTs expression? The recent data shed the light on the role of sulfhydration in cholesterol metabolism regulation. It is known that Sterol regulatory element-binging protein (SREBP) is a transcription factor which induces the transcription of cholesterol biosynthesis genes [69]. There are several studies which show that H_2S stimulates the cholesterol biosynthesis through SREBP regulation [9–11]. For example, a treatment of pancreas beta-cells with H_2S donors, or the transfection with constitutional active *cse* gene induced up-regulation of (SREBP)-1c [9]. An adipocytes maturation is accompanied by the H_2S biosynthesis genes overexpression. Moreover, this study indicates the main role of H_2S in lipogenesis [10]. It describes a CBS-dependent translocation of Sp1 to the nucleus and the SREBP gene promoter binding in the experiments with the ovarian cancer cells [11]. The research of the H_2S dependent mechanism of SREBP regulation results in the discovery of Sp1 sulfhydration at Cys68 and Cys755 [12]. Furthermore, the authors proved that such PTM is a driving force for SREBP up-regulation and subsequent lipogenesis through the regulation of Sp1 nuclear translocation and transcriptional activity [12].

Consequently, H_2S donors and inhibitors of the gas biosynthesis could be promise agents in the cholesterol metabolism regulation. There are some cholesterol-dependent cell processes, which are relevant for the hypothesis of the review, and their regulation by H_2S should be tested in future. The first one is the H_2S-generated regulation of Ras-ERK-dependent DNMTs transcription through modulation of cholesterol in a plasma membrane (PM). The second one is the H_2S-generated regulation of the Ras-ERK dependent DNMTs transcription through the modulation of protein prenylation.

Conclusions

The review presents the data which support our hypothesis about H_2S regulation of the Ras-ERK signaling dependent DNMTs transcription. The relevant literature showed a series of experiments, whereby both H_2S exogenous donors and endogenous gas could affect PTMs of Ras, Raf, MEK1 and ERK proteins. H_2S can regulate sulfhydration, oxidation, nitrosylation and prenylation thereby modulating the Ras-ERK signaling dependent and independent DNMTs expression *in vitro* and *in vivo*. We believe our hypothesis can be the basis for developing new drugs or transforming the existing treatment strategies for different diseases associated with the DNA methylation disorders. There is a need for further studies to elucidate the detailed mechanisms of H_2S impact on the Ras-ERK signaling dependent DNMTs transcription.

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Потенційна роль сірководню (H_2S) в регуляції залежної від Ras-ERK сигналізації транскрипції ДНК метилаз

Т. О. Нікітіна

Існують дані стосовно регуляції Ras-ERK клітинною сигналізацією транскрипції ДНК метилтрансфераз (DNMTs). Також є дані стосовно ролі H_2S в регуляції активності Ras-ERK сигналізації та експресії DNMTs. В представленому огляді висунута гіпотеза про те, що H_2S регулює Ras-ERK залежну транскрипцію DNMTs. Було продемонстровано, що окисний стрес , метаболізм ліпідів, сульфгідрування та нітрозилювання білків є головними цілями H_2S-опосередкованої регуляції. Дані клітинні процеси є важливими для після-трансляційної модифікації (ПТМ) ферментів Ras-ERK сигналізації. В огляді представлені дані, що демонструють залежність транскрипції DNMTs від H_2S-опосередкованої ПТМ ферментів Ras-ERK сигналізації.

Ключові слова: Ras-ERK сигналізація, ДНК метилтрансферази, H_2S.

Потенциальная роль сероводорода (H_2S) в регуляции зависимой от Ras-ERK сигнализации ДНК метилаз

Т. А. Никитина

Существуют данные о регуляции Ras-ERK клеточной сигнализацией транскрипции ДНК метилтрансфераз (DNMTs). Также есть данные о роли H_2S в регуляции активности Ras-ERK сигнализации и экспрессии DNMTs. В данном обзоре выдвинута гипотеза о том, что H_2S регулирует Ras-ERK-зависимую транскрипцию DNMTs. Было продемонстрировано, что окислительный стресс, метаболизм липидов, сульфгидрирование и нитрозилирование белков является главными целями H_2S-опосрдованной регуляции. Данные клеточные процессы являются важными для пост-транляционной модификации (ПТМ) ферментов Ras-ERK сигнализации. В обзоре представлены данные, демонстрирующие зависимость транскрипции DNMTs от H_2S-опосредованной ПТМ ферментов Ras-ERK сигнализации.

Ключевые слова: Ras-ERK сигнализации, ДНК метилтрансферазы, H_2S.

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