REVIEW

New possible silver lining for pancreatic cancer therapy: Hydrogen sulfide and its donors

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\textbf{Abstract:} Hydrogen sulfide (H\textsubscript{2}S) is a gaseous molecule that has been studied in recent years as a potential therapeutic agent in various diseases, including cancer. In pancreatic cancer, a significant unmet medical need, H\textsubscript{2}S has shown promise in improving patient outcomes. This review focuses on the role of hydrogen sulfide and its donors in pancreatic cancer therapy. We discuss the mechanisms of action of H\textsubscript{2}S and its potential therapeutic applications in this disease. Additionally, we highlight recent advances in the development of H\textsubscript{2}S donors as therapeutic agents.

\textbf{Key words:} Hydrogen sulfide, Pancreatic cancer, Therapeutic potential, donors, inhibitors.
KEY WORDS
Pancreatic cancer; Hydrogen sulfide donor; Sulfur-containing compound; Cell proliferation; Antitumor effect; Signaling pathway

Abstract
As one of the most lethal diseases, pancreatic cancer shows a dismal overall prognosis and high resistance to most treatment modalities. Furthermore, pancreatic cancer escapes early detection during the curable period because early symptoms rarely emerge and specific markers for this disease have not been found. Although combinations of new drugs, multimodal therapies, and adjuvants prolong survival, most patients still relapse after surgery and eventually die. Consequently, the search for more effective treatments for pancreatic cancer is highly relevant and justified. As a newly re-discovered mediator of gasotransmission, hydrogen sulfide (H2S) undertakes essential functions, encompassing various signaling complexes that occupy key processes in human biology. Accumulating evidence indicates that H2S exhibits bimodal modulation of cancer development. Thus, endogenous or low levels of exogenous H2S are thought to promote cancer, whereas high doses of exogenous H2S suppress tumor proliferation. Similarly, inhibition of endogenous H2S production also suppresses tumor proliferation. Accordingly, H2S biosynthesis inhibitors and H2S supplementation (H2S donors) are two distinct strategies for the treatment of cancer. Unfortunately, modulation of endogenous H2S on pancreatic cancer has not been studied so far. However, H2S donors and their derivatives have been extensively studied as potential therapeutic agents for pancreatic cancer therapy by inhibiting cell proliferation, inducing apoptosis, arresting cell cycle, and suppressing invasion and migration through exploiting multiple signaling pathways. As far as we know, there is no review of the effects of H2S donors on pancreatic cancer. Based on these concerns, the therapeutic effects of some H2S donors and NO–H2S dual donors on pancreatic cancer were summarized in this paper. Exogenous H2S donors may be promising compounds for pancreatic cancer treatment.

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1. Introduction
The increasing number of cases and cancer deaths has critically affected human life and health7. Pancreatic cancer causes the fourth highest mortality rate in developed countries, and is estimated to be the second most deadly neoplasm in the next decade, surpassed only by lung cancer7. Moreover, unhealthy living habits, such as alcohol or nicotine consumption, and pre-existing conditions like type 2 diabetes mellitus, chronic pancreatitis and obesity favor the development of pancreatic cancer7−9. Frustratingly, the prognosis of this cancer is extremely poor in major malignancies. The lack of early diagnosis, strong invasiveness and early distant metastases are thought to be responsible for the poor outcomes following radical surgical resection7. In addition, the microenvironment of pancreatic cancer is complex8, and the neoplasm is thought to result from the accumulation of multiple genetic and epigenetic modifications, including multiple tumor suppressor 1 (P16), kirsten rat sarcoma viral oncogene (KRAS), mothers against decapentaplegic homolog 4 (SMAD4), breast cancer 2 (BRCA2), human ribosomal protein L10 (RPL10), human HEAT repeat-containing protein 1 (HEATR1) and others8−14. All these factors lead to <7% 5-year overall survival rate, with most patients expiring within the first year after diagnosis15. Although surgery continues to be employed as first choice of treatment strategies, late diagnosis limits surgical treatment, prompting the need for adjuvant therapy, radiotherapy and chemotherapy16. The chemotherapy drugs contain gemcitabine, and the combination of irinotecan, oxaliplatin and nab-paclitaxel or 5-fluorouracil17,18. Furthermore, radiotherapy and targeted therapies also fail to produce significant clinical benefits18. With intensifying research, new emerging strategies for the treatment of pancreatic cancer have evolved, including immunotherapies20. molecularly targeted therapies21,22, focusing on the tumor microenvironment as a potential target21, have also been developed. Because these therapies are still far from satisfactory, the search for more drug candidates to treat pancreatic cancer is critical.

Hydrogen sulfide (H2S) is the third gasotransmitter possessing a regulatory effect on vascular function and intracellular signaling. It is generated from l-cysteine mainly through the catalysis of cysteine aminotransferase (CAT), cystathionine-β-synthase (CBS), 3-mercaptoppyruvate sulfurtransferase (3-MST) and cystathionine-γ-lyase (CSE) in the mammalian tissues including pancreas, liver, kidney, intestine, heart and central nervous system23−25. Great interest has been shown in H2S due to the extensive pharmacological and pathological activities in human26. As brief examples, in the cardiovascular system, H2S mitigates oxidative stress and myocardial injury connected with ischemia–reperfusion events26,27. For the central nervous system, H2S exerts the protective effects against neurodegenerative diseases by the antioxidant properties28,29. In the immune system, H2S presents anti-inflammatory effects through binding with zinc, ferric iron or copper residues of metalloproteins and enabling sulfidation of protein cysteine residues30,31. In addition, H2S functions in homeostatic mechanisms and affects pancreatic β-cells by inhibiting the release of insulin and reducing cellular stress caused by glucose32,33. It can also function in repairing the damage of inflammation and is used as to protect gastrointestinal mucosa34. It is well documented that H2S regulates the kidney excretory capacity on renal tubular cells by inhibiting sodium transporters35. Many studies have documented that the extensive physiological functions of H2S are mediated by numerous molecular mechanisms, including the persulfidation of target
proteins, interactions with ion channels and others41. Persulfa-
dation, a key post-translational modification, regulates the function of the proteins. H2S is oxidized to polysulfide, or the target cysteine is oxidized to sulfonic acid or disulfide to form a cysteine persulfide, which then accesses to the cytosol to affect the activity of the protein75. Moreover, H2S also interacts with the metal center of the target protein, especially heme protein, by inducing the covalent modification of heme to form sulf-
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native pathway mainly contains three groups: ERK, P38, and c-Jun NH2-terminal kinase (JNK), which play vital roles in cell proliferation, differentiation, survival and apoptosis75. In addition, pancreatic cancer cell lines are characterized by mutations in the KRAS gene, which leads to a KRAS hyperactivation with a resulting hyperphosphorylation of the downstream kinases ERK1/256. FAS and binding of the human tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) to the death receptor (DR4) lead to the recruitment of an adaptor protein FAS-associated death domain (FADD), which functions as a molecular bridge to caspase-8. This activated caspase-8 directly cleaves and activates caspase-3 and -7, which further cleaves the downstream substrates poly ADP ribose polymerase (PARP) to stimulate apoptosis77,78.

Chen et al.79 explored the in vitro and in vivo antitumor effect of SFN (Fig. 2) on pancreatic cell lines PANC-1 and Mia Paca-2. The results showed that SFN inhibited cancer cells proliferation, colony formation, migration and invasion. Moreover, after SFN treatment, excessively generated ROS activated adenosine 5’-monophosphate-activated protein kinase (AMPK), and subsequently elevated the NRF2 nuclear translocation, which inhibited pancreatic cancer cell proliferation (Fig. 3). In a pancreatic cancer transgenic mouse model, SFN treatment (50 mg/kg, i.p.) inhibited tumor growth, consistent with the antiproliferative effects of SFN through ROS activated AMPK signaling pathway and NRF2 nuclear translocation. Kalifatidis et al.80 verified that SFN induced apoptosis of pancreatic AsPC-1, Mia Paca-2, Capan-1 and BxPC-3 cells by the repression of nuclear factor kappa B (NF-κB) through inhibiting the subunit c-Rel activity and down-regulation of anti-apoptotic genes XIAP and cIAP1 expression. Mia Paca-2 cells were xenografted subcutaneously into nude mice, and tumor growth was measured in untreated mice or upon treatment with SFN, tumor necrosis factor-related apoptosis-inducing ligand (TRAIL), or both. The results demonstrated that SFN (4.4 mg/kg) alone or combined with TRAIL potentially reduced tumor growth by inhibiting NF-κB activity, tumor angiogenesis, proliferation and inducing apoptosis without exhibiting toxicity to normal tissue. Soon afterwards, the same research group81 reported that SFN induced the expression of miR-365a-3p to restrain NF-κB activity through down-regulating c-Rel, eventually leading to the apoptosis of pancreatic cancer cells AsPC-1, BxPC-3, PANC-1 and Mia Paca-2. After the miR-365a-5p functional effects were established in vitro, xenograft egg model studies were performed, and lipofected BxPC-3 cells were transplanted to the chorioallantoic membrane in chick development. The findings revealed that the miR-365a-3p expression induced by SFN were 6-fold higher after xenotransplantation than

2. Antitumor mechanisms of H2S donors against pancreatic cancer

Natural isothiocyanates (ITCs) isolated from Brassicaceae plants, including erucin (ERU), sulforaphane (SFN), benzyl isothiocya-
nate (BITC) and phenethyl isothiocyanate (PEITC, Fig. 2), slowly release H2S in biological environments89–91. Due to H2S release, the relatively high concentrations of ITCs exhibit significant inhibitory effects on cancer cell growth by inducing apoptosis, arresting cell cycle, interacting with the recombinant protein 1-nuclear factor erythroid-2 related factor 2-antioxidant response element (KEAP1–NRF2–ARE) pathway and by up-regulating phase II detoxification enzymes55,56. Notably, ITCs have high bioavailability and are easily absorbed, making them potential compounds for anticancer therapy73.

Recently, H2S donors were found to possess potential in the treatment of pancreatic cancer. In 2019, Citi et al.82 reported that ERU (Fig. 2) could cross cell membranes of AsPC-1 and release H2S at the intracellular level. Furthermore, high concentration of ERU (30–100 μmol/L) inhibited cell proliferation by reducing phosphorylated extracellular signal regulated kinase (ERK1/2) levels, and inducing cell apoptosis through up-regulating the apoptosis marker caspase-3 and caspase-7 expression (Fig. 3). As shown in Fig. 3, the mitogen-activated protein kinase (MAPK) pathway mainly contains three groups: ERK, P38, and c-Jun NH2-terminal kinase (JNK), which play vital roles in cell proliferation, differentiation, survival and apoptosis75. In addition, pancreatic cancer cell lines are characterized by mutations in the KRAS gene, which leads to a KRAS hyperactivation with a resulting hyperphosphorylation of the downstream kinases ERK1/256. FAS and binding of the human tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) to the death receptor (DR4) lead to the recruitment of an adaptor protein FAS-associated death domain (FADD), which functions as a molecular bridge to caspase-8. This activated caspase-8 directly cleaves and activates caspase-3 and -7, which further cleaves the downstream substrates poly ADP ribose polymerase (PARP) to stimulate apoptosis77,78.
those in control cells. Moreover, the xenografts tumor sizes with high miR-365a-3p expression were significantly decreased. Anti-proliferative effects were also reported on AsPC-1, BxPC-3 and PANC-1 cells, and tumor growth in the BxPC-3 xenograft model was strongly inhibited by SFN through inducing miR-135b-5p expression, followed by enhanced expression of the RAS protein activator like 2 (RASAL2) protein (Fig. 3)\textsuperscript{82}. Subsequently, Li et al.\textsuperscript{83,84} revealed that SFN inhibited the proliferation of PANc-1 and MIA PaCa-2 cells by disrupting HSP90—P50\textsuperscript{GHD} and, by directly interacting with the amino acid residues of HSP90. Srivastava et al.\textsuperscript{85} reported that SFN induced pancreatic cancer cell apoptosis by inhibiting X-linked inhibitor of apoptosis protein (XIAP) and the phosphorylation of FKHR, alterations in the levels of B-cell lymphoma-2 (BCL-2), and activation of caspase-3 in MIA PaCa-2, BxPC-3, AsPC-1 and PANC-1 cells. Additionally, it also inhibited early metastasis by down-regulating the epithelial–mesenchymal transition (EMT) related proteins vimentin, $\beta$-CATENIN, TWIST-1 and zinc finger E box-binding protein-1 (ZEB1, Fig. 3). Li et al.\textsuperscript{86} observed that SFN significantly inhibited proliferation and angiogenesis of stem cells of mice NOD/SCID/IL2R\textsuperscript{SFN} significantly inhibited proliferation and angiogenesis of stem cells of mice NOD/SCID/IL2R

Figure 1  The schematic diagram of bell-shaped effects of the exogenous and endogenous H\textsubscript{2}S on cancer. In short, endogenous or low concentrations of exogenous H\textsubscript{2}S promotes cancer growth by stimulating angiogenesis, and promoting cell proliferation and metastasis. Inhibition of endogenous H\textsubscript{2}S production or high-dose exogenous H\textsubscript{2}S administration enables cancer cell death through inhibiting proliferation, inducing apoptosis and DNA damage, and arresting cell cycle. The models suggest that the inhibitors of H\textsubscript{2}S biosynthetic enzymes and H\textsubscript{2}S donors represent two strategies to treat cancer.
tumor growth by inducing apoptosis which was related to the inhibition of PI3K/AKT pathway. This group then showed that BITC impeded cell proliferation by inhibiting tumor angiogenesis through the signal transducer and activator of transcription 3 (STAT-3)-dependent pathway by suppressing vascular endothelial growth factor (VEGFR-2) phosphorylation and hypoxia inducible factor (HIF-1α) levels, and increased expression of Rho-GTPases (Fig. 3). Following these results, in vivo tumor xenograft experiments were conducted in female athymic nude mice. Treatment of mice with 12 μmol/L BITC markedly suppressed BxPC-3 tumor growth, and BITC treated tumor xenografts showed 61% reduced hemoglobin content, compared with untreated xenografts. Tumors were then analyzed by Western blot, which showed that the phosphorylation of STAT-3, VEGR-2 and the expression of HIF-1α and RhoC in the tumors of mice treated with BITC were significantly reduced, consistent with the in vitro results. In 2016, Kasiappan et al. revealed that BITC inhibited cell growth and invasion in PANC-1, L3.6pl and MIA PaCa-2 through enhancing the generation of ROS to down-regulate the expression of SP transcription factors, STAT3 and c-MYC (Fig. 3). These findings are consistent with the results of L3.6pl xenograft mice, which showed that treatment of mice with 20 mg/kg BITC by i.p. injection remarkably inhibited tumor growth and did not affect body weights. In addition, Western blot analysis of tumor lysates affirmed that STAT3 levels were decreased in tumors from BITC-treated mice.

In related studies, Stan et al. demonstrated that PEITC (Fig. 2) also dose-dependently inhibited the viability of MIA PaCa-2, PL-45 and BxPC-3 cells through apoptosis. The treatment of PEITC up-regulated BAK and down-regulated BCL-2 and BCL-XL expression (Fig. 3). PEITC also suppressed cell proliferation by reducing the levels of NOTCH 1 and 2 (Fig. 3). In a MIA PaCa-2 xenograft mouse model with a tumor size of approximately 673.8 mm³, oral administration of 12 μmol/L PEITC suppressed growth, with 37% lower tumor volume compared with control. Notably, PEITC treatment was relatively safe and did not cause organ damage.

In another approach, Fortunato et al. exploited the large amount of sugar consumption of cancer cells by overexpressing the membrane glucose transporters (GLUTs), especially glucose and fructose, to develop a series of H2S-releasing glycoconjugates. These agents delivered high amounts of H2S to cytoplasm with a resulting antitumor effect. More importantly, the aqueous solubility of the derivatives was improved by the glycoconjugation with H2S-releasing unit (isothiocyanate portions). Among them, glycoconjugated H2S donors 1 and 2 (Fig. 2) released H2S in AsPC-1 cells which altered the cell cycle and showed potent inhibitory effects on cell viability.

In other related work, diallyl trisulfide (DATS, Fig. 2) was shown to react with thiols in the cell, then crossed the cell membranes and interacted with intracellular glutathione to generate H2S, which contributed to the antitumor effect. Ma et al. showed that DATS inhibited Capan-2 cell proliferation by arresting cell cycle and inducing apoptosis. Western blot results indicated that cell cycle retention was related to increased P21 expression and decreased levels of cyclin B1. BCL-2 down-regulation and the increase of P53, FAS and BAX protein levels were involved in the apoptosis process (Fig. 3).

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Figure 2  The chemical structures of H2S donors and NO–H2S dual donor derivatives with potential anti-pancreatic cancer activity.
In vitro studies found that HS-ASA inhibited the growth of MIA PaCa-2 and BxPC-3 cells with the IC50 values of 2.1 and 1.9 \( \mu \text{mol/L} \), respectively. Moreover, HS-ASA inhibited proliferation, arrested the cell cycle at G0/G1 phase, and induced apoptosis.

Like H2S, nitric oxide (NO), as a gasotransmitter, possesses a wide range of physiological and pathological effects. Accumulating evidence indicates that high concentrations of NO, either biologically generated by inducible nitric oxide synthase (iNOS) or by NO donors, exert antitumor activities by suppressing cell proliferation, improving the sensitivity of tumor cells to radiotherapy, chemotherapy and immune-toxicities, and also inhibiting metastasis and EMT. Mechanically, NO-mediated effects mainly regulate the NF-κB/SNAIL/RKIP/PTEN signaling pathway in cancer cells. In pancreatic cancer, NO plays a significant role in the invasion of PANC-1 cells by a JAK independent and MEK-ERK-dependent mechanism. In addition, excessive production of NO can lead to epigenetic and genetic changes in pancreatic cancer. Recently, Kashfi et al. reported a series of ASA hybrids consisting of both NO and H2S-releasing moieties. Among them, NOSH-1 (NBS-1120, Fig. 2) was the most potent one in MIA PaCa-2 and BxPC-3 cells with the IC50 values of 0.047 and 0.057 \( \mu \text{mol/L} \), respectively. Moreover, the lactate dehydrogenase release assay indicated that NBS-1120 possessed a remarkable degree of safety. In-depth study showed that NBS-1120 inhibited proliferation, arrested cell cycle and eventually led to increased apoptosis, which was associated with the increased levels of caspase-3 and ROS. Furthermore, in MIA PaCa-2 xenograft mice model with the tumor size of approximately 70 mm³, 100 mg/kg NBS-1120-treated mice by gavage showed a significant reduction in tumor volume (330 ± 95 mm³), compared with control mice (3265 ± 520 mm³). Tumor mass was also inhibited in NBS-1120-treated mice (0.62 ± 0.25 g) vs. controls (2.47 ± 0.24 g). Immunohistochemical examination of tumor sections demonstrated inhibition of tumor growth, accompanied by the induction of apoptosis, cell cycle arrest by increasing the

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**Figure 3** Possible signaling pathways of ITCs and DATS involved in the antiproliferation of pancreatic cancer. ITCs, including ERU, SFN, BITC and PEITC, belong to natural H2S donors. They slowly release H2S in biological environments and the relatively high concentrations of ITCs and DATS exhibit antiproliferative effects on pancreatic cancer by inducing apoptosis, arresting cell cycle and suppressing invasion and migration of tumor cells. In brief, these donors suppressed cell proliferation by inhibiting SHH, PI3K/AKT/mTOR, SPTFs, STAT3, RAC1, and NOTCH, and activating AMPK and RASAL2 signaling pathways. Moreover, they also inhibited early metastasis by down-regulating ZEB1, \( \beta \)-CATENIN, TWIST-1, and vimentin. Further, they arrested cell cycle by up-regulating P21, activating CHK2, and down-regulating cyclin B1/CDK1 and CDC25B. In addition, they induced apoptosis through activating caspase-3, caspase-7, BAK, BAX, P38, JNK, DR4 and ERK, and inhibiting BCL-2, BCL-XL, NF-κB and PARP.
expression of P53, and decreased expression of NF-κB and forkhead box protein M1 (FOXM1). In short, these signaling pathways contributed to NBS-1120 mediated pancreatic cancer inhibition in vitro and in vivo\textsuperscript{110}.

Subsequently, Kashfi et al.\textsuperscript{111} developed another compound (NOSH-sulindac, AVT-18A, Fig. 2) which could also release both NO and H\textsubscript{2}S. The antiproliferative activity test results showed that AVT-18A possessed potent effects on inhibiting BxPC-3 and MIA PaCa-2 growth with the IC\textsubscript{50} values of 0.098 and 0.12 \textmu mol/L, respectively, which was at least 8000-fold more potent than sulindac. AVT-18A also inhibited proliferation through inducing apoptosis and G\textsubscript{2}/M phase cell cycle arrest.

3. Conclusions and perspectives

Despite advances in therapy strategy, pancreatic cancer remains a fatal disease, due to the late diagnosis, poor prognosis, and extensive resistance to most treatment modalities. To date, the mortality caused by pancreatic cancer still gradually increases, which shows the increased need for effective therapeutic drugs.

Currently, H\textsubscript{2}S is a rapidly developing field in biomedical research. H\textsubscript{2}S donors which release H\textsubscript{2}S under different conditions are constantly emerging. Although the pathways involved in endogenous H\textsubscript{2}S production have not been clearly elucidated in pancreatic cancer, current data suggest that some H\textsubscript{2}S-donors including mainly ITCs, DATS and ADT—OH—aspirin hybrids have been shown to have beneficial effects. For example, many chemotherapeutic drugs exert drug resistance by inhibiting FOXO proteins or activating AKT, but BITC boosts FOXO nuclear shutting by inhibiting AKT phosphorylation to weaken the resistance of tumor cells and induce cell apoptosis. BITC-mediated generation of ROS and inhibition of NF-κB cause pancreatic cancer cell cycle arrest and apoptosis. It also restrains tumor angiogenesis and proliferation through blocking HIF-1α/VEGF/Rho-GTPases pathways. Moreover, the synergistic interaction of H\textsubscript{2}S and NO maintains and enhances the expression of cGMP to promote angiogenesis and vasodilation\textsuperscript{112,113}. Furthermore, the crosstalk of H\textsubscript{2}S and NO under physiological conditions has been proved to exert antitumor activity\textsuperscript{14}. Based on these considerations, the dual H\textsubscript{2}S and NO donor drugs (NBS-1120 and AVT-18A) are currently being developed, and various pharmacological activities are evaluated, particularly for the anti-pancreatic cancer actions by suppressing cell proliferation, inducing apoptosis, and arresting cell cycle through increasing ROS, iNOS and P53, and decreasing NF-κB and FOXM1. As previously noticed, H\textsubscript{2}S donors are expected to be further developed in pancreatic cancer. Yet some problems also need to be addressed urgently, such as, how to specifically deliver therapeutic concentrations of H\textsubscript{2}S to pancreatic cancer cells, and how to clarify the function of each of the two gaseous transmitters in dual H\textsubscript{2}S/NO donors. With progress in the understanding of molecular mechanisms of the pancreatic cancer driver genes, molecular targeted drugs are being applied to pancreatic cancer treatments, yet the overall benefit is limited\textsuperscript{115,116}. Despite the lack of targeted therapy drugs, it is still a promising direction that deserves research and exploration. Recent research shows that ROS-activated, pH-controlled and photo-controllable H\textsubscript{2}S donors can be applied based on the special tumor microenvironment\textsuperscript{117–119}. Last but not least, H\textsubscript{2}S donors can be used to combine with the marketed pancreatic cancer drugs or drug candidates, hoping to increase the efficacy and selectivity, and reduce drug resistance and side effects.

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Author contributions

Xu Hu designed and wrote the paper. Yan Xiao revised the manuscript according to the reviewers’ suggestions. Jianan Sun, Bao Ji, Shanshan Luo, Bo Wu, Chao Zheng, Peng Wang and Keguang Cheng wrote and revised the original manuscript. Fanxing Xu, Huiming Hua, and Dahong Li were responsible for the conception and design of the review.

Conflicts of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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