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ORIGINAL ARTICLE

Investigation of the Molecular Effects of Temperature Change on Cold Shock Domain-containing Protein E1 in Hepatocellular Carcinoma Cells

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OBJECTIVE

Cold shock domain-containing protein E1 (CSDE1) is a multifunctional RNA-binding protein implicated in translation regulation, apoptosis, and cancer progression. While CSDE1 overexpression has been reported in several malignancies, its role in hepatocellular carcinoma under environmental stress conditions remains poorly understood.

METHODS

Human hepatocellular carcinoma hepatoma G2 (HepG2) cells were cultured under standard conditions (37°C) and cold stress (24°C). Morphological changes were assessed using phase-contrast microscopy and hematoxylin and eosin staining. CSDE1 messenger RNA (mRNA) expression was analyzed by reverse transcription quantitative real-time polymerase chain reaction, while protein levels in culture supernatants were measured using enzyme-linked immunosorbent assay (ELISA). In addition, molecular docking simulations were performed to evaluate the interaction of CSDE1 with the tyrosine kinase inhibitors lenvatinib and sorafenib.

RESULTS

Cold stress induced marked morphological alterations, including decreased cell density and disrupted cellular integrity. Although no significant change was observed in CSDE1 mRNA expression, CSDE1 protein levels were significantly elevated (p=0.019), suggesting possible post-transcriptional or post-translational regulation. Docking analysis showed that sorafenib had a more negative predicted binding score compared with lenvatinib; however, this finding does not demonstrate functional modulation of the therapeutic response. This study provides a basis for further studies to clarify the mechanistic and translational significance of CSDE1 under cold stress.

CONCLUSION

These findings show an increase in ELISA-detected CSDE1 signal in the culture supernatant of HepG2 cells under cold-stress conditions. This increase may reflect a passive release associated with the observed decrease in cell density and disruption of cellular integrity and provide direction for further studies aimed at distinguishing it from active secretion. This study provides a basis for further studies to clarify the mechanistic and translational significance of CSDE1 under cold stress.

Keywords: Cold shock protein; cold shock domain containing E1; hepatocellular carcinoma; hepatoma G2; molecular docking.

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INTRODUCTION

Temperature change is one of the most common environmental stressors encountered by living organisms. Organisms exposed to significant shifts in temperature have developed intricate cellular mechanisms to respond and adapt to these challenges, ensuring survival and functionality under stress conditions.[1]

In cancer biology, the tumor microenvironment (TME) plays a critical role in tumor growth, progression, and response to therapy. The TME comprises various components, including stromal cells, immune cells, cytokines, growth factors, extracellular matrix, and physicochemical conditions such as pH and temperature.[2] The TME orchestrates multiple tumorigenic processes, including epithelial-mesenchymal transition (EMT), migration, invasion, apoptosis, and resistance to chemotherapy.[3] Various types of microenvironments are commonly used and identified in *in vitro* cell cultures, including thermal and serum conditions.[4]

One notable environmental factor influencing the TME is temperature. While hypothermia promotes cellular adaptation and survival in non-physiological conditions,[5] hyperthermia can modulate tumor behavior by affecting temperature-sensitive signaling pathways.[6] In clinical oncology, hyperthermia has been used as an adjunct therapy for various cancers, such as prostate, melanoma, bladder, esophageal, and cervical cancers. Although some of the cellular effects of hypothermia and hyperthermia are known, studies on the full explanation of their molecular mechanisms remain limited.[7]

Among the key molecules responding to temperature fluctuations are cold shock proteins (CSPs). These evolutionarily conserved proteins are rapidly upregulated in response to a temperature drop and participate in the regulation of transcription, translation, cell cycle, differentiation, and apoptosis.[1] A hallmark of these proteins is the cold shock domain (CSD), which enables them to bind DNA and RNA and modulate gene expression.[8] CSD proteins can also bind to specific cell surface receptors, inducing various downstream effects.[9] Notably, overexpression of CSPs has been implicated in tumorigenesis by promoting malignant transformation, cell proliferation, inflammatory responses, and resistance to apoptosis. In many cancers, elevated CSP levels are associated with poor clinical outcomes.[10] One of the prominent members of the CSP family is CSD containing E1 (CSDE1), which plays a critical role in translation regulation, cell differentiation, apoptosis, and stress response. CSDE1 controls the initiation of messenger RNA (mRNA) translation and modulates the expression of target genes.[11] In human embryonic stem cells (hESCs), CSDE1 has been shown to bind to fatty acid-binding protein 7 (FABP7) and vimentin mRNAs and has been suggested to be an important post-transcriptional regulator of hESC identity.[12] Dysregulation of CSDE1 has been linked to cancer progression, with studies showing its overexpression in tumors such as melanoma, where it enhances invasion and metastasis.[13] In addition, CSDE1 has emerged as a potential drug target, prognostic biomarker, and anticancer drug sensitizer in various malignancies.[11–14] Hepatocellular carcinoma (HCC) is the most prevalent form of primary liver cancer, ranking fifth among global cancer types and fourth in cancer-related mortality. The pathogenesis of HCC is complex, involving alterations in signaling pathways, DNA methylation patterns, microRNA expression, and cell cycle regulation. Although the role of CSPs in cancer has been explored in several studies, the specific relationship between CSDE1 and HCC remains largely understudied.[15]

Despite increasing interest in CSPs in oncology, limited research exists on the role of CSDE1 in HCC. This study addresses this gap by examining how temperature stress impacts CSDE1 expression and secretion in HCC cells. In addition, molecular docking analysis was conducted to predict the interaction between CSDE1 and potential ligands or regulators which have been used for cancer therapy. Molecular docking is a computational approach used to model the binding between a receptor (e.g., protein) and a ligand, providing insights into binding affinity, interaction specificity, and potential drug-target relationships. In the context of CSDE1, docking simulations may help identify molecules that modulate its function, potentially altering cancer-related signaling pathways under temperature-induced stress.[16]

This study aims to evaluate the molecular effects of temperature variation on CSDE1 in HCC cells and explore its potential as a therapeutic target through expression profiling and computational docking analysis.

MATERIALS AND METHODS

Cell Culture and Study Design

Human HCC cell line hepatoma G2 (HepG2) was obtained from ATCC (American Type Culture Collection, USA). Cells were initially cultured in Dulbecco's Modified Eagle's Medium supplemented with 10% fetal bovine serum and 1% antibiotics (penicil-

lin-streptomycin). Cells reaching 60–70% confluence were treated with trypsin, removed from the culture dish, counted, and divided into two main groups. In the control group, cells were seeded in 12- and 6-well culture dishes containing round coverslips with 50,000 and 300,000 cells, respectively. When HepG2 cells covered 60-80% of the culture surface in an incubator (37°C and 5% carbon dioxide); further, analyses described below were performed. In the experimental group, HepG2 cells were cultured in the same number in appropriate culture dishes and placed in culture conditions at 24°C. To ensure temporal consistency between conditions, the experimental group was initiated simultaneously with the control group, with temperature maintained in a separate incubator set to 24°C, while the control group was maintained under standard culture conditions at 37°C. Further analyses were performed in parallel with the control group.

Monitoring of Morphological Changes

To evaluate the changes in the morphology of HepG2 cells, live images of the cells were examined under an inverted phase microscope (Primovert, Zeiss, AG), and the images were recorded. When the cells in the control group were 60–80% confluent, both groups of cells were fixed simultaneously with appropriate fixative and stained with hematoxylin-eosin stain after fixation. The stained samples were examined and photographed under a light microscope (Primo Star, Zeiss, AG).

Total RNA Isolation and Complementary DNA (cDNA) Synthesis

RNA extraction of the experimental groups was then performed using an RNA Purification kit (innuPREP RNA Mini kit 2.0, Cat. No: 049-21, Innuscreen GmbH, Germany), according to the manufacturer's instructions. The concentration and purity of the extracted RNA samples were subsequently assessed with a BioTek Synergy Microplate Reader (Agilent Technologies, Inc.), utilizing ultraviolet absorbance. The Thermo Scientific RevertAid First Strand cDNA Synthesis kit (Cat. no. Thermo Fisher Scientific, Inc.) was employed to synthesize cDNA from total RNA, following the instructions provided by the manufacturer.

Reverse Transcription Quantitative Real-Time Polymerase Chain Reaction

Quantitative polymerase chain reaction (qPCR) was conducted on a LightCycler® 96 instrument (Roche Diagnostics) using the Ampliqon RealQ Plus Master Mix Green Without ROX kit (cat. no. A323402, Ampliqon A/S) and gene-specific primers for CSDE1 (forward sequence. 5′-CGAGAAATGGGTGTGATTGCT-3′ and reverse sequence 5′- CACGATCCACACACTTGATGAA-3′) and GAPDH (forward sequence, 5′- GCACCGTCAAGGCTGAGAAC-3′ and reverse sequence, 5′- GGATCTCGCTCCTGGAAGATG-3′). qPCR was performed using the following thermocycling conditions: Initial denaturation at 95°C for 10 min, followed by 40 cycles of denaturation at 95°C for 15 s, annealing at 58°C for 15 s, and extension at 72° C for 10 s. qPCR primer sequences were obtained from BMLabosis. The 2-ΔΔCq was employed for the relative quantification of gene expression, with GAPDH serving as the internal control.[17]

Measurement of CSDE1

CSDE1 levels in the supernatant of cell culture of the experimental groups were measured by the use of a commercial colorimetric kit (ELK Biotechnology, Turkey, Cat: ELK6392, Lot:36451010).

Molecular Docking Analysis

In the present study, the molecular interactions between CSDE1 and the drugs lenvatinib and sorafenib were investigated. The full-length, three-dimensional model of the human CSDE1 protein, as predicted by AlphaFold, was obtained from the AlphaFold Protein Structure Database (UniProt accession number: O75534, AlphaFold model ID AF-O75534-F1). In the molecular docking analysis, CSDE1 was used as the receptor, with lenvatinib and sorafenib acting as the anticancer drugs. The CSDE1 structure used is a computationally predicted AlphaFold model. The structures of lenvatinib (PubChem CID: 9823820) and sorafenib (PubChem CID: 216239) were obtained from the PubChem database. Hydrogen atoms were added to the ligand structures and partial atomic charges were then assigned. After the preparation of the ligand and receptor molecules, molecular docking experiments were performed using the AutoDock Vina program.[18] The best binding positions were then selected based on AutoDock Vina scores. The interactions between the receptor and ligand molecules were visualized using BIOVIA Discovery Studio Visualizer (Dassault Systèmes BIOVIA, 2019, San Diego).

Statistical Analysis

The Statistical Package for Social Sciences (SPSS) for Windows 20 (IBM SPSS Inc., Chicago, USA) was used for statistical assessments. All experiments were carried out with at least three independent biological replicates ($n \geq 3$). First, the Shapiro–Wilk test was used to assess whether the obtained data were distributed normally.

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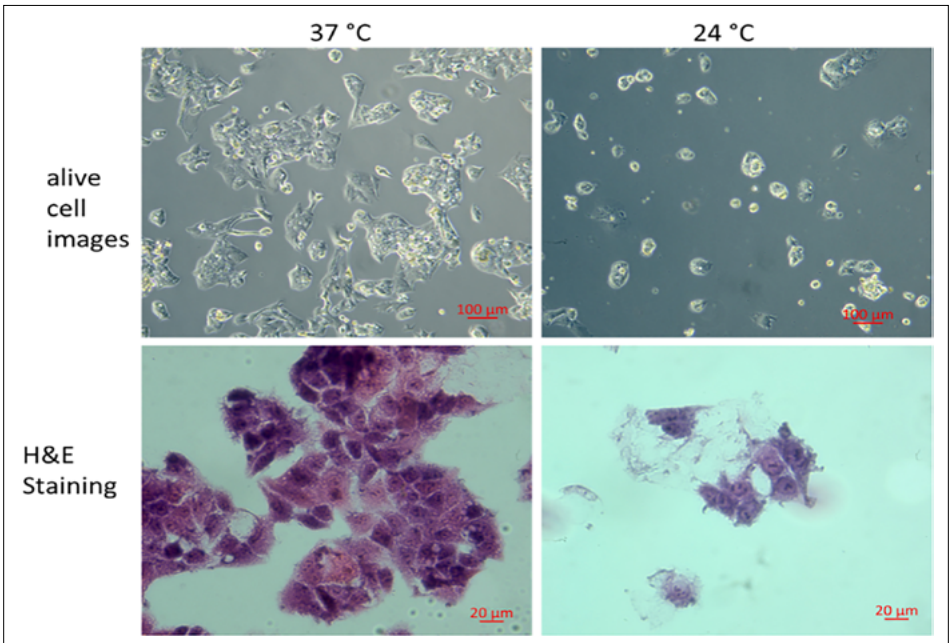


Fig. 1. Morphological images. Hepatoma G2 cells under an inverted microscope and a light microscope, with hematoxylin and eosin staining.

Subsequently, the independent-samples Student's t-test was used to analyze the experimental groups. Relative gene expression was calculated using the $2^{-\Delta\Delta Ct}$ method. P<0.05 was considered statistically significant.

RESULTS

Morphological Change

The morphological findings obtained from phase-contrast live-cell microscopy were consistent with those observed in hematoxylin and eosin-stained sections across both groups; notably, cells in the experimental group cultured at 24°C showed reduced cell density and impaired cellular integrity relative to the control group (Fig. 1).

CSDE1 Gene Expression Level

As shown in Figure 2, the effects of temperature change on CSDE1 gene expression level were higher in the cold-shocked (24°C) group compared to the control group (t(4)=−1.03, p=0.360). However, the difference was not found to be statistically significant.

CSDE1 Protein Level in Culture Supernatant

As shown in Figure 3, CSDE1 protein detected from HepG2 cell supernatants was found to be significantly higher in 24°C cell culture conditions compared to the control group at 37°C (t(4)(6)=−3.81, p=0.009).

Molecular Docking

The predicted interactions between CSDE1 and lenvatinib and sorafenib are illustrated in Figure 4 and 5, respectively. The predicted binding score for lenvatinib and sorafenib were -3.8 kcal/mol and -8.7 kcal/mol, respectively. The drugs lenvatinib and sorafenib are tyrosine kinase inhibitors are used in the treatment of cancer . Sorafenib showed a more negative predicted binding score against CSDE1 than lenvatinib in this in silico analysis; however, no binding assay, drug-treatment experiment, target-engagement analysis, or functional validation was performed, and this computational finding does not demonstrate physical binding or a functional role for CSDE1 in the response to these drugs.

DISCUSSION

CSPs are evolutionarily conserved proteins found across almost all organisms and are known to play critical roles in gene expression regulation, cellular differentiation, proliferation, and survival under environmental stress conditions.[12] Among these, CSDE1 has emerged as a key regulator in several cancers due to its ability to control mRNA translation and modulate oncogenic pathways.[11] In our study, morphological evaluation of HepG2 cells under cold shock (24°C) revealed decreased cell density and disrupted cell in-

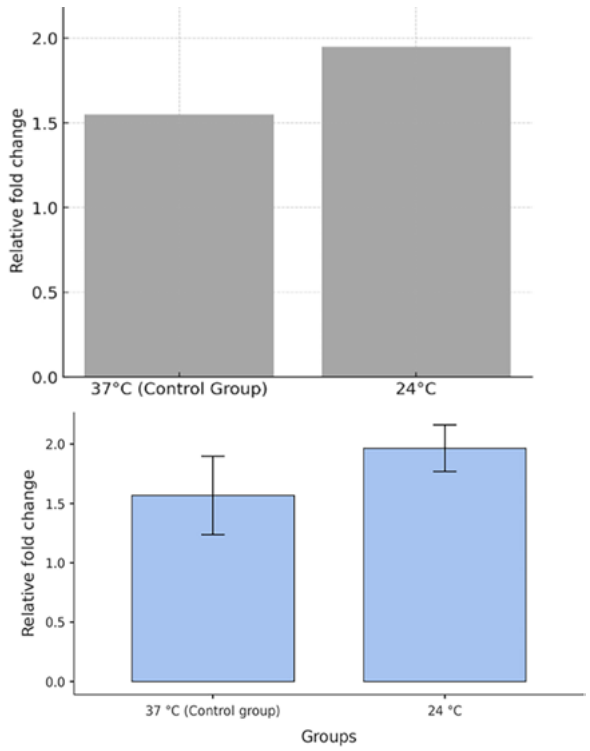


Fig. 2. Cold shock domain-containing protein E1 relative messenger RNA fold change ($2^{-\Delta\Delta Ct}$) in hepatoma G2 cells cultured at 37°C (control) and 24°C (cold shock). Bars represent group means; error bars indicate the standard deviation. Individual biological replicate values are overlaid as dots (n=3/group). Analyzed by independent samples t-test using the Statistical Package for Social Sciences statistical software.

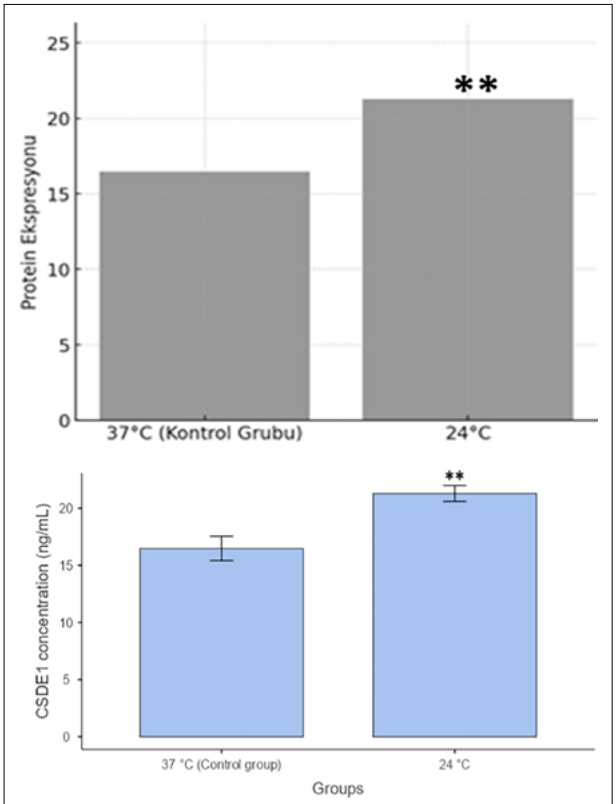


Fig. 3. Cold shock domain-containing protein E1 protein concentration (ng/mL) in hepatoma G2 cell culture supernatants, measured by enzyme-linked immunosorbent assay (450 nm) and calculated from the kit standard curve. Bars represent group means; error bars indicate the standard deviation. Individual biological replicate values are overlaid as dots (n=4/group). Analyzed by independent-samples t-test using the Statistical Package for Social Sciences statistical software (**p<0.01).

tegrity compared to control conditions, together with increased cytoplasmic granularity in some surviving cells; whether this reflects a stress-induced adaptive response or early cytotoxicity cannot be determined from morphology alone. These observations are consistent with reports that temperature-induced stress can lead to apoptosis or trigger adaptive responses in cancer cells,[5] although the present study did not include a dedicated viability or apoptosis assay to distinguish between these possibilities.

Although CSDE1 gene expression showed a nonsignificant increase under cold-shock conditions, the CSDE1 signal detected by enzyme-linked immunosorbent assay (ELISA) in the culture supernatant was significantly higher in the cold-shock group (p=0.019, two-way). A nonsignificant change in mRNA level does not by itself demonstrate that transcription was unaffected, particularly given the small sample size, and the increase in supernatant signal does not by itself establish increased intracellular protein production, stability, or active secretion. Because cold shock also reduced cell density and disrupted cellular integrity in our morphological assessment, passive release of intracellular CSDE1 from damaged or dying cells is a plausible alternative explanation for the elevated supernatant signal, one that could be evaluated in future work using viability and membrane-damage assays, together with parallel measurement of intracellular CSDE1 and normalization to viable cell number or total cellular protein. Cold-stress-associated changes in protein handling have been described in other contexts,[19] but the present data cannot establish which specific mechanism underlies the finding in HepG2 cells.

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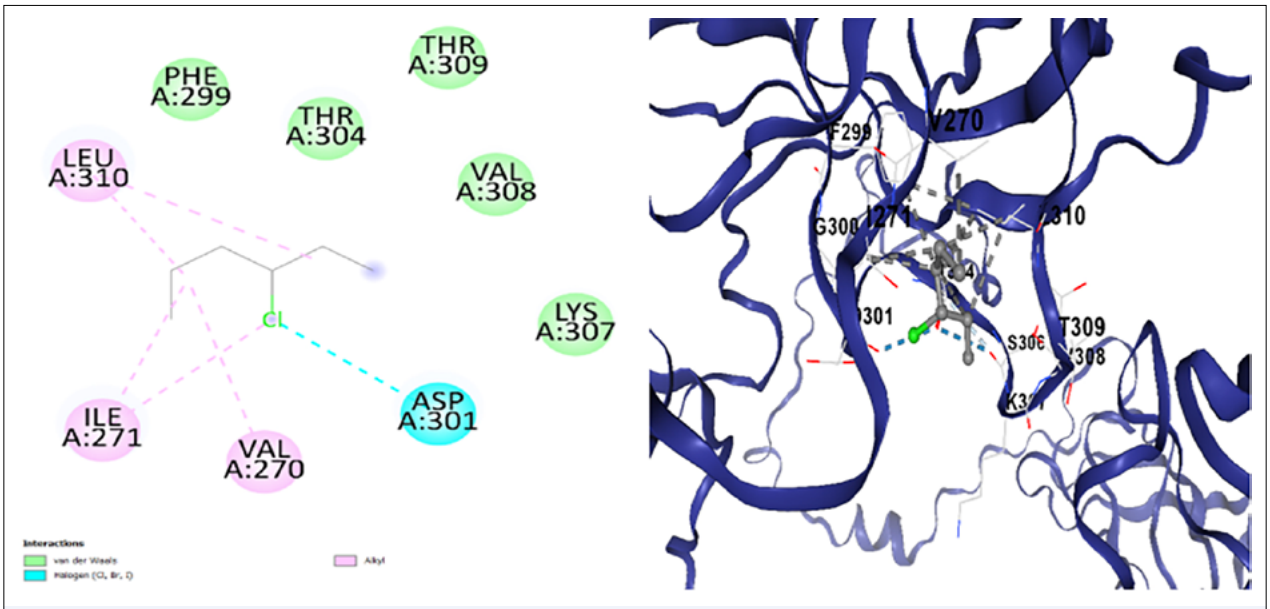


Fig. 4. Interactions of lenvatinib docked to the cold shock domain-containing protein E1.

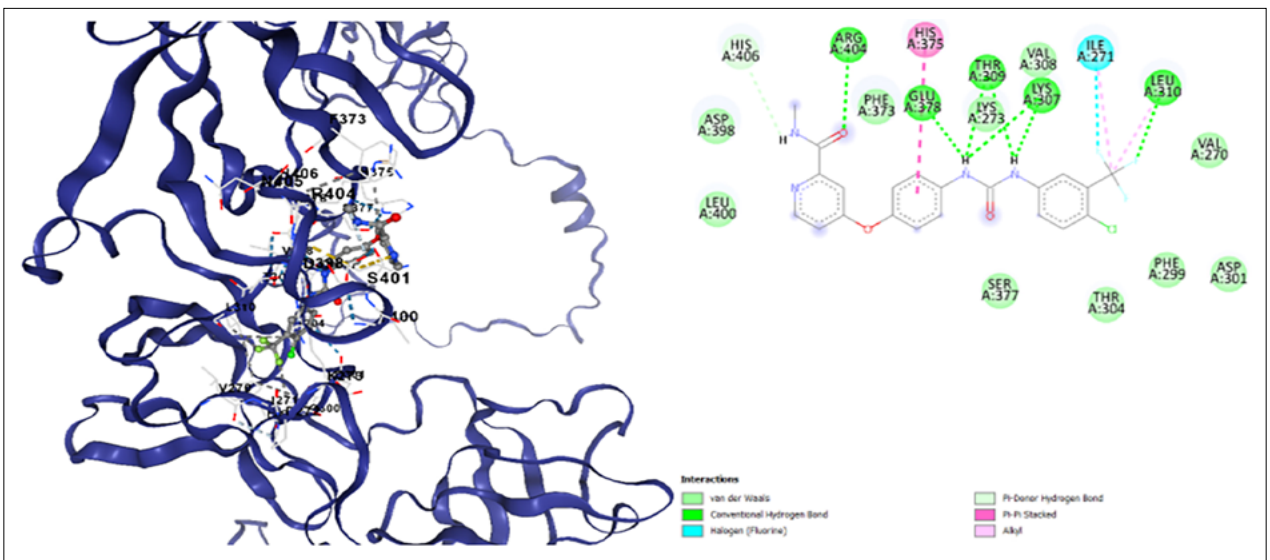


Fig. 5. Interactions of sorafenib docked to the cold shock domain-containing protein E1 macromolecule and amino acid residues involved in hydrogen bonding.

Previous studies have shown that CSDE1 is upregulated in various cancer types, including colorectal, pancreatic, melanoma, and breast cancers, where it promotes proliferation, migration, EMT, and resistance to apoptosis.[11] In triple-negative breast cancer, CSDE1 knockdown has been shown to downregulate RAC1 signaling; whether an analogous CSDE1-RAC1-ERK axis operates in HCC has not, to our knowledge, been directly demonstrated, and our data-based on a single cell line without gene knockdown or pathway-level analysis -do not test this possibility. Any parallel between our findings and RAC1/ERK-mediated oncogenic signaling in HCC should therefore be regarded as a hypothesis for future testing rather than a conclusion supported by the present study.[20]

Interestingly, while CSDE1 is generally described as an oncogene, tumor-suppressive roles have also been reported, such as in pheochromocytoma and paraganglioma[21] and oral squamous cell carcinoma.[22] This duality underscores the context-depen-

dent nature of CSDE1's role across tumor types and argues against extrapolating a single functional role to HCC without direct evidence.

Overall, culturing HepG2 cells at 24°C was associated with morphological changes, a nonsignificant increase in CSDE1 mRNA, and a significant increase in ELISA-detected CSDE1 signal in the culture supernatant. These observations are compatible with, but do not establish, post-transcriptional or post-translational regulation of CSDE1 under cold stress, and they do not distinguish active secretion from passive release associated with reduced cell viability. Given the single-cell-line design, the small number of replicates, and the absence of functional validation (e.g., CSDE1 knockdown or overexpression), we regard these findings as preliminary and hypothesis-generating rather than as evidence that CSDE1 functions as an adaptive survival factor, a prognostic biomarker, or a therapeutic target in HCC.

CONCLUSION

This study examined the effect of cold stress (24°C) on CSDE1 in HepG2 cells. Morphological assessment showed reduced cell density and disrupted cellular integrity at 24°C compared with standard culture conditions. CSDE1 mRNA expression was not significantly altered, whereas ELISA-detected CSDE1 signal in the culture supernatant was significantly higher under cold stress. Because this increase coincided with signs of reduced cell density and disrupted membrane integrity, it may reflect passive release of intracellular protein rather than confirmed active secretion; the present data cannot distinguish between these mechanisms. Molecular docking indicated a more negative predicted binding score for sorafenib than for lenvatinib against CSDE1; in the absence of binding or functional assays, this should be regarded as an exploratory, hypothesis-generating observation rather than evidence of a functional interaction.

Based on a single cell line, without independent biological replication, viability or membrane-damage assays, intracellular CSDE1 measurement, or functional validation, CSDE1 cannot at this stage be presented as an established prognostic biomarker, therapeutic target, or mediator of adaptive survival in HCC. Further studies incorporating independent biological replicates, viability/membrane-integrity assays, parallel intracellular and extracellular CSDE1 measurement, and functional experiments such as CSDE1 knockdown or overexpression are needed to clarify whether the changes observed here reflect a regulated biological response and to evaluate their relevance to HCC biology and therapy.

Ethics Committee Approval: Since this is a cell culture study, an ethics committee approval is not required.

Informed Consent: It is a cell culture study.

Conflict of Interest Statement: The authors declare that they have no conflicts of interest with the contents of this article.

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