Original Article

Unveiling the role of HACE1 in cervical cancer: implications for human papillomavirus infection and prognosis

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Background: Cervical cancer, one of the prevalent malignancies among females, is closely associated with human papillomavirus (HPV) infection. Homologous to the E6-AP carboxyl terminus (HECT) domain and ankyrin repeat containing E3 ubiquitin-protein ligase 1 (HACE1) plays pivotal roles in various cancers. This study aimed to elucidate the expression of HACE1 in cervical cancer and its correlation with clinical features.

Methods: From The Cancer Genome Atlas Cervical Squamous Cell Carcinoma and Endocervical Adenocarcinoma (TCGA-CESC) and Gene Expression Omnibus (GEO, GSE6791) datasets, we obtained RNA-Seq profiles and associated clinical information. Differential gene analysis was conducted using the R "limma" package. Implications for HPV infection and the overall survival (OS) of cervical cancer were determined by performing differential expression analysis and the Cox proportional hazards regression model. Immunohistochemical analyses were used to validate the expression in cervical cancer and normal cervical tissue. Further, nomogram was constructed to predict OS in cervical cancer. Whether the model was credible was evaluated according to receiver operating characteristic (ROC) curves and concordance curves. To further evaluate the potential functions of HACE1, we conducted functional enrichment analysis. Finally, we assessed methylation levels in HPV+ and HPV– patients in the TCGA-CESC dataset.

Results: Utilizing TCGA and GSE6791 datasets, we observed significant upregulation of HACE1 in cervical cancer patients, particularly linked to HPV infection. Immunohistochemical staining revealed enhanced HACE1 expression in tumor tissues. Further analysis demonstrated a significant positive correlation between elevated HACE1 and HPV-associated proteins (E1, E6, and E7). Moreover, high HACE1 expression was associated with adverse prognosis in cervical cancer patients. Multivariate Cox analysis indicated that HACE1 could serve as an independent prognostic factor. We developed a prognostic model integrating HPV subtypes, the International Federation of Gynecology and Obstetrics (FIGO) staging, and HACE1, exhibiting strong predictive efficacy for cervical cancer prognosis. Gene enrichment analysis indicated HACE1's potential involvement in multiple signaling pathways during cervical cancer progression, while the demethylation of cg03002526 in HPV-positive patients might contribute to HACE1 upregulation.

Conclusions: Our study reveals that HACE1 upregulation is associated with cervical cancer, particularly in HPV-positive patients. HACE1 emerges as an independent prognostic factor, linked to unfavorable outcomes.

Keywords: Homologous to the E6-AP carboxyl terminus (HECT) domain and ankyrin repeat containing E3 ubiquitin-protein ligase 1 (HACE1); cervical cancer; human papillomavirus infection (HPV infection); prognosis; biomarker

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Introduction

Cervical cancer ranks as the fourth most common cancer in women globally and stands as a leading cause of female cancer-related mortality (1). Despite advances in human papillomaviruses (HPV) screening and treatment approaches that have improved the prognosis for early-stage patients, the prognosis for those with metastatic and advanced cervical cancer remains suboptimal (2-4). Persistent infection with high-risk HPV types constitutes a critical factor in cervical cancer onset and progression. HPV infection triggers cervical cell abnormalities and malignant transformation, pivotal steps in cervical cancer development. Certain HPV subtypes are also linked to adverse prognosis in cervical cancer (5,6). While surgery, chemotherapy, and radiotherapy remain primary treatment modalities, immunotherapy presents a promising novel approach (7). The search for novel cervical cancer prognostic biomarkers and therapeutic targets is imperative for developing more effective treatment strategies.

Against this backdrop, homologous to the E6-AP carboxyl terminus (HECT) domain and ankyrin repeat containing E3 ubiquitin-protein ligase 1 (HACE1), a conserved protein involving the HECT domain, has gained attention. Studies have indicated HACE1's interaction with Rac1 and its ubiquitination at its lysine residues, modulating processes such as cell motility, protein translation, and cell growth (5,8). Furthermore, HACE1 mediates optineurin (OPTN) ubiquitination, promoting OPTN-p62 interaction to activate autophagy (9). In various cancers, HACE1 plays diverse roles; its deficiency leads to conditions like mitochondrial dysfunction (10) in astrocytes and neural developmental defects (11). HACE1 inhibits the activity of Ras-related C3 botulinum toxin substrate (RAC) family GTPases, preventing lung cancer development (12). In liver cancer, HACE1 expression correlates with pathology grading and prognosis (13). In melanoma and glioma cells, HACE1 exhibits pro-oncogenic characteristics (14,15). However, HACE1's biological relevance in cervical cancer remains unexplored.

Given the ambiguity surrounding HACE1 in cervical cancer, this study aimed to assess its expression in cervical cancer patients and ascertain its potential as a prognostic risk factor. By mining differentially expressed genes between high and low HACE1 expression groups in Gene Expression Omnibus (GEO) and The Cancer Genome Atlas (TCGA) database, along with Gene Ontology (GO), Kyoto Encyclopedia of Genes and Genomes (KEGG), and Gene Set Enrichment Analysis (GSEA), we enriched the understanding of HACE1-related molecular functions (MFs) and pathways. We validated HACE1's expression at the protein level using clinical samples. We aimed to explore whether HACE1 could serve as a potential prognostic risk factor for cervical cancer, providing guidance for clinical intervention and enhancing survival rates for late-stage cervical cancer patients. We present this article in accordance with the TRIPOD reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-2120/rc).

Highlight box

Key findings

- Homologous to the E6-AP carboxyl terminus (HECT) domain and ankyrin repeat containing E3 ubiquitin-protein ligase 1 (HACE1) may be a prognostic biomarker in cervical cancer, particularly in human papillomavirus (HPV)-positive patients.

What is known and what is new?

- Cervical cancer, one of the prevalent malignancies among females, is closely associated with HPV infection.
- HACE1 can predict the prognosis of cervical cancer.

What is the implication, and what should change now?

- The role of HACE1 in cervical cancer needs further research.

Methods

Data sources and selection

The Cancer Genome Atlas Cervical Squamous Cell Carcinoma and Endocervical Adenocarcinoma (TCGA-CESC) dataset from the TCGA database (https://portal.gdc.cancer.gov/) encompassed 306 RNA-Seq profiles and associated clinical information. HPV subtype data were based on research from The Cancer Genome Atlas Research Network (16). Given the absence of normal cervical samples in TCGA, the GSE6791 dataset (https://www.ncbi.nlm.nih.gov/geo) comprising gene expression microarray

data from 20 cervical cancer tumor samples and 8 normal cervical samples was utilized. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by Ethics Committee of The People's Hospital of Chongqing Liangjiang New Area (No. 2023-19) and individual consent for this retrospective analysis was waived.

Survival analysis and prognostic model construction

Kaplan-Meier methodology was employed for survival analysis, employing the R "survival" package to generate survival curves. The optimal cut off value is obtained based on the "survminer" package of R. Specifically, the optimal cut off value of HACE1 in this article is 1.92 [log(TPM+1)]. Cox proportional hazards regression models were used to evaluate the impact of HACE1 and other clinical features on cervical cancer prognosis [overall survival (OS)]. Prognostic forest plots, receiver operating characteristic (ROC) curves, and concordance curves were produced and analyzed using the R "survminer" package.

Functional enrichment analysis

Differential gene analysis was conducted using the R "limma" package, setting criteria for differential genes as |log fold change (FC)| >1 and P<0.05. GO enrichment analysis was carried out using the R "org.Hs.eg.db" package. Furthermore, differential genes underwent molecular complex detection algorithm analysis using the Metascape tool (https://metascape.org/) to identify potential protein interaction network components. GSEA software was employed for KEGG pathway enrichment analysis in patients with high and low HACE1 expression. The SMART database (http://www.bioinfo-zs.com/smartapp/) was used to obtain the methylation site beta-value of HACE1.

Immunohistochemical analysis

Six cervical cancer HPV-positive samples and six normal cervical tissue samples were obtained from the Pathology Department of The People's Hospital of Chongqing Liangjiang New Area. Samples were subjected to deparaffinization, antigen retrieval, endogenous peroxidase inhibition (3% hydrogen peroxide solution, incubated at room temperature in the dark for 25 min), protein blocking, primary antibody incubation (Proteintech, Wuhan, China, Cat No. 24104-1-AP, incubated overnight at 4 ℃), and secondary antibody incubation (Servicebio, Wuhan, China, Cat No. GB23303, incubated at room temperature for 50 min), staining reaction (using DAB staining solution, positive staining appeared as brown-yellow. Cell nuclei were counterstained with hematoxylin, resulting in blue staining of the nuclei), and dehydration and sealing of the slides. Immunohistochemical sections were photographed, and the expression levels of HACE1 in cervical cancer tissues were evaluated using an optical microscope.

Statistical analysis

For expression data, *t*-tests or analysis of variance (ANOVA) were utilized for differential analysis, with P values indicating significance. Kaplan-Meier methodology was used for survival analysis, with significance determined via log-rank tests. Multivariate Cox regression analysis assessed HACE1's potential as an independent prognostic factor. All statistical analyses were performed using R 4.2.1, considering P<0.05 as the threshold for significance.

Results

Upregulation of HACE1 in cervical cancer associated with HPV infection

Due to the absence of normal cervical samples in the TCGA-CESC dataset, we analyzed differential gene expression between tumor and normal samples in the GSE6791 dataset. We observed significant upregulation of HACE1 in tumor samples (*Figure 1A*, P<0.001). Immunohistochemical staining of cervical cancer and normal cervical tissues revealed stronger HACE1 staining in tumor tissues (*Figure 1B*). Subsequently, based on previous reports on HPV subtyping in the TCGA-CESC, we found upregulated HACE1 expression in HPV-infected patients (*Figure 1C*, P<0.05), but no statistically significant differences among different HPV subtypes (*Figure 1D*). This suggests that HACE1 expression is linked to HPV infection without subtype specificity. Furthermore, in HPV-positive patients, HACE1 expression exhibited a significant positive correlation with HPV protein expression, with the highest correlation observed for E1, E6, and E7 proteins (*Figure 1E*, Rho =0.37, 0.36, 0.36, P<0.001). Additionally, we analyzed HACE1 expression under different clinical features and found no significant associations with the International Federation of Gynecology and Obstetrics (FIGO) stage, histopathological grade, or age, implying

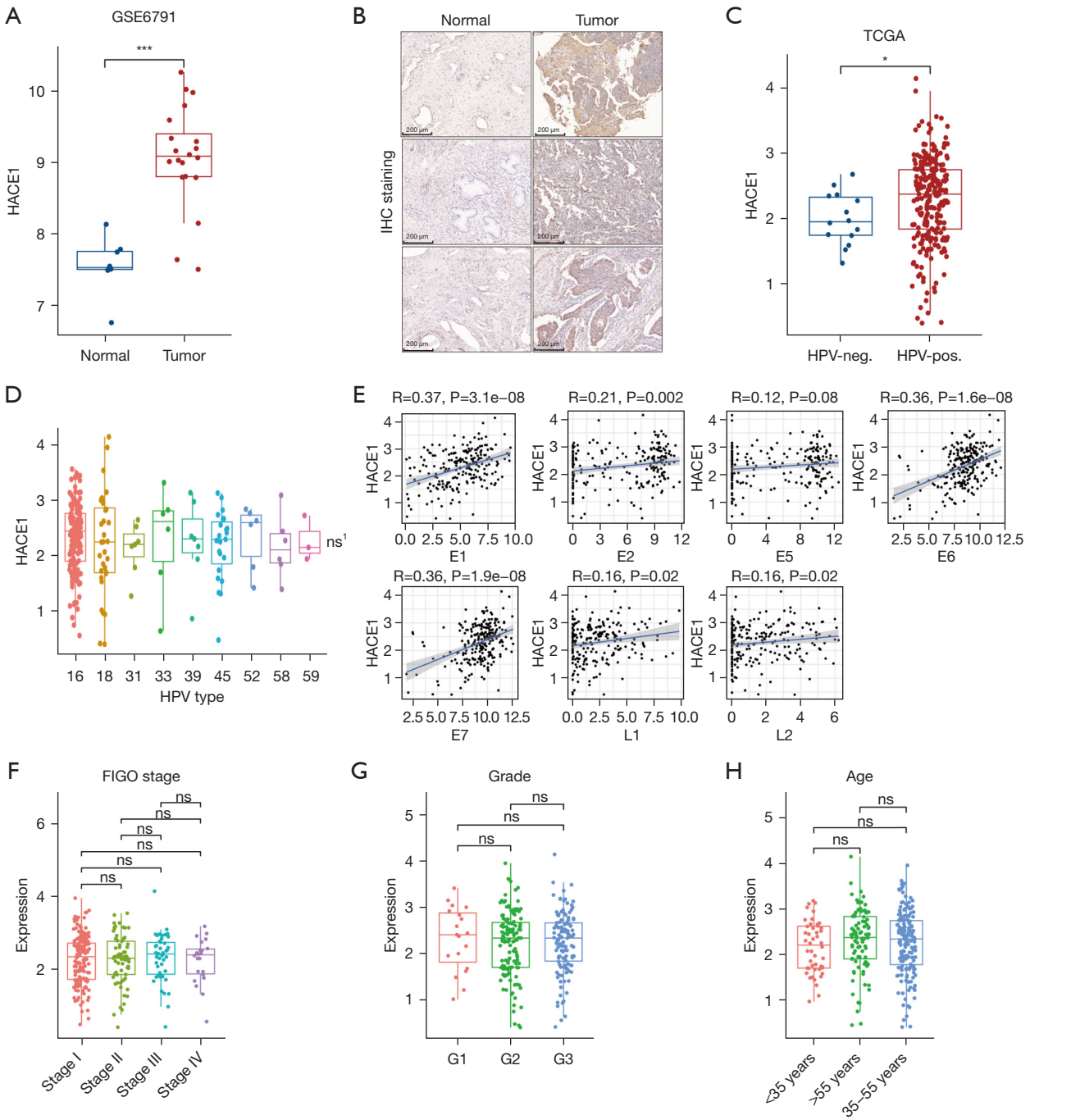

Figure 1 HACE1 expression is upregulated in cervical cancer and correlated with HPV infection. (A) Comparison of HACE1 expression between tumor samples and normal samples in the GSE6791 dataset (***, P<0.001). (B) Representative immunohistochemical staining images of HACE1 expression in cervical tumor tissues and adjacent normal tissues (20× magnification). (C) HACE1 expression is elevated in HPV-infected patients compared to non-infected patients (*, P<0.05). (D) No significant differences in HACE1 expression were observed among different HPV subtypes ([1], using analysis of variance to compare the expression differences of HACE1 between different HPV subtypes and HPV16 type; ns, P>0.05). (E) Correlation analysis between HACE1 and HPV protein expressions in HPV-positive patients. (F) HACE1 expression in cervical cancer patients based on FIGO stage (ns, P>0.05). (G) HACE1 expression in cervical cancer patients based on histological grade (ns, P>0.05). (H) HACE1 expression in cervical cancer patients based on age groups (ns, P>0.05). HACE1, homologous to the E6-AP carboxyl terminus (HECT) domain and ankyrin repeat containing E3 ubiquitinprotein ligase 1; IHC, immunohistochemistry; TCGA, The Cancer Genome Atlas; HPV, human papillomavirus; neg., negative; pos., positive; ns, not significant; FIGO, the International Federation of Gynecology and Obstetrics.

stable upregulation of HACE1 expression across different clinical profiles (*Figure 1F-1H*).

Association of HACE1 expression with adverse prognosis in cervical cancer patients

We further analyzed the impact of HACE1 on cervical cancer patient survival. The results demonstrated that patients with high HACE1 expression had significantly worse OS than those with low expression (*Figure 2A*, P=0.02). Subgroup analysis based on clinical features indicated that this survival difference was primarily concentrated in FIGO stage III/IV patients (*Figure 2B*, P=0.02), poorly differentiated (G3) histology patients (*Figure 2C*, P=0.01), and patients in the high-incidence age range for cervical cancer (*Figure 2D*, P=0.005). Although HACE1 expression did not exhibit statistically significant differences in these subgroups, the observed survival differences within these subgroups suggest that HACE1 has the potential to serve as an independent prognostic factor for cervical cancer.

HACE1 as an independent prognostic factor for cervical cancer patients

To further verify whether HACE1 could act as an independent prognostic factor for predicting cervical cancer patient prognosis, we conducted multivariate Cox analysis of HACE1 and clinical pathological features. The results indicated that HACE1, independent of age, FIGO stage, histopathological grade, and HPV subtype, served as an independent prognostic factor for cervical cancer patient prognosis (*Figure 3A*, P=0.048). Given the prognostic significance of HACE1, we integrated statistically significant indicators from multivariate Cox analysis into a prognostic forest plot (*Figure 3B*). The ROC curve demonstrated an area under the curve (AUC) value of 0.802 for the prognostic model, indicating robust predictive performance (*Figure 3C*). The concordance curves for 1, 3, and 5 years further confirmed the reliability of incorporating HACE1 as a prognostic indicator (*Figure 3D-3F*).

Functional enrichment analysis of HACE1 in cervical cancer

To further evaluate the potential functions of HACE1, we first conducted gene differential analysis between patients with high and low HACE1 expression and performed GO enrichment analysis across three dimensions: biological processes (BPs), MFs, and cellular components (CCs). Results indicated that BP pathways were mainly associated with cell cycle regulation and the TGF-β pathway, while CC pathways involved various cellular compartments such as RNA polymerase II transcription regulation complexes, nuclear outer membranes, and vesicle cavities. MF pathways were primarily related to DNA-binding transcriptional activator activity, phosphatidylinositol 3-kinase regulatory subunit binding, and RNA polymerase II-specific DNA-binding transcription factor binding (*Figure 4A*). Furthermore, employing Metascape, we conducted molecular complex detection algorithm analysis on differential genes to identify densely connected protein interaction network components, identifying several tumor-related pathways, including angiogenesis and TP53 pathways in MCODE_1, DNA damage-induced cellular response regulation and cell cycle regulation in MCODE_2, and the IL-17 signaling pathway in MCODE_4 (*Figure 4B*). Additionally, using GSEA enrichment analysis, upregulated KEGG pathways in patients with high HACE1 expression were found to significantly overlap with multiple pro-oncogenic pathways [normalized enrichment score (NES) >2, false discovery rate (FDR) <0.05], including MAPK signaling, mTOR signaling, NOTCH signaling, and WNT signaling pathways (*Figure 4C*). Collectively, these findings suggest that HACE1 may promote cervical cancer progression through multiple pathways, ultimately leading to adverse prognosis.

HPV-positive patient's low methylation of cg03002526 associated with adverse prognosis

To further explore the cause of HACE1 upregulation, we assessed methylation levels in HPV+ and HPV– patients in the TCGA-CESC dataset. We found that most methylation sites exhibited minimal fluctuations in beta-value, while cg08460464, cg03002526, and cg02098413 showed more significant variability (*Figure 5A*). Differential analysis of methylation sites revealed that HPV-positive patients had significantly lower methylation levels at cg03002526 compared to HPV-negative patients (P<0.01, *Figure 5B*). Moreover, patients with low methylation levels at cg03002526 had significantly worse prognosis than those with high methylation levels (P=0.008, *Figure 5C*). This indicates that HPV infection may affect the methylation level of cg03002526 of HACE1 and ultimately affect the prognosis of patients.

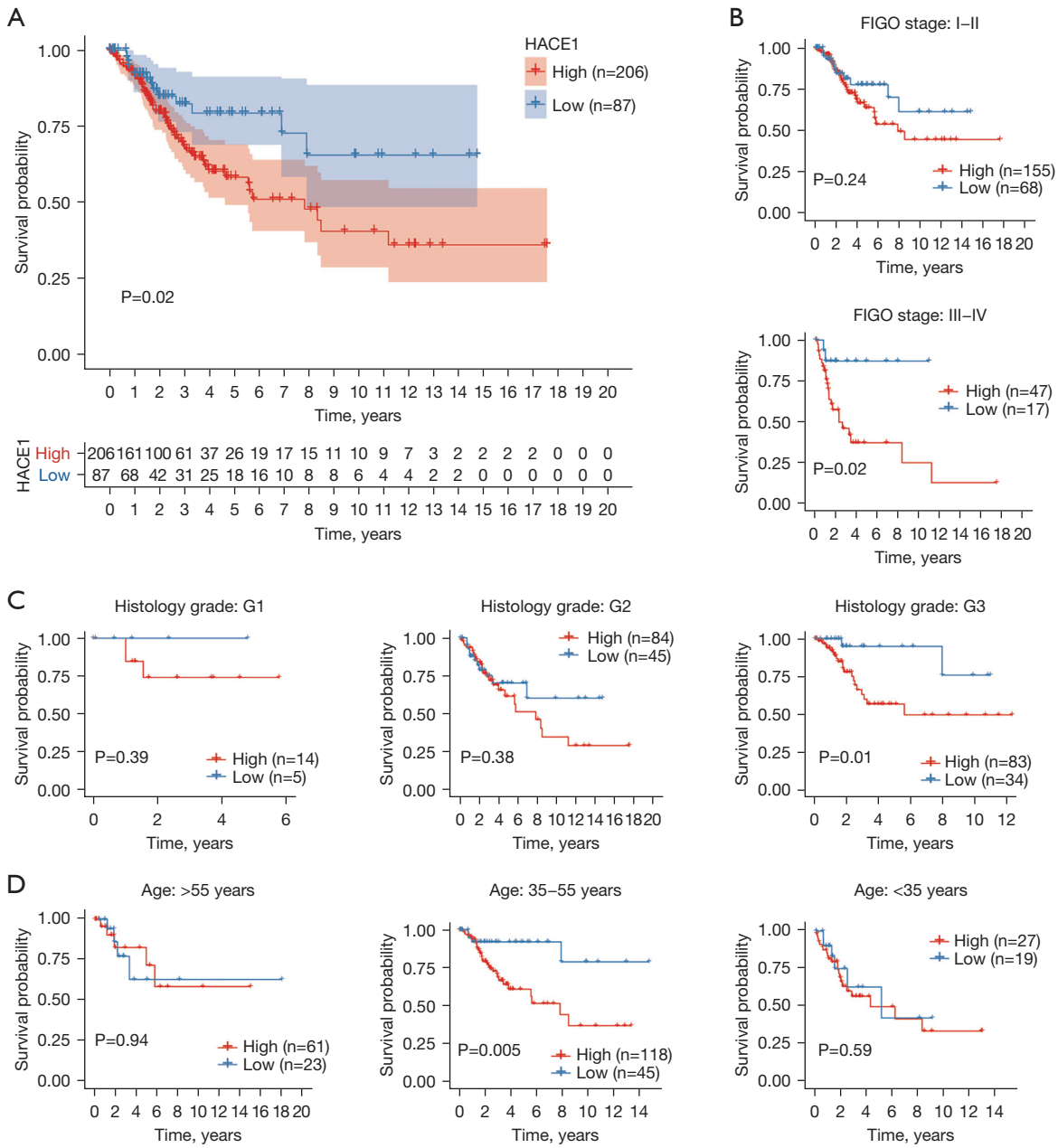

Figure 2 High HACE1 expression is associated with poor prognosis in cervical cancer patients. (A) Kaplan-Meier survival curve comparing the prognosis of cervical cancer patients with high and low HACE1 expression. (B) Survival differences associated with HACE1 expression in FIGO stage I–II/III–IV patients. (C) Survival differences associated with HACE1 expression in G1/G2/G3 histological grade patients. (D) Survival differences associated with HACE1 expression in different age group patients. HACE1, homologous to the E6-AP carboxyl terminus (HECT) domain and ankyrin repeat containing E3 ubiquitin-protein ligase 1; FIGO, the International Federation of Gynecology and Obstetrics.

Discussion

HACE1 is an E3 ubiquitin ligase that exhibits differential expression in various cancer types. Its primary role involves protein degradation and ubiquitination of specific signaling molecules, thereby regulating multiple crucial cellular signaling pathways. Prior research commonly identified it as a tumor suppressor gene. In gastric cancer, HACE1 downregulates the Wnt/β-catenin pathway, inhibiting cancer

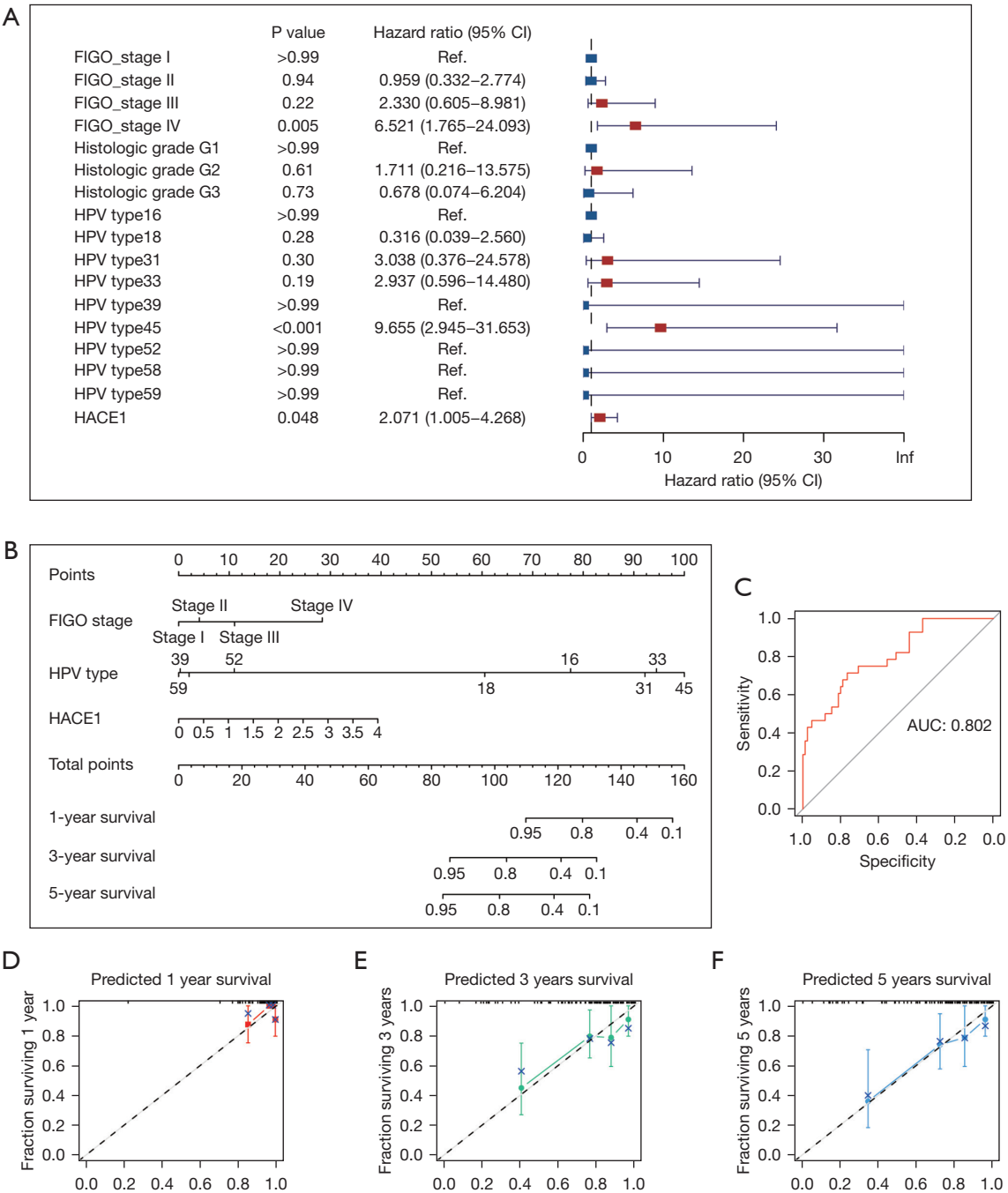

Figure 3 HACE1 functions as an independent prognostic factor for cervical cancer patients. (A) Multivariate Cox analysis demonstrates that HACE1 is an independent prognostic factor for cervical cancer patients (P=0.048). Age, stage, histologic grade, and HPV type are categorical variables, and HACE1 is a continuous variable. (B) Prognostic nomogram incorporating statistically significant factors (HPV subtype, FIGO stage, and HACE1) predicting patient outcomes. (C) ROC curve for the prognostic nomogram with an AUC value. (D-F) Calibration curves at 1, 3, and 5 years demonstrating the reliability of the prognostic model with HACE1 inclusion. FIGO, the International Federation of Gynecology and Obstetrics; HPV, human papillomavirus; HACE1, homologous to the E6-AP carboxyl terminus (HECT) domain and ankyrin repeat containing E3 ubiquitin-protein ligase 1; CI, confidence interval; AUC, area under the curve; ROC, receiver operating characteristic.

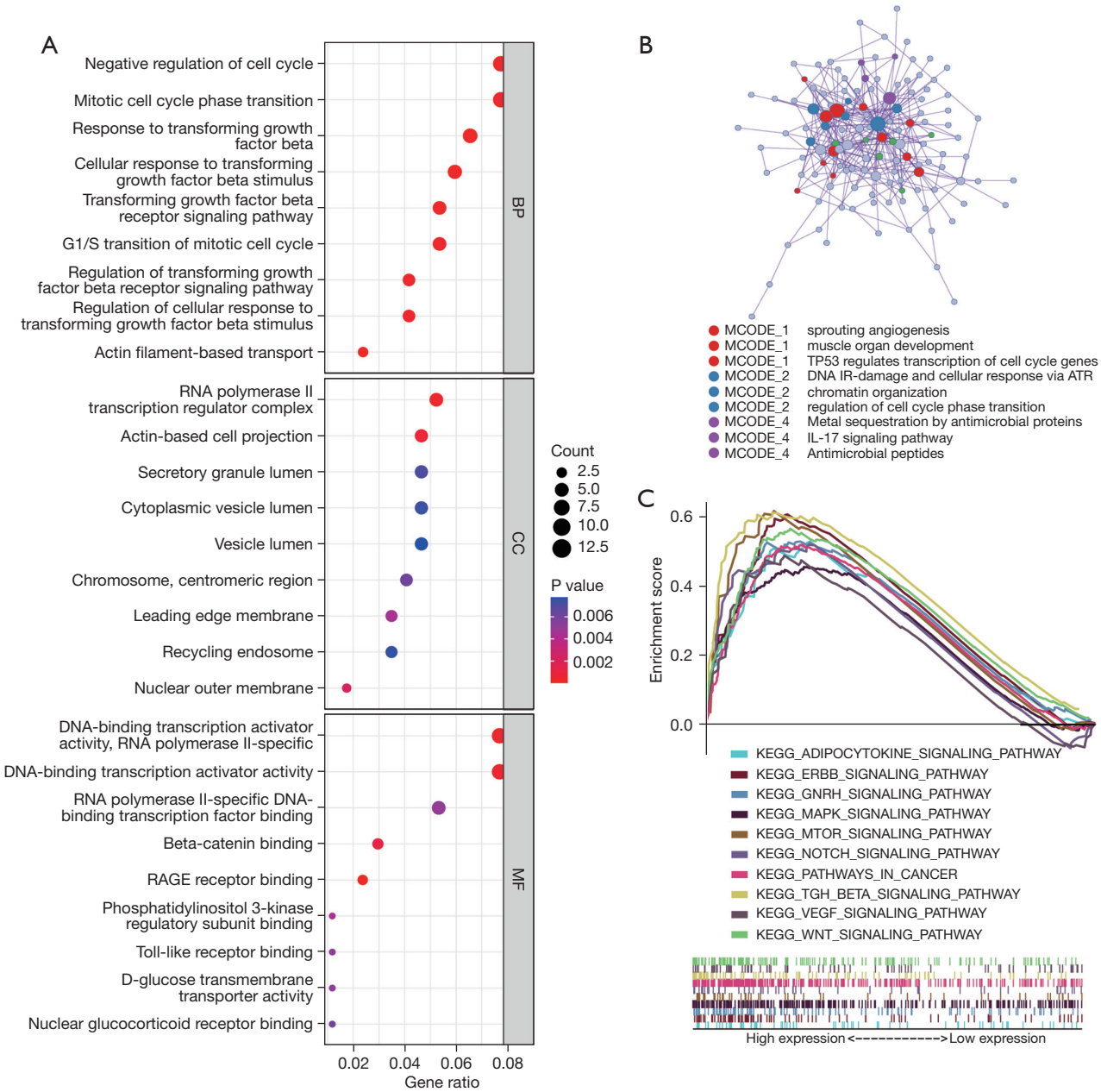

Figure 4 Functional enrichment analysis of HACE1 in cervical cancer. (A) GO enrichment analysis of differentially expressed genes associated with HACE1 in BPs, MFs, and CCs. (B) MCODE algorithm identified protein interaction networks related to HACE1-associated pathways. (C) GSEA reveals upregulated KEGG pathways in high HACE1 expressing patients. BP, biological process; MF, molecular function; CC, cellular component; MCODE, molecular complex detection; IR, ionizing radiation; KEGG, Kyoto Encyclopedia of Genes and Genomes; HACE1, homologous to the E6-AP carboxyl terminus (HECT) domain and ankyrin repeat containing E3 ubiquitin-protein ligase 1; GO, Gene Ontology; GSEA, Gene Set Enrichment Analysis.

cell proliferation, migration, and inducing apoptosis (17). HACE1 ubiquitinates OPTN to promote the formation of an autophagic receptor complex with p62/SQSTM1, thereby accelerating autophagic flux to suppress lung cancer cell growth and tumorigenicity (9). Additionally, in liver cancer, DNA demethylation of the *HACE1* gene promoter upregulates HACE1 expression, facilitating ubiquitination of OPTN and enhancing autophagic activity in liver cancer

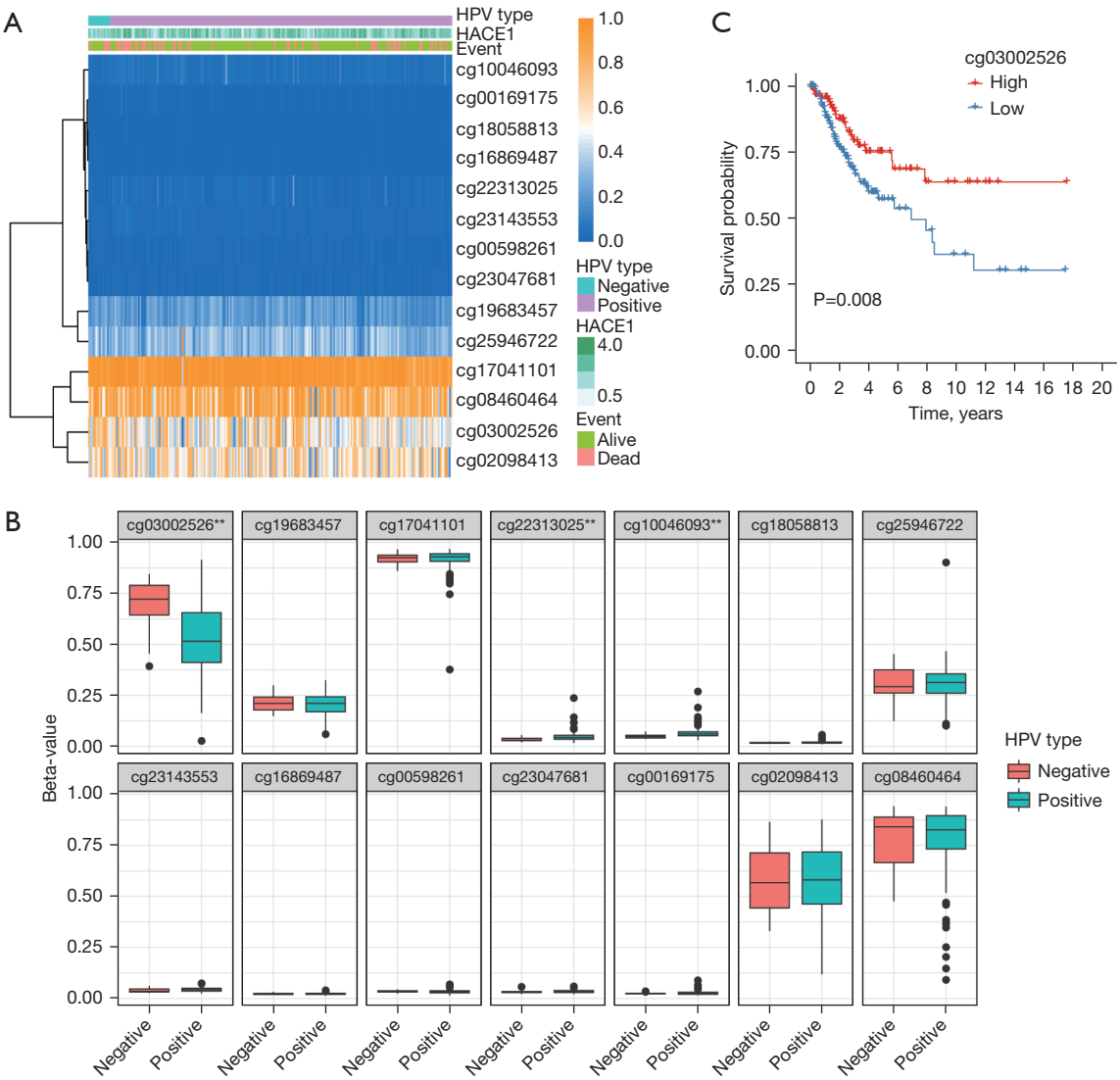

Figure 5 Methylation status of cg03002526 and its association with HPV-positive patients' prognosis. (A) Methylation profiles of selected CpG sites in the *HACE1* gene in TCGA-CESC dataset. (B) Differential methylation analysis of cg03002526 in HPV-positive and HPV-negative patients (**, P<0.01). (C) Kaplan-Meier survival curve comparing the prognosis of cervical cancer patients with high and low of cg03002526 methylation levels. HPV, human papillomavirus; HACE1, homologous to the E6-AP carboxyl terminus (HECT) domain and ankyrin repeat containing E3 ubiquitin-protein ligase 1; TCGA-CESC, The Cancer Genome Atlas Cervical Squamous Cell Carcinoma and Endocervical Adenocarcinoma.

cells, consequently inhibiting their proliferation (18). However, Sako *et al.* suggest that HACE1 is not a tumor suppressor in natural killer (NK) cell malignancies (19). Research has revealed HACE1's role in melanoma, where it promotes K27 branched ubiquitination to regulate fibronectin (FN) secretion, thereby enhancing cell adhesion and migration, exerting a pro-oncogenic effect (14). HACE1 activates nuclear factor erythroid 2-related factor 2 (NRF2) to enhance malignant behavior in glioblastoma cells, closely associated with poorer prognosis in grade III and IV glioblastoma patients (15). In this study, we have unveiled the significance of HACE1 expression in cervical cancer for the first time, constructing a clinical prognosis model based on HACE1 and achieving robust predictive efficacy. Our findings suggest that HACE1 can serve as an independent prognostic factor for cervical cancer. Moreover,

functional enrichment analysis indicates that enhanced HACE1 expression is linked to activation of multiple pro-oncogenic signaling pathways, including TGF-β.

TGF-β has intricate roles in tumors, often acting as a tumor suppressor in early stages, but its aberrant activation during tumor progression can promote occurrence, invasion, and metastasis (20,21). TGF-β promotes tumor progression through various mechanisms, including cell proliferation, epithelial-mesenchymal transition (EMT) regulation, immune evasion, and drug resistance (22-24). In this study, we discovered significant enrichment of TGF-β-related pathways in GO-BP and GSEA analyses, further supporting the significant correlation between HACE1 expression and the TGF-β signaling pathway, indicating HACE1's likely crucial role in tumor development.

E1, E6, and E7 are three major proteins of HPV, tightly associated with cervical cancer (25). Elevated E1 gene expression leads to abnormal proliferation of cervical epithelial cells, driving cervical cancer. E6 and E7 proteins mainly regulate cervical epithelial cell proliferation, transformation, and evasion from immune surveillance by inhibiting the expression of multiple tumor suppressor genes. Therefore, HPV's E6 and E7 viral oncoproteins play a pivotal role in driving cellular oncogenesis (26,27). This study found that HACE1 was upregulated in HPV-positive patients and significantly correlated with HPV-related proteins E1, E6, and E7. This suggests that HACE1 might exert its influence by impacting the interaction between HPV viral proteins and host cells.

DNA methylation is a form of epigenetic modification that does not alter DNA sequence but affects cellular function by regulating gene expression. DNA methylation regulatory mechanisms include direct inhibition of transcription factor binding and interactions between methyl-CpG-binding proteins and other transcriptional repressors (28,29). Previous studies indicate that DNA methylation status of the *HACE1* gene is linked to tumor occurrence and development (30,31). In this study, we observed cg03002526 demethylation in HPV-positive patients, associated with poor prognosis. This likely activates cancer-related signaling pathways, ultimately impacting cervical cancer prognosis.

Of course, our study has limitations. Firstly, due to sample limitations, we only validated HACE1 expression in clinical samples, without assessing the expression of other related genes. Secondly, the critical role of HACE1 in cervical cancer requires further *in vitro/in vivo* experiments to confirm, which is our next step.

Conclusions

Our study reveals that HACE1 upregulation is associated with cervical cancer, particularly in HPV-positive patients. HACE1 emerges as an independent prognostic factor, linked to unfavorable outcomes. Notably, HACE1's involvement in pro-oncogenic pathways, including TGF-β, highlights its importance in tumor progression. Further research is needed for comprehensive validation and mechanistic insights.

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Footnote

Reporting Checklist: The authors have completed the TRIPOD reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-2120/rc

Data Sharing Statement: Available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-2120/dss

Peer Review File: Available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-2120/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-2120/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by Ethics Committee of The People's Hospital of Chongqing Liangjiang New Area (No. 2023-19) and individual consent for this retrospective analysis was waived.

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References

1. WHO guideline for screening and treatment of cervical pre-cancer lesions for cervical cancer prevention [Internet]. 2nd ed. Geneva: World Health Organization; 2021 [cited 2023 Aug 9]. (WHO Guidelines Approved by the Guidelines Review Committee). Available online: http://www.ncbi.nlm.nih.gov/books/NBK572317/
2. Li H, Wu X, Cheng X. Advances in diagnosis and treatment of metastatic cervical cancer. J Gynecol Oncol 2016;27:e43.
3. Cohen PA, Jhingran A, Oaknin A, et al. Cervical cancer. Lancet 2019;393:169-82.
4. Feng CH, Mell LK, Sharabi AB, et al. Immunotherapy With Radiotherapy and Chemoradiotherapy for Cervical Cancer. Semin Radiat Oncol 2020;30:273-80.
5. Shanmugasundaram S, You J. Targeting Persistent Human Papillomavirus Infection. Viruses 2017;9:229.
6. Okunade KS. Human papillomavirus and cervical cancer. J Obstet Gynaecol 2020;40:602-8.
7. Ferrall L, Lin KY, Roden RBS, et al. Cervical Cancer Immunotherapy: Facts and Hopes. Clin Cancer Res 2021;27:4953-73.
8. Castillo-Lluva S, Tan CT, Daugaard M, et al. The tumour suppressor HACE1 controls cell migration by regulating Rac1 degradation. Oncogene 2013;32:1735-42.
9. Liu Z, Chen P, Gao H, et al. Ubiquitylation of autophagy receptor Optineurin by HACE1 activates selective autophagy for tumor suppression. Cancer Cell 2014;26:106-20.
10. Ehrnhoefer DE, Southwell AL, Sivasubramanian M, et al. HACE1 is essential for astrocyte mitochondrial function and influences Huntington disease phenotypes in vivo. Hum Mol Genet 2018;27:239-53.
11. Nagy V, Hollstein R, Pai TP, et al. HACE1 deficiency leads to structural and functional neurodevelopmental defects. Neurol Genet 2019;5:e330.
12. Kogler M, Tortola L, Negri GL, et al. HACE1 Prevents Lung Carcinogenesis via Inhibition of RAC-Family GTPases. Cancer Res 2020;80:3009-22.
13. Zhang Z, Teng M, Xu Z, et al. Correlations of HACE1 expression with pathological stages, CT features and prognosis of hepatocellular carcinoma patients. J BUON 2020;25:2570-5.
14. El-Hachem N, Habel N, Naiken T, et al. Uncovering and deciphering the pro-invasive role of HACE1 in melanoma cells. Cell Death Differ 2018;25:2010-22.
15. Da C, Pu J, Liu Z, et al. HACE1-mediated NRF2 activation causes enhanced malignant phenotypes and decreased radiosensitivity of glioma cells. Signal Transduct Target Ther 2021;6:399.
16. Cancer Genome Atlas Research Network, Albert Einstein College of Medicine, Analytical Biological Services, et al. Integrated genomic and molecular characterization of cervical cancer. Nature 2017;543:378-84.
17. Chen YL, Li DP, Jiang HY, et al. Overexpression of HACE1 in gastric cancer inhibits tumor aggressiveness by impeding cell proliferation and migration. Cancer Med 2018;7:2472-84.
18. Yu Z, Li Y, Han T, et al. Demethylation of the HACE1 gene promoter inhibits the proliferation of human liver cancer cells. Oncol Lett 2019;17:4361-8.
19. Sako N, Dessirier V, Bagot M, et al. HACE1, a potential tumor suppressor gene on 6q21, is not involved in extranodal natural killer/T-cell lymphoma pathophysiology. Am J Pathol 2014;184:2899-907.
20. Luo F, Huang Y, Li Y, et al. A narrative review of the relationship between TGF-β signaling and gynecological malignant tumor. Ann Transl Med 2021;9:1601.
21. Xie F, Ling L, van Dam H, et al. TGF-β signaling in cancer metastasis. Acta Biochim Biophys Sin (Shanghai) 2018;50:121-32.
22. Chan MK, Chan EL, Ji ZZ, et al. Transforming growth factor-β signaling: from tumor microenvironment to anticancer therapy. Explor Target Antitumor Ther 2023;4:316-43.
23. Yang L, Pang Y, Moses HL. TGF-beta and immune cells: an important regulatory axis in the tumor microenvironment and progression. Trends Immunol 2010;31:220-7.
24. Larson C, Oronsky B, Carter CA, et al. TGF-beta: a master immune regulator. Expert Opin Ther Targets 2020;24:427-38.
25. Bhattacharjee R, Das SS, Biswal SS, et al. Mechanistic role of HPV-associated early proteins in cervical cancer: Molecular pathways and targeted therapeutic strategies. Crit Rev Oncol Hematol 2022;174:103675.

26. Balasubramaniam SD, Balakrishnan V, Oon CE, et al. Key Molecular Events in Cervical Cancer Development. Medicina (Kaunas) 2019;55:384.
27. Malla R, Kamal MA. E6 and E7 Oncoproteins: Potential Targets of Cervical Cancer. Curr Med Chem 2021;28:8163-81.
28. Moore LD, Le T, Fan G. DNA methylation and its basic function. Neuropsychopharmacology 2013;38:23-38.
29. Wang Q, Xiong F, Wu G, et al. Gene body methylation in cancer: molecular mechanisms and clinical applications. Clin Epigenetics 2022;14:154.
30. Sakata M, Kitamura YH, Sakuraba K, et al. Methylation of HACE1 in gastric carcinoma. Anticancer Res 2009;29:2231-3.
31. Hibi K, Sakata M, Sakuraba K, et al. Aberrant methylation of the HACE1 gene is frequently detected in advanced colorectal cancer. Anticancer Res 2008;28:1581-4.

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