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UBE2C promotes malignancy of cutaneous squamous cell carcinoma

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Abstract

Background: Our study aimed to study the involvement of ubiquitin-conjugating enzyme E2C (UBE2C) in cutaneous squamous cell carcinoma (cSCC). As the second most common malignancy with a rising incidence, understanding the molecular mechanisms driving cSCC is crucial for improved diagnosis and treatment.

Methods: We combined multiple datasets of cSCC in Gene Expression Omnibus (GEO) repository to investigate its expression and diagnostic value. We collected patient specimens and performed immunohistochemistry to examine its expression in patients and its correlation with tumor histological grade. Moreover, we compared UBE2C expression between cSCC cells and primary human epidermal keratinocytes. Subsequently, we explored the effects of UBE2C inhibition on tumor cell proliferation, migration and apoptosis through CCK8, wound healing, Transwell, and flow cytometry assay.

Results: The integrated analysis revealed an upregulation of UBE2C level in cSCC. Immunohistochemistry demonstrated high UBE2C expression was associated with poorer tumor histological grade. Cell experiments further supported the crucial role of UBE2C in promoting the malignant behavior of cSCC cells.

Conclusion: Our findings indicate UBE2C is up-regulated in cSCC and contributes to its malignant behavior. These results suggest UBE2C has the potential to serve as both a cSCC biomarker and a therapeutic target.

KEYWORDS
biomarker, cell apoptosis, cell migration, cell proliferation, cutaneous squamous cell carcinoma, UBE2C

1 | INTRODUCTION

Cutaneous squamous cell carcinoma (cSCC) is the second most prevalent tumor.[1,2] The primary factor attributed to cSCC is sunlight exposure. Occupational UV exposure has been shown to increase the risk of cSCC, and the strength of the association increases with decreasing latitude.[3] Additionally, numerous other factors have been confirmed to be closely associated with the occurrence and development of cSCC, including chemical carcinogens, ionizing radiation, human papillomavirus infection, immunosuppression, genetic mutations, and others.[4] Notably, genetic research remains a pivotal focal point in current research endeavors. Hence, it is imperative to delve into the molecular level to explore the pathogenic mechanisms of cSCC.

Ubiquitin-conjugating enzyme E2C (UBE2C) is an integral component of the ubiquitin-proteasome system and plays a crucial role in mediating the transfer of ubiquitin from the anaphase-promoting

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complex/cyclosome (APC/C) to target proteins, promoting ubiquitination labeling and protein degradation.[5] The ubiquitin-proteasome system is primarily responsible for intracellular protein degradation, and it is involved in various cellular processes such as cell proliferation and DNA repair.[6] Dysregulation of this pathway may contribute to the initiation and progression of multiple tumors.

In order to explore the role of UBE2C in cSCC, we combined multiple datasets in the Gene Expression Omnibus (GEO) repository to analyze the expression of UBE2C and its diagnostic value as a biomarker. Subsequently, we collected patient specimens to investigate the correlation between UBE2C expression and tumor histological grade. Finally, we detected the biological function of UBE2C in cSCC cells.

2 | MATERIALS AND METHODS

2.1 | Bioinformatics analysis

We downloaded datasets from GEO database using the R package "GEOquery", which included samples of normal skin and cSCC. The R package "sva" was employed to remove batch effects between GSE108008, GSE117247, GSE39612, GSE42677, GSE45164, and GSE7553, followed by dataset combination. The "limma" package was used for normalization and differential expression analysis. Differential genes were defined as adj.P.Val < 0.01 and abs(logFC) > 1. The volcano plot was generated using the R package "ggplot2". The heatmap was presented using the R package "pheatmap". The "clusterProfiler" package was utilized for Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) analysis. The violin and box plot of UBE2C expression was generated using the R package "ggstatsplot" through Hiplot Pro (https://hiplot.com.cn/), a comprehensive web service for biomedical data analysis and visualization. The receiver operating characteristic curve (ROC) was displayed using the R package "pROC" through Hiplot Pro.

2.2 | Immunohistochemistry (IHC)

A total of nine normal skin tissues after cosmetic surgery and 13 cSCC tissues were derived from the second affiliated hospital of Xi'an Jiaotong University. Immunohistochemistry follows the steps described earlier.[7] The primary antibody was UBE2C antibody (12134-2-AP, Proteintech, USA). The slides were evaluated by two pathologists as: −, negative; +, weakly positive; ++, moderately positive; +++, strongly positive.

2.3 | Isolation of primary human epidermal keratinocytes-adult (Heka)

Heka cells were extracted from two pieces of adult foreskin. Circumcision tissues were collected from the department of urology, the first affiliated hospital of Xi'an Jiaotong University. Tissues were treated with 0.25% Dispase II (Sigma) at 4°C for 16 h to separate epidermis and dermis. Keratinocytes were then obtained by digesting the epidermis with 0.25% trypsin at 37°C for 5 min. RNA and protein were extracted from the third passage primary cells.

2.4 | Cell culture

Heka cells were cultured in keratinocyte medium (Sciencell, USA). SCL-1 cells were purchased from Xi'an Youbios Biotechnology (Xi'an, China). A431 cells were purchased from Procell Life Science & Technology (Wuhan, China). SCL-1 and A431 cells were cultured in DMEM (Dulbecco's Modified Eagle's Medium) supplemented with 10% fetal bovine serum (FBS). All cells were maintained in a humidified incubator at 37°C with a 5% CO_2 atmosphere.

2.5 | Construction of a stable cell line with low UBE2C expression

When SCL-1 cells reached a confluency of 40%, 80 μL of lentivirus with a titer of 1×10^8 TU/mL was added. The customized shRNA sequences were: shUBE2C, 5′-GGACCATTCTGCTCTCCAT-3′; shCtrl, 5′-TTCTCCGAACGTGTCACGT-3′. The lentivirus was synthesized by GenePharma (Shanghai, China), and had a puromycin resistance gene, but did not include a fluorescent tag. Knockdown efficiency was validated by Western blot.

2.6 | Cell proliferation assay using CCK-8

After transfection, SCL-1 cells were seeded in 96-well plates at a density of 1500 cells. CCK-8 reagent was added and incubated for 1.5 h at 37°C. The absorbance was measured at 450 nm using a microplate reader.

2.7 | Flow cytometry detection of cell apoptosis

Cells were resuspended in 100 μL binding buffer and stained with an PE Annexin V Apoptosis Detection Kit (559763, BD Biosciences, USA). Apoptotic cells were identified as PE-positive and 7-AAD-negative. The stained cells were analyzed using a NovoCyte flow cytometer.

2.8 | Cell scratch assay

SCL-1 cells were seeded in 6-well culture plates and allowed to grow to full confluency. A scratch was made using a 200 μL microliter sterile pipette tip. Scratches were imaged after 48 h. The percentage of wound healing was calculated as (width of the scratch at the start—width of the scratch at the end)/width of the scratch at the start × 100%.

2.9 | Transwell assay for cell migration

Transwell cell migration assay was performed using 24-well transwell inserts with 8 μm pores. Cells were starved overnight and seeded in the upper chamber at a density of 20,000 per well, and 600 μL serum-free medium was added to the lower chamber. The plates were incubated for 24 h. Non-migratory cells on the upper side were removed with a cotton swab, and cells that had migrated to the lower side of the membrane were fixed with 4% paraformaldehyde and stained with 0.1% crystal violet. At last the chamber was photographed using an inverted microscope.

2.10 | RNA extraction and qRT-PCR

Total RNA was extracted using RNAiso Plus (9109, Takara, Japan), and cDNA was synthesized using high-capacity cDNA reverse transcription kit (AG11706, Accurate Biology, China) following the manufacturer's instructions. Next, qRT-PCR was performed using SYBR Green qPCR Kit (AG11701, Accurate Biology, China). Primers were designed with the following sequence (UBE2C: forward primer, 5′-GGATTTCTGCCTTCCCTGAA-3′ and reverse primer, 5′-GATAGCAGGGCGTGAGGAAC-3′; GAPDH: forward primer, 5′-CCCCACCACACTGAATCTCC-3′ and reverse primer, 5′-GTACATGACAAGGTGCGGCT-3′). The expression level of UBE2C was normalized to that of GAPDH. The results were analyzed using ΔΔCt method and expressed as the relative levels compared to control group.

2.11 | Western blot

A total of five normal skin tissues and five cSCC tissues were collected for Western blot experiments. Cells and tissue blocks were lysed on ice using RIPA buffer (Beyotime, China) containing protease and phosphatase inhibitors. Total protein was separated by a SDS-PAGE gel and then transferred to a polyvinylidene difluoride (PVDF) membrane (Millipore, USA). After blocking in 5% skim milk for 2 h, the membrane was incubated with primary antibodies (UBE2C, 12134-2-AP, Proteintech, USA; GAPDH, 10494-1, Proteintech, USA) at 4°C overnight and horseradish peroxidase (HRP)-conjugated secondary antibody (goat anti-rabbit, AB0101, Abways, China) for 1 h at room temperature. Finally, the membrane strips were visualized using an ECL system (Millipore, USA).

2.12 | Statistical analysis

The Mann–Whitney *U* test was employed to analyze the expression of UBE2C in GEO database. The Wilcoxon rank test for two independent samples was used to analyze the expression of UBE2C in patients. Kendall's Tau-b correlation analysis [8,9] was utilized to examine the correlation between UBE2C level (ordinal variable) and histological grade (ordinal variable) in cSCC patients. Two-Way ANOVA was used to compare the differences in CCK8 assay. Student's *t*-test was employed to compare the differences between two groups in other experiments. All data were presented as mean ± standard deviation. Each experiment was repeated three times, and $p < 0.05$ was considered statistically significant.

3 | RESULTS

3.1 | UBE2C was highly-expressed in cSCC

The integrated dataset comprised a total of 159 samples, including 101 normal and 58 cSCC samples. After normalization, the medians of all samples aligned along a single horizontal line (Figure 1A), with a difference observed between normal and cSCC groups (Figure 1B). Prior to conducting UBE2C analysis, we performed further analysis on the differentially expressed genes in the merged dataset. A total of 355 differentially expressed genes were identified, including 147 up-regulated genes and 208 down-regulated genes in cSCC (Figure 1C). The heatmap displayed the top 50 genes exhibiting the most significant differences (Figure 1D). GO/KEGG analysis revealed that the differentially expressed genes were primarily enriched in biological processes such as skin development, cell growth, and nuclear division (Figure 1E). The expression of UBE2C was higher than normal in cSCC, with statistical significance (Figure 1F). Moreover, UBE2C demonstrated a high diagnostic value for distinguishing cSCC (Figure 1G).

3.2 | High UBE2C levels suggested a poorer degree of cSCC differentiation

We performed Western blot using skin tissue protein extracted from normal individuals and cSCC patients to validate the bioinformatics results. The expression of UBE2C in SCC tissues was significantly higher than in normal tissues to varying degrees (Figure 2A). Next, we compared UBE2C expression in cells and observed that the mRNA and protein levels of UBE2C were significantly elevated in cSCC cell lines such as A431 and SCL −1, compared to the Heka (Figure 2B,C). Considering the differential expression of UBE2C in SCC tissues, we hypothesized that this might be related to different degrees of differentiation. Therefore, we collected skin tissue samples from normal individuals and SCC patients for IHC. UBE2C was weakly expressed in the basal layer of normal epidermis, but the staining intensity and extensity of UBE2C increased significantly in cSCC tissues, and the staining in low-differentiated tumor was stronger than that in well differentiated tumor (Figure 2D–F). We collected a total of nine normal tissues and 13 SCC tissues, including six moderately or poorly differentiated cases and seven well-differentiated cases. The IHC results demonstrated increased expression of UBE2C in cSCC (Table 1), and its high levels were correlated with poor degree of tumor differentiation (Table 2).

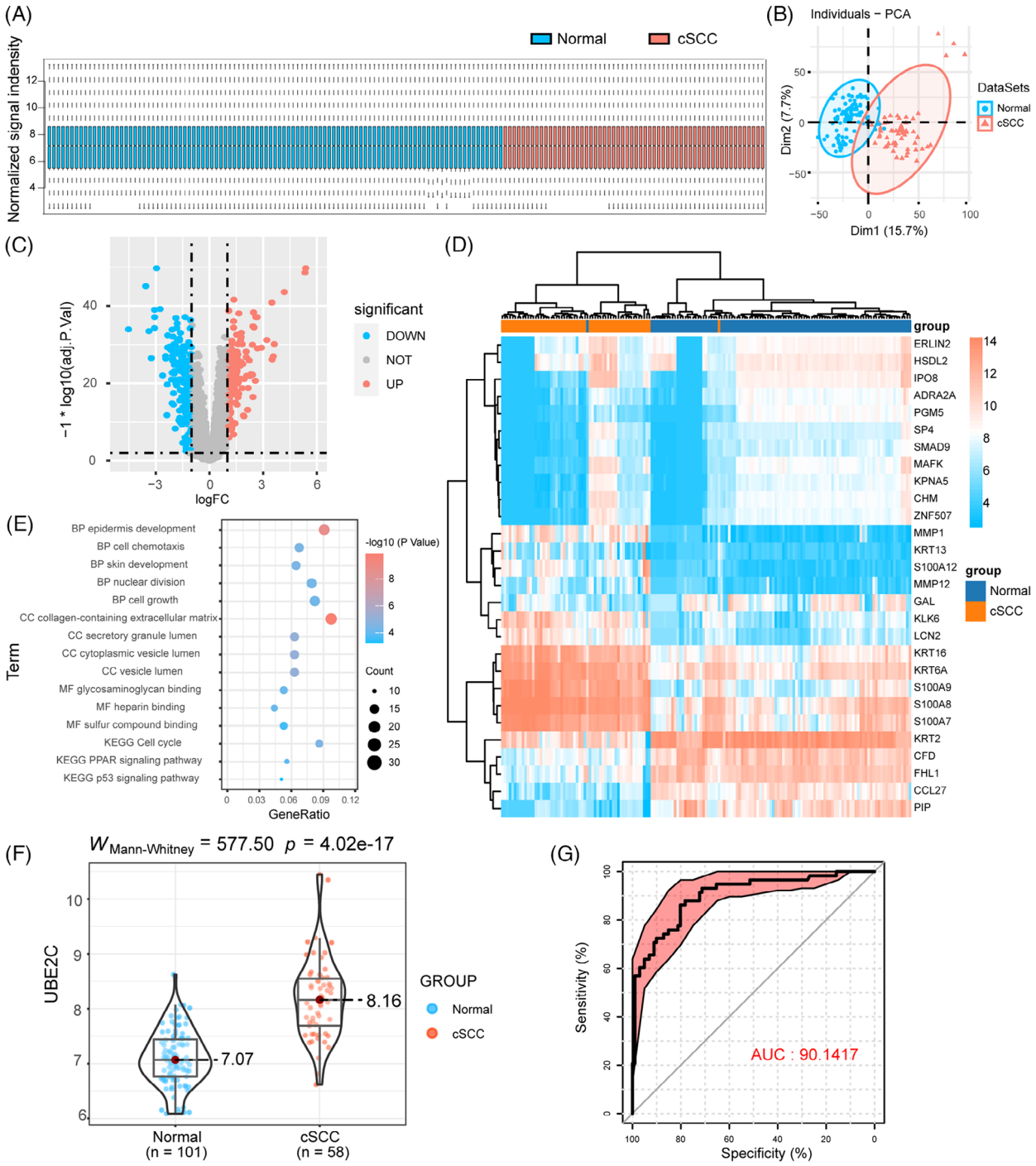

FIGURE 1 Combined bioinformatics analysis of multiple datasets in GEO database. (A) Normalized processing results for each sample. (B) Principal component analysis of normal group and cSCC group. (C) Volcano map of differential expressed genes. (D) Heat map of the top 50 genes with the most significant expression difference. (E) GO/KEGG analysis of differential expressed genes. (F) UBE2C expression in normal and cSCC group in GEO database. (G) ROC of the expression level of UBE2C in distinguishing patients with cSCC.

3.3 | Inhibition of UBE2C attenuated the malignant phenotype of cSCC cells

We constructed SCL-1 cells with low UBE2C expression by lentivirus infection. Western blot confirmed a decreased UBE2C level in SCL-1 cells, indicating successful gene suppression (Figure 3A). After UBE2C silencing, cell growth rate slowed down and cell number reduced (Figure 3B). In addition, the proportion of apoptotic cells in sh-UBE2C group significantly increased, particularly early apoptosis, with the ratio rising from 12.54% to 21.29% (Figure 3C). Scratch assay results showed that the scratch healing rate decreased after UBE2C expression was inhibited (Figure 3D). Transwell assay revealed the number

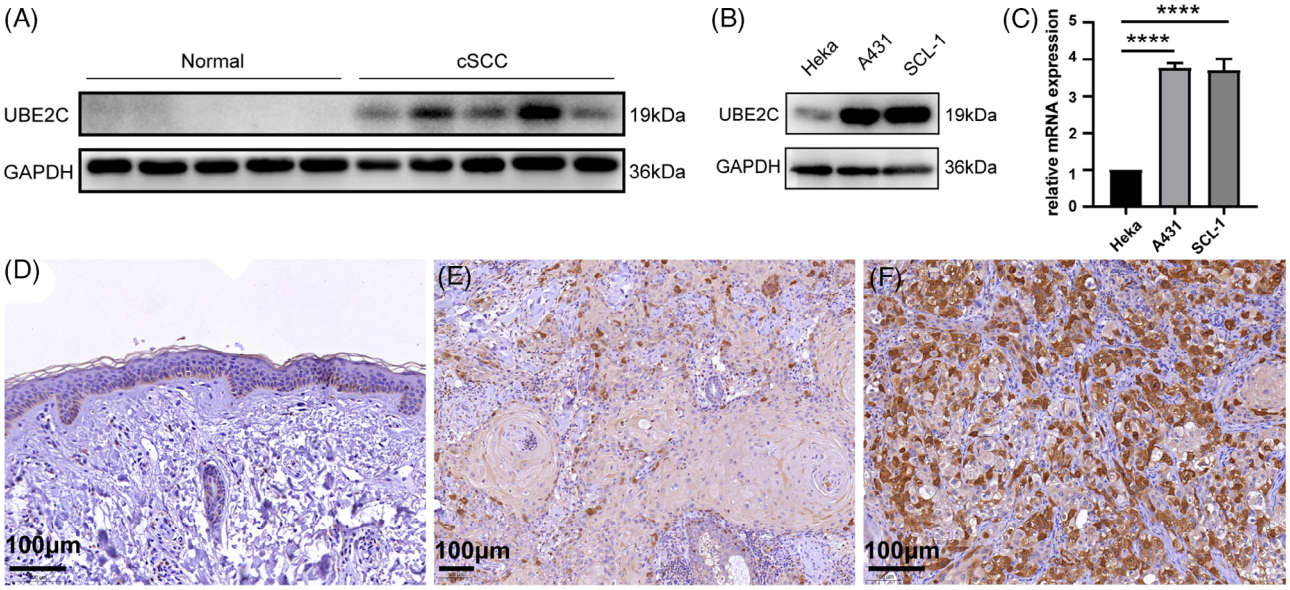

FIGURE 2 UBE2C expression in cSCC cells and patients. (A) Western blot results of UBE2C in healthy skin and cSCC tissues. Western blot (B) and qRT-PCR (C) analysis of UBE2C levels in primary keratinocytes and cSCC cells. Immunohistochemistry staining of normal skin (D), highly differentiated cSCC (E) and moderately/poorly differentiated cSCC (F). **** $p < 0.001$.

TABLE 1 UBE2C expression in normal skin and cutaneous squamous cell carcinoma.

		UBE2C					
Group	*n*	−	+	++	+++	*T*	*p*
Normal	9	5	4	0	0	57	<0.001
cSCC	13	0	6	4	3		

T, Wilcoxon rank test for two independent samples; −, negative; +, weakly positive; ++, moderately positive; +++, strong positive.

of SCL-1 cells migrating to the lower chamber decreased after UBE2C was deleted (Figure 3E). These experiments indicated that UBE2C was essential for cell proliferation, apoptosis and migration, and UBE2C inhibition can weaken the malignant phenotype of cSCC cells.

4 | DISCUSSION

The incidence of cSCC is increasing globally. In addition to sunlight exposure being a known inducer of cSCC, multiple genes are closely associated with the occurrence of cSCC. In this article, we investigated the role of UBE2C in cSCC.

UBE2C belongs to the E2 ubiquitin-conjugating enzyme family and mainly delivers ubiquitin to target proteins such as CyclinA and Cyclin B through APC/C, thereby ensuring orderly progression of the cell cycle.[10,11] Additionally, during cell mitosis, UBE2C can mediate the degradation of securin, an inhibitor of the separase enzyme, thereby facilitating the separation of sister chromatids and promoting the continuation of mitosis.[12] Currently, there is limited research on the association between UBE2C and skin. Kraft et al.[7] demonstrate UBE2C is up-regulated in melanoma compared to normal epidermis, and exhibite strong staining in mitotic cells. Another study further confirms the overexpression of UBE2C in melanoma, and UBE2C silencing is shown to induce G2/M arrest, thereby inhibiting cell growth.[13]

We conducted multidimensional experiments including bioinformatics, histology, and cytology to investigate the expression of UBE2C in cSCC. Our findings revealed varying degrees of UBE2C upregulation in cSCC. UBE2C is involved in cell cycle progression and mitosis, and its aberrant expression can disrupt normal cell cycle and division processes, which is a common feature of tumors.[14] Studies have shown that UBE2C is up-regulated in multiple types of cancer, such as hepatocellular carcinoma,[15] Endometrial Cancer,[16] breast cancer,[17] and Cervical Cancer.[18]

In addition, high UBE2C level was significantly associated with poor histological grade. Tumors characterized by moderate to poor differentiation indicate a higher degree of malignancy. Therefore, we believe that elevated UBE2C expression in cSCC signifies a higher malignant potential. In invasive breast cancer, high UBE2C expression is associated with adverse prognostic features such as high tumor grade, lymphovascular invasion, hormone receptor negativity, and HER2 positivity.[17] In gastric cancer, it has been found that the expression of UBE2C is associated with lymph node metastasis, TNM staging, and adverse prognosis, making it an independent prognostic indicator.[19] Some researchers collected data from malignant glioma patients and performed Cox analysis, revealing that patients with high levels of UBE2C exhibit a significant decrease in overall survival time, suggesting its potential as a reliable prognostic indicator.[20] These results are consistent with our hypothesis that higher levels of UBE2C in malignant tumors correlate with poorer histological grade, thereby affecting tumor malignancy and patient prognosis. Therefore, we proceeded to validate our hypothesis.

TABLE 2 Correlation between UBE2C expression and histological grade in patients with cutaneous squamous cell carcinoma.

		UBE2C					
Histological grade	***n***	**−**	**+**	**++**	**+++**	**Correlation coefficient**	***p***
High differentiated	7	0	5	2	0	0.609	0.026
Moderate/poor differentiated	6	0	1	2	3		

Correlation coefficient, Kendall's Tau-b correlation analysis; −, negative; +, weakly positive; ++, moderately positive; +++, strong positive.

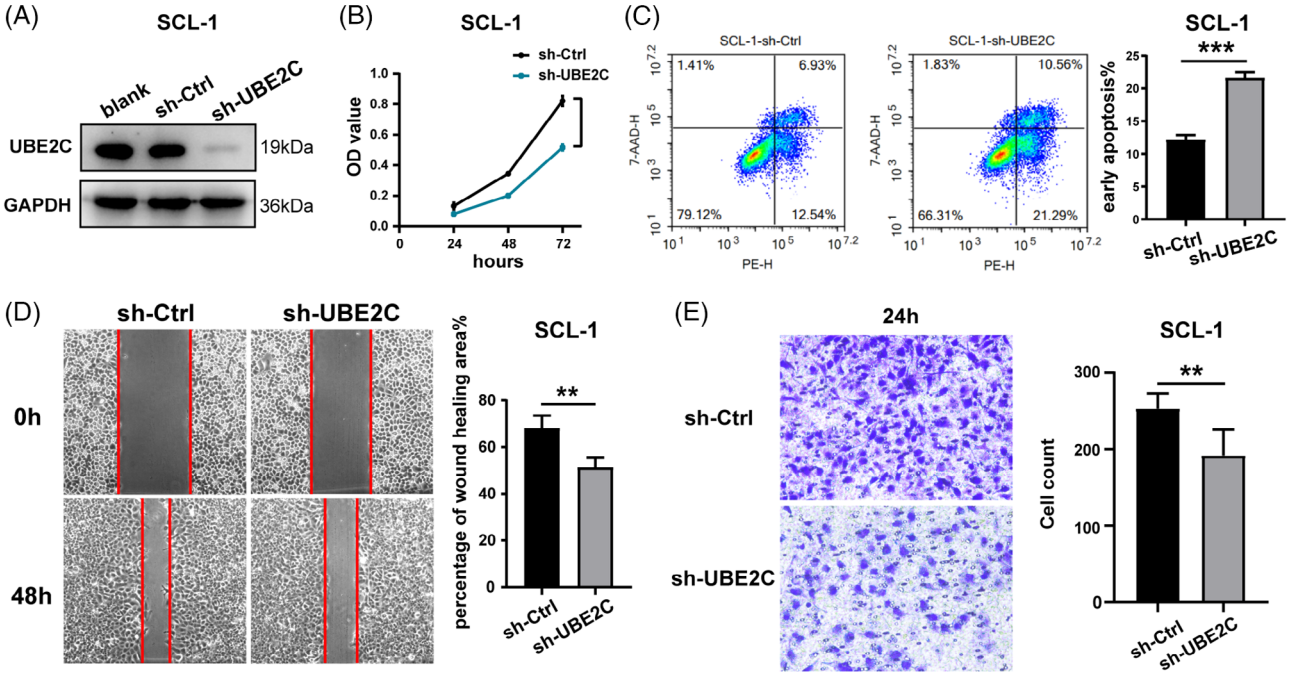

FIGURE 3 Effects of UBE2C deletion on cSCC cells. (A) The efficiency of UBE2C inhibition detected by Western blot. (B) The effect of UBE2C inhibition on cell proliferation detected by CCK8. (C) The effect of UBE2C inhibition on cell apoptosis detected by flow cytometry. (D) Scratch assay was employed to detect the scratch healing rate of cSCC cells after UBE2C depletion. (E) Transwell assay was used to examine the number of migrated cSCC cells after UBE2C silencing. $^{**}p < 0.01$; $^{***}p < 0.001$.

Next, we validated the role of UBE2C in cSCC through in vitro cell experiments. Following UBE2C reduction, we observed a significant decrease in cell proliferation, cell migration, and an increase in cell apoptosis. These results suggest that inhibition of UBE2C can alleviate the malignant phenotype of cSCC cells. Similar results have also been observed in other types of tumors. UBE2C overexpression promote endometrial cancer cell proliferation, migration, invasion, and epithelial-mesenchymal transition.[16] Besides, UBE2C-mediated ubiquitination and degradation of SIRT1 contribute to the malignant progression of endometrial cancer through epigenetic inhibition of autophagy.[21] In breast cancer cells, overexpression of UBE2C has been shown to decrease Numb expression, a tumor suppressor in various cancers, and increase the malignancy of tumor cells.[22] Guo et al.[23] propose that dysregulated UBE2C-autophagy repression axis enhanced the malignancy of non-small cell lung cancer, and interfering with UBE2C can impede cancer progression.

This study confirmed the upregulation of UBE2C in cSCC through bioinformatics, histology and cell experiments. In cSCC, high expression of UBE2C was significantly associated with poor histological grade. Inhibition of UBE2C resulted in decreased cell proliferation and migration, as well as increased apoptosis in cSCC cells. Our experiments demonstrate that UBE2C promotes the malignant phenotype of cSCC and provide a new insight for molecular targeted therapy. Limitations of this study include the insufficient clinical sample size and the need for further exploration of downstream mechanisms.

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have no conflict of interest.

DATA AVAILABILITY STATEMENT

The data used in this study are available in the Gene Expression Omnibus (GEO) repository. Other experimental data are available from the corresponding author on reasonable request.

ETHICS STATEMENT

This study has been approved by the Biomedical Ethics Committee of Xi 'an Jiaotong University Health Science Center. Informed consent was obtained from all patients before collecting specimens.

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