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BIOINFORMATICS-BASED PREDICTION OF THE IMPACT OF ASCL2 ON THE PROGNOSIS OF ESOPHAGEAL CANCER

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Abstract: Objective: To investigate the expression characteristics, clinical significance, molecular mechanisms, and drug sensitivity of Achaete-scute family BHLH transcription factor 2 (ASCL2) in esophageal cancer, and to clarify its value as a prognostic marker and potential therapeutic target for esophageal cancer. Methods: RNA sequencing data and clinical information of esophageal cancer were downloaded from The Cancer Genome Atlas (TCGA) database. After standardization, 163 samples were included. Bioinformatics methods were used to analyze the expression difference of ASCL2 and its correlation with clinicopathological features and prognosis. Maftools package was employed for gene mutation characteristic analysis, immunedeconv package for immune scoring and immune checkpoint-related gene analysis, Limma package and ClusterProfiler package for differential gene screening and GO/KEGG enrichment analysis, and Genomics of Drug Sensitivity in Cancer (GDSC) database for drug sensitivity prediction. Meanwhile, 20 pairs of esophageal cancer tissue samples were collected, and the expression level of ASCL2 was verified by quantitative real-time PCR (qRT-PCR). Results: Both bioinformatics analysis and clinical sample verification showed that the expression of ASCL2 in esophageal cancer tissues was significantly higher than that in adjacent normal tissues, and its expression was partially correlated with tumor differentiation grade and clinical stage. Survival analysis revealed that the median overall survival (OS) of patients in the ASCL2 high-expression subgroup was significantly shorter than that in the low-expression subgroup (1.9 years vs 3.2 years), and the area under the curve (AUC) of ASCL2 for predicting 5-year survival rate was 0.732, indicating that ASCL2 could serve as an independent prognostic factor for the overall survival of esophageal cancer patients. Differential gene and enrichment analysis showed that ASCL2-related differential genes were mainly enriched in lipid metabolism reprogramming, DNA damage repair, cell cycle regulation, as well as Wnt and TGF-beta signaling pathways. Drug sensitivity prediction indicated that the ASCL2 high-expression subgroup had significantly reduced sensitivity to paclitaxel and cisplatin. Conclusion: ASCL2 is highly expressed in esophageal cancer tissues and is closely associated with lymph node metastasis and poor prognosis of patients, which can be used as a potential biomarker for prognostic evaluation of esophageal cancer. ASCL2 may promote the malignant progression of esophageal cancer by interacting with TP53, constructing an inhibitory tumor immune microenvironment, regulating tumor-related signaling pathways, and reducing chemotherapeutic drug sensitivity, thus providing a new target for the personalized treatment of esophageal cancer.
Keywords: ASCL2; Esophageal Cancer (ESCA); Prognosis; Bioinformatics; Drug sensitivity

1 INTRODUCTION

According to the early screening report of esophageal cancer issued by the National Health Commission of the People's Republic of China, there were 224,000 new cases of esophageal cancer in China in 2022, accounting for 4.64% of all malignant tumors, and 187,500 deaths, accounting for 7.28% of all malignant tumors[1]. In recent years, the incidence and mortality of esophageal cancer in China have shown an overall downward trend, and the 5-year survival rate has improved[2]. However, the overall situation remains severe. The characteristic that the mortality rate of esophageal cancer is higher than the incidence rate indicates a huge difference in prognosis between advanced and early esophageal cancer. If early detection and treatment of esophageal cancer can be implemented, the mortality rate of patients can be further controlled. Unfortunately, due to the insidious symptoms of early esophageal cancer and the lack of specific tumor markers, nearly half of the patients are diagnosed at an advanced stage for the first time[3]. Therefore, finding specific tumor markers for esophageal cancer is an important clinical problem that urgently needs to be solved.

The occurrence and development of tumors are the result of the interaction between internal genetic factors and external environmental factors, with complex molecular mechanisms involving a series of biological processes such as abnormal expression of multiple genes, signal pathway disorders, and immune microenvironment imbalance[4-7]. As core molecules in regulating gene expression, transcription factors specifically bind to the promoter regions of target genes to regulate the transcriptional activation or inhibition of downstream genes, playing a key role in the occurrence, development, invasion, and metastasis of tumors[8]. Therefore, screening transcription factors closely related to the occurrence and development of esophageal cancer and exploring their biological functions and clinical significance in depth can provide new ideas for the early diagnosis, prognostic evaluation, and targeted therapy of esophageal cancer.

Achaete-scute complex homolog 2 (ASCL2) was first discovered in Drosophila, and the homologous genes in mammals were named accordingly[9]. ASCL2 belongs to the basic helix-loop-helix (BHLH) transcription factor family[10]. It directly binds to DNA through the basic region, while the helix-loop-helix structure is used for protein-protein interaction. ASCL2 first forms a heterodimer with another BHLH protein of the ubiquitously expressed E proteins (such as E12/E47) and specifically binds to the E-box sequence (5'-CANNTG-3') in the promoter region of target genes, then recruits additional transcriptional cofactors (such as coactivators or corepressors) to initiate or inhibit the transcription of target genes[11]. Thus, it is involved in processes such as nervous system development, placental development, intestinal epithelial cell renewal, and tumorigenesis[12-13].

In recent years, studies have found that ASCL2 is abnormally expressed in a variety of malignant tumors and is closely related to the malignant phenotype of tumors and the prognosis of patients. For example, in colorectal cancer, ASCL2 has been confirmed as a key regulatory factor of intestinal stem cells, and its high expression can promote the proliferation, invasion, and distant metastasis of tumor cells, and is associated with poor prognosis of patients[14]. In tumors such as breast cancer and gastric cancer, ASCL2 has also been reported to be involved in the occurrence and development of tumors by regulating downstream target genes and related signal pathways[15-16]. However, the expression characteristics, biological functions, correlation with clinicopathological parameters and patient prognosis, as well as the molecular mechanism of ASCL2 in esophageal cancer have not been fully clarified.

Based on this, this study systematically analyzed the expression difference of ASCL2 in esophageal cancer tissues through bioinformatics methods combined with clinical sample verification, explored its relationship with clinicopathological features and prognosis of patients, and deeply excavated ASCL2-related gene mutation characteristics, immune microenvironment changes, biological functions, and drug sensitivity. The aim is to clarify the clinical value and potential molecular mechanism of ASCL2 in esophageal cancer, and provide new biomarkers and therapeutic targets for the prognostic evaluation and personalized treatment of esophageal cancer.

2 MATERIALS AND METHODS

2.1 ASCL2 Gene Expression Difference and Clinical Characteristics

STAR-counts data and corresponding clinical information of esophageal cancer were downloaded from the TCGA database (https://portal.gdc.cancer.gov). Then, data in TPM format were extracted and normalized by log2(TPM+1). Finally, 163 samples with both RNAseq data and clinical information were retained for subsequent analysis. A P value less than 0.05 was considered statistically significant.

2.2 Survival Analysis

STAR-counts data and corresponding clinical information of esophageal malignant tumors were downloaded from the TCGA database (https://portal.gdc.cancer.gov). Then, data in TPM format were extracted and normalized by log2(TPM+1). Finally, 163 samples with both RNAseq data and clinical information were retained for subsequent analysis.

Log-rank test was used to compare the survival differences between the above two groups in KM survival analysis. A P value less than 0.05 was considered statistically significant.

2.3 Gene Mutation Analysis

After downloading data from TCGA and quality control, the somatic mutation data of esophageal cancer patients were downloaded and visualized using the maftools package in R software. A P value less than 0.05 was considered statistically significant.

2.4 Immune Scoring and Immune Checkpoint-Related Gene Analysis

After downloading data from TCGA and quality control, immunedeconv, an R package integrating six latest immune cell infiltration assessment algorithms (including TIMER, xCell, MCP-counter, CIBERSORT, EPIC, etc.), was used for reliable immune scoring evaluation. These algorithms have undergone systematic benchmarking, and each algorithm shows unique performance and advantages.

2.5 Differential Gene and Enrichment Analysis

After downloading data from TCGA and quality control, the Limma package (version: 3.40.2) in R software was used to study the differential expression of mRNA, and the adjusted P value was analyzed to correct false positive results. We defined "adjusted P value < 0.05 and log2 (fold change) > 1 or log2 (fold change) < -1" as the threshold for screening mRNA differential expression. The ClusterProfiler package in R was used to analyze the GO functions of potential mRNAs and enrich KEGG pathways.

2.6 Drug Sensitivity Analysis

After downloading data from TCGA and quality control, the chemotherapeutic response of each sample was predicted

according to the public pharmacogenomics database [Genomics of Drug Sensitivity in Cancer (GDSC), https://www.cancerrxgene.org/]. The prediction process was implemented by the R package pRRophetic, where the half-maximal inhibitory concentration (IC50) of samples was estimated by ridge regression. All parameters were set as default, with batch effect by combat and tissue type as "all", and duplicate gene expressions were summarized as the mean value.

2.7 Quantitative Real-Time PCR (qRT-PCR)

Twenty pairs of esophageal cancer tissue samples (March 2021 to August 2024) were collected and RNA was extracted. RNA was reverse-transcribed into cDNA. The reaction system was configured strictly according to the instructions of the PCR kit (Nanjing Vazyme Biotechnology Co., Ltd.). The reaction conditions were set as follows: pre-denaturation: 95 °C for 2 min; denaturation: 95 °C for 15 s, 60 °C for 20 s, 72 °C for 15 s; annealing/extension: 60 °C for 30 s, with a total of 40 cycles of amplification. According to the Ct value, β-actin was used as the internal reference gene, and the relative transcription level of ASCL2 was calculated by the 2-ΔΔCt method

2.8 Statistical Analysis

*, **, and *** represent P values less than 0.05, 0.01, and 0.001, respectively.

3 RESULTS

3.1 ASCL2 is Highly Expressed in Esophageal Cancer Tissues and Partially Correlated with the Differentiation Grade and Stage of Esophageal Cancer Tissues

Bioinformatics results showed that the expression of ASCL2 in esophageal cancer tissues was significantly higher than that in adjacent normal esophageal tissues. The mRNA level of ASCL2 in 20 esophageal cancer patients' tissues was consistent with the bioinformatics results (Figure 1A-B). Further stratified analysis using the UALCAN website showed that the expression abundance of ASCL2 was partially correlated with poor tumor differentiation and stage (Figure 1C-D).

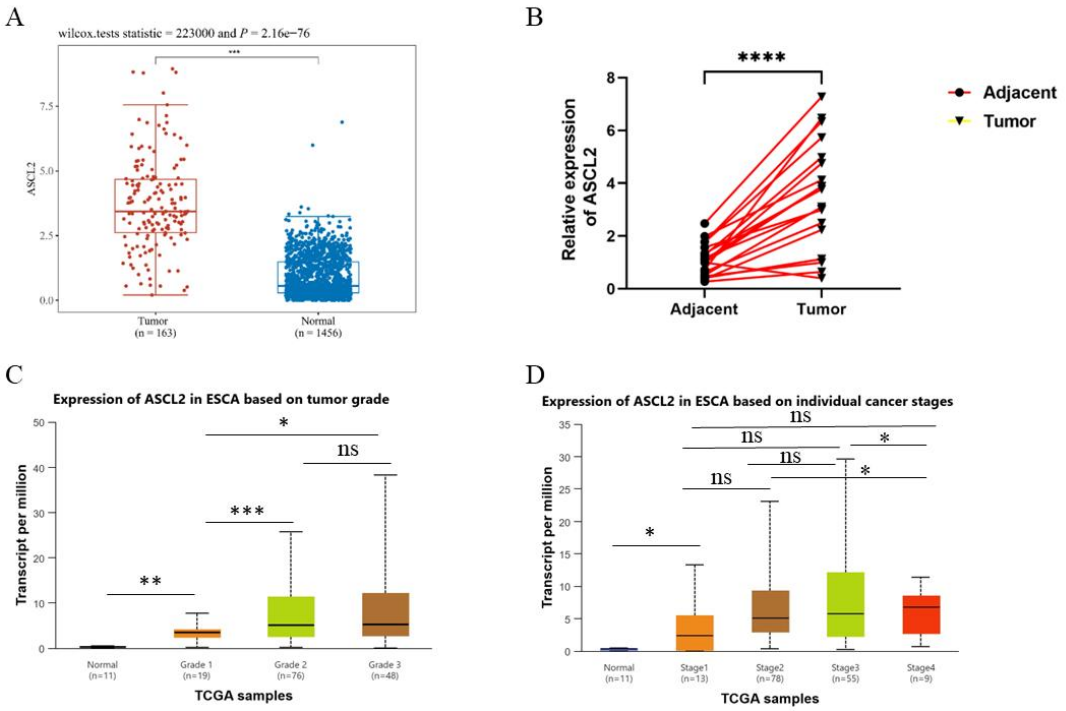

Figure 1 Bioinformatics and Clinical Samples Jointly Verify the Expression of ASCL2 in Esophageal Cancer Tissues
Note: A: Box plot and dot plot showing the difference of ASCL2 between esophageal cancer tissues and adjacent tissues in TCGA+GTEx database; B: qRT-PCR comparing the mRNA difference between tumor tissues and adjacent tissues of 20 esophageal cancer patients; C-D: UALCAN website analysis of the correlation between ASCL2 and the differentiation degree and stage of esophageal cancer.

3.2 Correlation Between ASCL2 Expression and Clinical Features of Patients

Bioinformatics results showed that ASCL2 expression was not significantly correlated with patients' age, gender, race, T stage, M stage, and TNM stage, but was significantly correlated with patients' lymph node metastasis. The high-expression subgroup was more prone to lymph node metastasis (Table 1).

Table 1 Clinical Characteristics of Patients in Different ASCL2 Subgroups

Variable	Feature	Low ASCL2	High ASCL2	*P* value
Age	Mean (SD)	62.8 (11.2)	61.7 (12.7)	
	Median [Min, Max]	61 [42,84]	59.5 [27,90]	0.561
Gender	FEMALE	12	11	
	MALE	69	71	0.975
Race	ASIAN	19	19	
	BLACK	2	4	
	WHITE	54	47	0.612
pT stage	T1	13	12	
	T2	21	20	
	T3	44	44	
	T4	2	3	
	Tx	1	2	
	T4a		1	0.963
pN stage	N0	41	24	
	N1	33	37	
	N2	1	8	
	N3	2	3	
	Nx	4	10	0.012
pM stage	M0	66	62	
	M1	4	6	
	M1a	2	4	
	Mx	8	7	
	M1b		1	0.741
pTNM stage	I	5	2	
	IA	2	2	
	IB	2	3	
	IIA	25	17	
	IIB	13	17	
	III	13	12	
	IIIA	11	5	
	IIIB	1	7	
	IIIC	2	4	
	IV	3	7	
	IVA	2	3	
	IVB		1	0.235

3.3 ASCL2 Can Serve as an Independent Prognostic Factor for Overall Survival (OS) of Esophageal Cancer Patients

Bioinformatics results showed that patients in the ASCL2 high-expression subgroup had shorter survival time (1.9 years vs 3.3 years) (Figure 2A). ASCL2 could predict the overall survival rate of patients, with an AUC of 0.732 for predicting 5-year survival rate (Figure 2B).

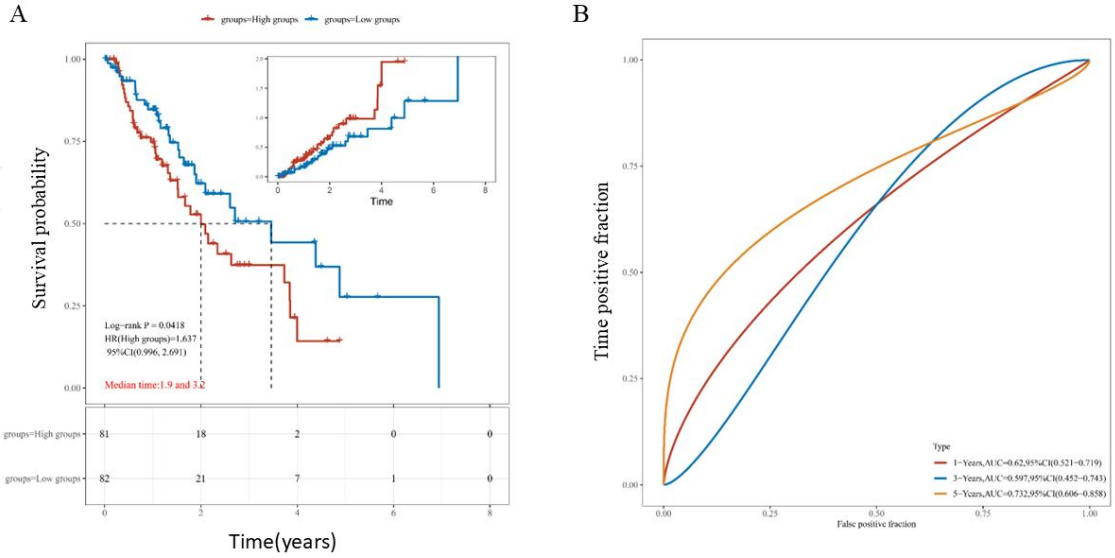

Figure 2 Survival Analysis of ESCA

Note: A: Kaplan-Meier survival curve analyzing the survival of patients in different subgroups; B: AUC curve comparing the predictive efficacy of ASCL2 expression level on 1-year, 3-year, and 5-year survival rates of patients.

3.4 Interaction Between ASCL2 and ESCA Driver Gene TP53

The waterfall plot showed the top ten genes with the highest mutation frequency in ESCA (Figure 3A). Subgroup analysis indicated that the ASCL2 high-expression subgroup had a higher TP53 mutation rate (Figure 3B). Another subgroup classification was used to compare whether TP53 mutation affects ASCL2 expression. The results showed that the expression level of ASCL2 in the TP53 mutant group was significantly higher than that in the TP53 wild-type group (Figure 3B).

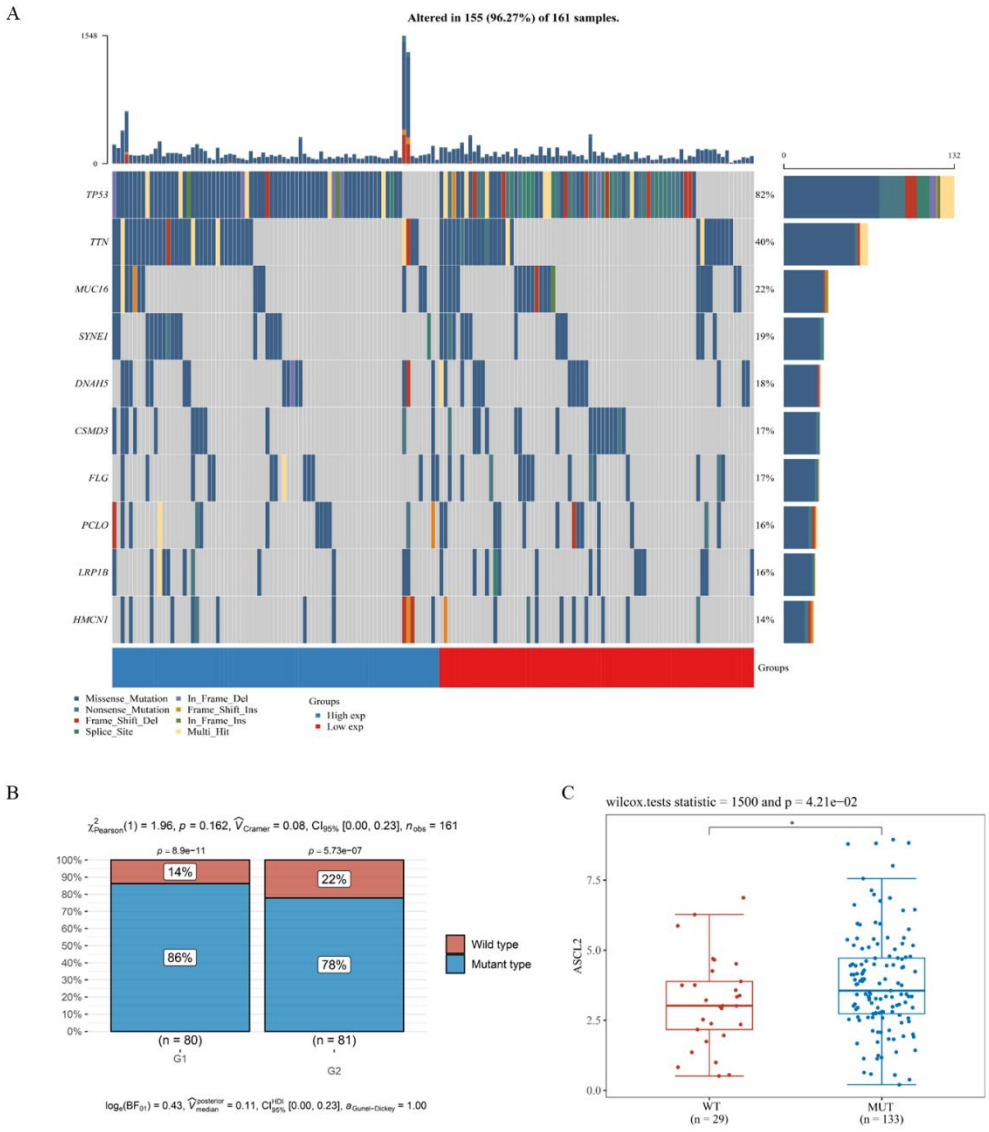

Figure 3 ESCA Mutation Landscape and the Interaction between ASCL2 and TP53

Note: A: Waterfall plot showing the top ten mutated genes in ESCA patients; B: Mutation status of TP53 mRNA in samples from different groups; C: Subgroup stratified analysis comparing the difference in ASCL2 expression between TP53 wild-type and TP53 mutant subgroups.

3.5 ASCL2 is Involved in the Formation of an Inhibitory Immune Microenvironment in Esophageal Cancer

Immune cell scoring results showed that the ASCL2 high-expression subgroup had lower infiltration of CD4+ T cells and myeloid dendritic cells (Figure 4A), while the expression profile of immune checkpoint-related genes showed that the ASCL2 high-expression subgroup had high expression of CD274, CTLA4, and TIGIT (Figure 4B).

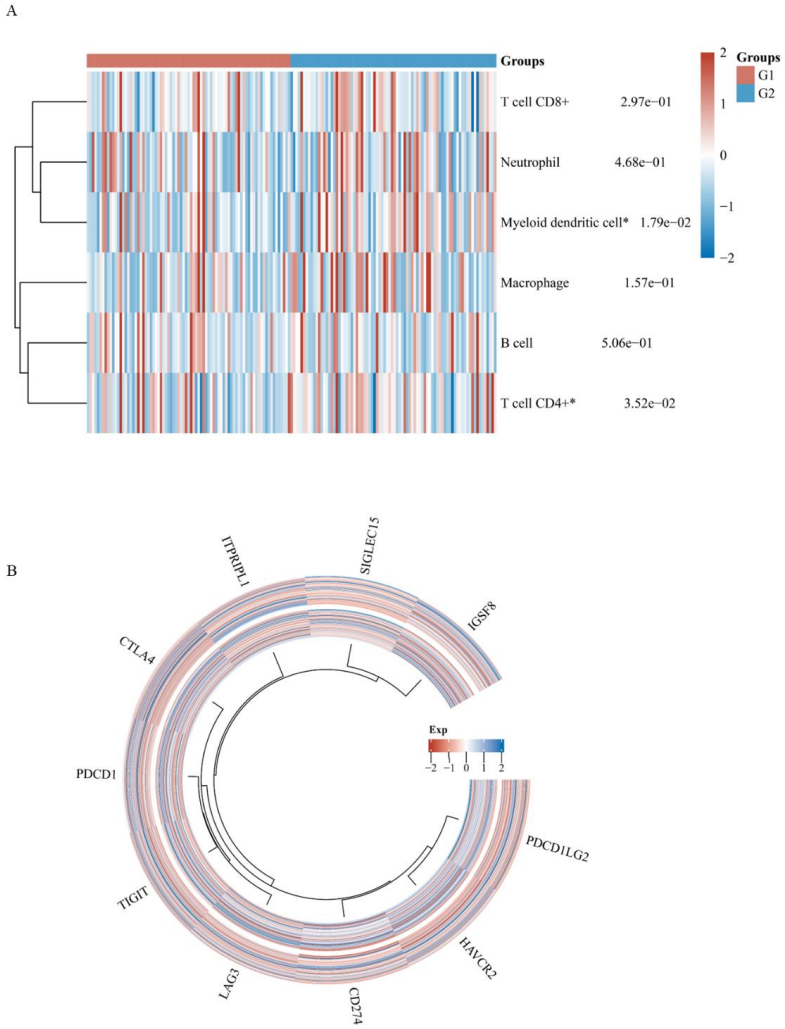

Figure 4 Immune Scores and Immune Checkpoint-Related Genes in Different Expression Subgroups of ASCL2 in ESCA

Note: A: Heatmap of immune cell scores, the significance between the two groups of samples was evaluated by Wilcoxon rank-sum test; B: Expression circle plot of immune checkpoint-related genes, with sample groups distributed from outside to inside. G1: ASCL2 high-expression subgroup, G2: ASCL2 low-expression subgroup.

3.6 Biological Function of ASCL2 in ESCA

DEGs showed that there were 98 up-regulated genes and 54 down-regulated genes in the ASCL2 high-expression subgroup. The heatmap showed the 50 most significantly changed genes (Figure 5A). Further GO analysis showed that the up-regulated genes were mainly concentrated in processes such as lipid metabolism reprogramming, DNA damage repair, and cell cycle regulation (Figure 5B). KEGG enrichment analysis showed that the up-regulated genes were mainly enriched in processes such as xenobiotic and drug metabolism, lipid metabolism, Wnt signaling pathway, and TGF-beta signaling pathway (Figure 5C). The analysis of ASCL2 and tumor-related pathways was basically consistent with GO and KEGG analysis (Figure 5D-H).

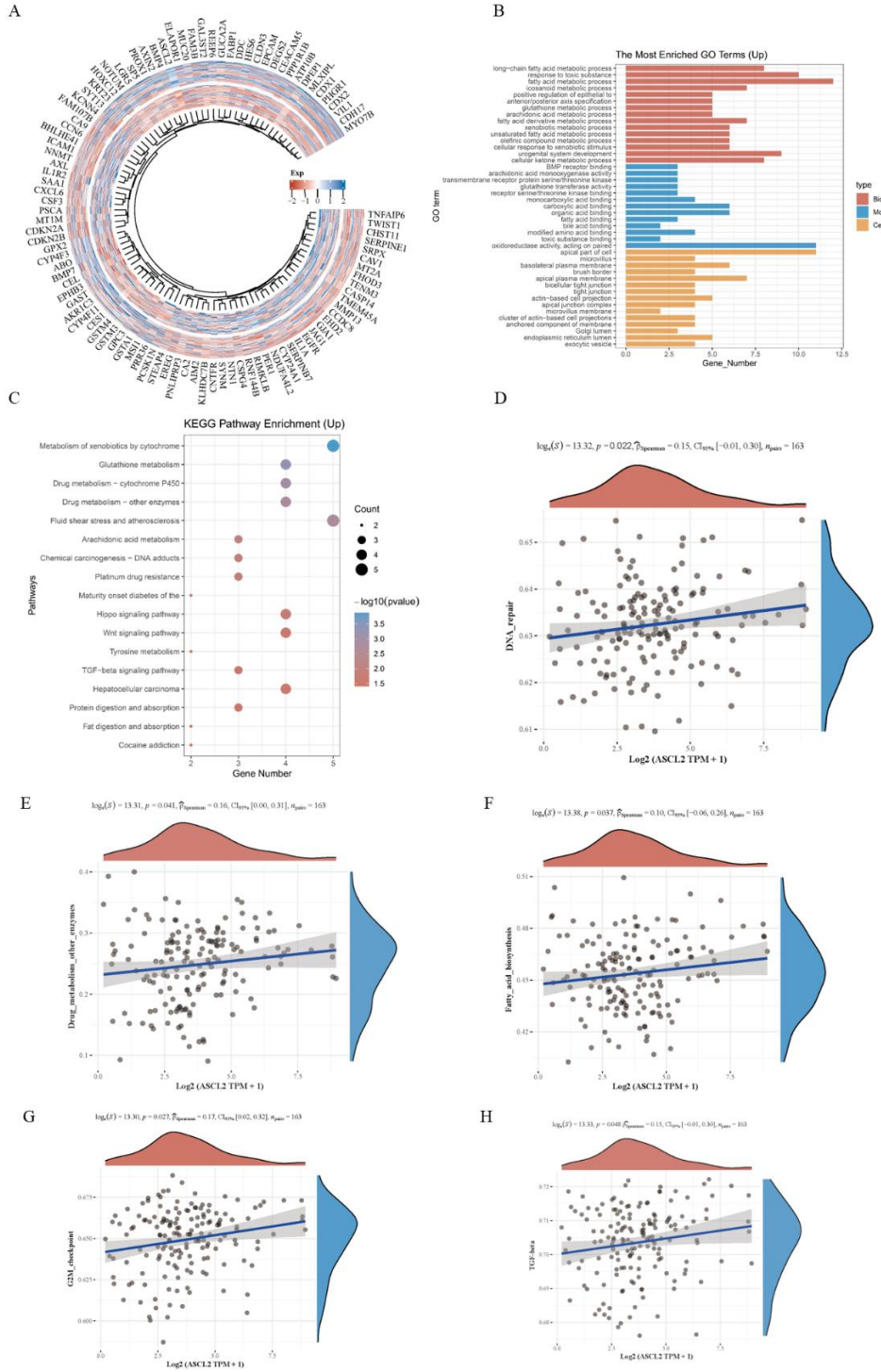

Figure 5 Biological Function of ASCL2 in ESCA and Correlation Analysis with Tumor Pathways

Note: A: Differential genes between ASCL2 high-expression subgroup and low-expression subgroup (Fold Change, FC=1.5); B: GO enrichment prediction showing the biological function of ASCL2 in ESCA; C: KEGG enrichment analysis predicting the relationship between ASCL2 and tumor-related pathways; D-H: Spearman correlation analysis diagrams analyzing the relationship between ASCL2 and DNA damage repair, drug metabolism, lipid metabolism, cell cycle regulation, and TGF-beta signaling pathway.

3.7 ASCL2 Affects the Drug Sensitivity of ESCA to Paclitaxel and Cisplatin

IC50 scores were used to compare the sensitivity of esophageal cancer patients in different ASCL2 expression subgroups to commonly used chemotherapeutic drugs. The results showed that the ASCL2 high-expression subgroup had lower sensitivity to paclitaxel and cisplatin (Figure 6A-B), while no significant differences were observed for gemcitabine, irinotecan, and 5-fluorouracil (Figure 6C-E).

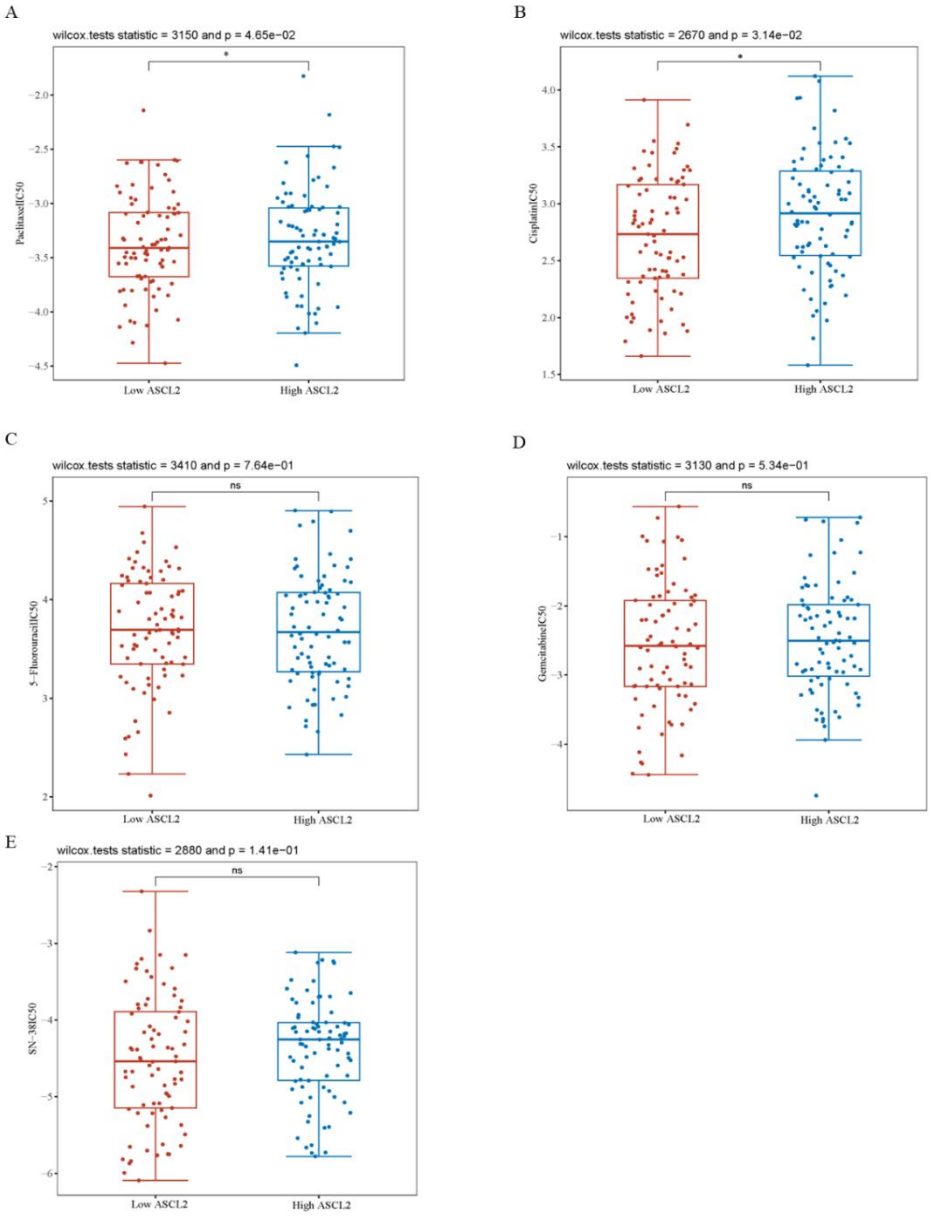

Figure 6 Differences in Sensitivity to Commonly Used Chemotherapeutic Drugs in Esophageal Cancer among ASCL2 Expression Subgroups

Note: A-E: Box plots and dot plots of IC50 score distribution in different groups. The significance between the two groups of samples was evaluated by Wilcoxon rank-sum test. A-E correspond to: paclitaxel, cisplatin, 5-fluorouracil, gemcitabine, irinotecan.

4 DISCUSSION AND CONCLUSION

As one of the high-incidence malignant tumors in China, esophageal cancer poses great challenges to clinical treatment due to its high mortality rate and poor prognosis. Finding reliable prognostic markers and potential therapeutic targets is crucial for improving the clinical outcomes of patients. This study systematically explored the expression characteristics, clinical significance, molecular mechanisms, and drug sensitivity of ASCL2 in esophageal cancer through bioinformatics analysis combined with clinical sample verification, providing new theoretical basis for the prognostic evaluation and personalized treatment of esophageal cancer.

This study is the first to confirm that ASCL2 is highly expressed in esophageal cancer tissues, which is mutually verified by TCGA+GTEx database analysis and qRT-PCR of clinical samples, indicating that the abnormal high expression of ASCL2 may be an important molecular event in the occurrence and development of esophageal cancer. Further stratified analysis showed that the expression abundance of ASCL2 is partially correlated with the differentiation grade and clinical stage of esophageal cancer, suggesting that ASCL2 may be involved in regulating the malignant progression of tumors. Clinical characteristic analysis results showed that the high expression of ASCL2 is significantly correlated with patients' lymph node metastasis, indicating that ASCL2 may promote the malignant progression of esophageal cancer mainly by promoting lymph node metastasis. Its mechanism may be related to regulating the invasive and migratory abilities of tumor cells, which is consistent with previous reports that ASCL2

promotes tumor metastasis in colorectal cancer, breast cancer, and other tumors[17].

Survival analysis results showed that the median survival time of patients in the ASCL2 high-expression subgroup was significantly shorter than that in the low-expression subgroup (1.9 years vs 3.2 years). Log-rank test indicated that the survival difference between the two groups was statistically significant (P=0.0418), and the AUC of ASCL2 for predicting 5-year survival rate was as high as 0.732, indicating that ASCL2 can serve as an independent prognostic factor for the overall survival of esophageal cancer patients. This result highlights the clinical value of ASCL2 in the prognostic evaluation of esophageal cancer. Compared with traditional clinicopathological indicators, ASCL2 as a molecular marker has higher specificity and sensitivity, which is expected to provide a new tool for risk stratification and prognostic judgment of esophageal cancer patients.

The occurrence and development of tumors are closely related to gene mutations. As the most frequently mutated driver gene in esophageal cancer (with a mutation rate of 82% in this study), the loss of TP53 function plays a key role in the occurrence and development of esophageal cancer[18-19]. This study found that the mutation rate of TP53 in the ASCL2 high-expression subgroup was significantly increased, and the expression level of ASCL2 in TP53 mutant patients was significantly higher than that in wild-type patients, suggesting that there may be an mutual regulatory relationship between ASCL2 and TP53. Previous studies have shown that TP53 mutation can affect the proliferation, apoptosis, and metabolic reprogramming of tumor cells by regulating downstream target genes[19]. ASCL2 may form a regulatory network with mutant TP53 to jointly promote the malignant progression of esophageal cancer. The specific molecular mechanism needs to be further verified by in vitro cell experiments and in vivo animal experiments.

The remodeling of the tumor immune microenvironment is an important feature of tumor progression. Abnormalities in immune cell infiltration and immune checkpoint gene expression are closely related to the prognosis and treatment response of tumor patients. Through immune scoring analysis, this study found that the infiltration levels of CD4+ T cells and myeloid dendritic cells in the ASCL2 high-expression subgroup were significantly reduced. As the core cells of the body's anti-tumor immunity, the reduced infiltration of CD4+ T cells can lead to weakened tumor immune surveillance function; myeloid dendritic cells, as antigen-presenting cells, their functional abnormalities will affect the activation of T cells, further inhibiting the anti-tumor immune response. At the same time, the analysis of immune checkpoint-related genes showed that immune checkpoint genes such as CD274 (PD-L1), CTLA4, and TIGIT were highly expressed in the ASCL2 high-expression subgroup. The high expression of these genes can promote tumor immune escape by inhibiting T cell function. The above results indicate that ASCL2 may construct an inhibitory immune microenvironment by inhibiting the infiltration of anti-tumor immune cells and up-regulating the expression of immune checkpoint genes, thereby promoting the progression of esophageal cancer. This provides a new idea for the immunotherapy of esophageal cancer, that is, targeting ASCL2 may reverse the tumor immune suppression state and enhance the efficacy of immunotherapy.

To further clarify the biological function of ASCL2 in esophageal cancer, this study found through differential gene analysis and enrichment analysis that the differentially up-regulated genes in the ASCL2 high-expression subgroup are mainly enriched in biological processes such as lipid metabolism reprogramming, DNA damage repair, and cell cycle regulation, as well as tumor-related pathways such as Wnt signaling pathway and TGF-beta signaling pathway. Lipid metabolism reprogramming is an important metabolic feature of rapid tumor cell proliferation, which can provide energy and biosynthetic precursors for tumor cells; enhanced DNA damage repair ability can enable tumor cells to resist chemotherapy-induced apoptosis; abnormal cell cycle regulation directly promotes the unlimited proliferation of tumor cells[20]. Both Wnt signaling pathway and TGF-beta signaling pathway are key pathways regulating tumor occurrence and development, and their abnormal activation can promote the proliferation, invasion, and metastasis of tumor cells. The above results indicate that ASCL2 may promote the malignant progression of esophageal cancer by regulating lipid metabolism, DNA damage repair, cell cycle, and related signal pathways, which is basically consistent with the functional reports of ASCL2 in other tumors.

Chemotherapy is one of the important means of comprehensive treatment for esophageal cancer. Paclitaxel and cisplatin are commonly used first-line chemotherapeutic drugs for the clinical treatment of esophageal cancer[21]. However, the occurrence of chemotherapy resistance seriously affects the treatment effect. Through drug sensitivity analysis, this study found that the IC50 values of paclitaxel and cisplatin in patients with ASCL2 high-expression subgroup were significantly higher than those in the low-expression subgroup, suggesting that high expression of ASCL2 may lead to reduced sensitivity of esophageal cancer patients to these two chemotherapeutic drugs. Its mechanism may be related to the enhanced DNA damage repair ability and changes in the expression of drug metabolism-related genes regulated by ASCL2. This finding provides a reference for the personalized chemotherapy of esophageal cancer, that is, by detecting the expression level of ASCL2 in patients' tumor tissues, the therapeutic response of patients to paclitaxel and cisplatin can be predicted, providing a basis for clinicians to formulate personalized treatment plans.

This study also has certain limitations: first, the bioinformatics analysis of this study is mainly based on the TCGA database. Although combined with the verification of 20 pairs of clinical samples, the sample size is relatively limited. In the future, it is necessary to expand the scale of clinical samples to further verify the expression characteristics and clinical significance of ASCL2; second, this study only predicted the biological functions and related molecular mechanisms of ASCL2 through bioinformatics analysis, lacking direct verification by in vitro cell experiments and in vivo animal experiments; finally, this study did not explore the downstream target genes regulated by ASCL2 in the progression of esophageal cancer, and its specific molecular regulatory network needs to be further clarified.

In conclusion, this study confirms that ASCL2 is highly expressed in esophageal cancer tissues and is closely associated with lymph node metastasis and poor prognosis of patients, which can be used as an independent prognostic marker for

esophageal cancer patients. ASCL2 may promote the malignant progression of esophageal cancer by interacting with TP53, constructing an inhibitory immune microenvironment, regulating lipid metabolism reprogramming, DNA damage repair, cell cycle, and related signal pathways, and reducing the chemosensitivity of patients to paclitaxel and cisplatin. This study provides new biomarkers and therapeutic targets for the prognostic evaluation and personalized treatment of esophageal cancer. In the future, it is necessary to further explore the molecular regulatory mechanism of ASCL2 to provide experimental basis for the development of ASCL2-targeted therapeutic strategies.

COMPETING INTERESTS

The authors have no relevant financial or non-financial interests to disclose.

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