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Differential expression gene screening and prognostic biomarkers of skin cutaneous melanoma based on GEPIA database

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Abstract

[Objective] To explore the differential gene expression profiles between skin cutaneous melanoma (SKCM) and normal tissues using bioinformatics methods, and to evaluate their predictive value for patient survival and prognosis. [Methods] Differentially expressed genes (DEGs) between tumor and normal tissues were identified using the GEPIA database. The correlation between key gene expression and overall survival was analyzed.[Results] A total of 6,457 significantly upregulated genes (FDR < 0.05) were identified. The top 10 genes with the highest expression levels included PRAME, RP11-40C6.2, SERPINE2, SDC3, UBE2SP2, ETV5, PLOD3, EIF5AP4, UBE2S, and HNRNPCP2. Survival analysis revealed that the expression levels of EIF5AP4, UBE2S, and SERPINE2 were significantly associated with clinical prognosis. Specifically, high EIF5AP4 expression was significantly associated with shortened disease-free survival (DFS), while high UBE2S expression was significantly associated with reduced overall survival (OS) and DFS. In contrast, high SERPINE2 expression was significantly associated with prolonged OS and DFS.[Conclusion] This study suggests that UBE2S and EIF5AP4 may function as oncogenic factors promoting SKCM progression, whereas SERPINE2 may play a protective role. The combined expression of these three genes may serve as a novel molecular signature for prognostic evaluation in SKCM.

Keywords Skin cutaneous melanoma; GEPIA database; Prognosis
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As a highly invasive cutaneous malignancy, skin cutaneous melanoma (SKCM) has shown a continuously rising global incidence, attracting widespread attention. In addition to severely affecting patients' quality of life, it poses a significant public health burden. Although advances in diagnostic and therapeutic technologies have been made, the five-year survival rate remains suboptimal. Unraveling the molecular mechanisms underlying SKCM has thus become a critical step toward improving therapeutic outcomes.

Abnormal gene regulatory networks play a pivotal role in tumor progression, as the expression of specific genes can significantly influence tumor cell proliferation, metastatic potential, and drug sensitivity.

By comparing the transcriptomic profiles of tumor and normal tissues, researchers can identify molecular markers of clinical relevance. Currently, the rapid advancement of bioinformatics offers new opportunities for such investigations. A prominent example is the Gene Expression Profiling Interactive Analysis (GEPIA) database, which integrates multidimensional genomic data from tumors to facilitate systematic comparative analyses across various cancer types. This study aims to utilize the advanced analytical functions of the GEPIA platform to comprehensively examine the gene expression profile of SKCM and to construct a prognostic gene network, thereby providing a theoretical foundation for the development of personalized diagnostic and therapeutic strategies.

1 Data and Methods

1.1 Differential Gene Screening Process

Data acquisition was conducted using the GEPIA database (http://gepia.cancer.pku.cn/) by accessing the *Differential Gene Expression Analysis* module. The disease type was set to **SKCM**, and the screening thresholds were defined as $|\log_2 \mathrm{FC}| \geq 1.0$ and q-value ≤ 0.01. The ANOVA statistical method was employed, and *Overexpression* was selected in the chromosomal distribution filter.

1.2 Survival Analysis Procedure

For survival analysis, the interface was switched to the *Survival Analysis* module on the GEPIA homepage. The significantly differentially expressed genes identified in the previous step were input individually. Both **Overall Survival (OS)** and **Disease-Free Survival (DFS)** were selected as survival indicators. Grouping was based on the median expression value, with 50% of cases classified into high- and low-expression groups, respectively. The hazard ratio (HR) and 95% confidence interval (CI) were displayed. The SKCM dataset was selected for validation. Finally, the *Build* button was clicked to generate and visualize the survival curves.

2 Results

2.1 Analysis of Differentially Expressed Genes in SKCM

Based on a combined dataset comprising TCGA tumor samples and GTEx normal tissues, a total of 6,457 genes were identified as significantly upregulated in SKCM tissues using the GEPIA platform (461 samples in the tumor group vs. 558 in the normal group). The top 10 genes with the most significant differences in expression were: *PRAME*, *RP11-40C6.2*, *SERPINE2*, *SDC3*, *UBE2SP2*, *ETV5*, *PLOD3*, *EIF5AP4*, *UBE2S*, and *HNRNPCP2*. In the gene expression box plots, SKCM tissues are indicated in red, while normal skin tissues are shown in gray (Figure 1-10).

2.2 Association of gene expression with survival prognosis

Survival analysis of 461 SKCM patients based on the GEPIA platform showed that gene expression levels of EIF5AP4, UBE2S and SERPINE2 showed specific associations with clinical prognosis (Figure 11/18/19). Among them, high expression of EIF5AP4 significantly shortened patients' disease free survival (P<0.05) but had no predictive value for overall survival; UBE2S showed a dual risk effect, with its high expression leading to a simultaneous decrease in overall survival and disease free survival(P<0.05); while high expression of SERPINE2 showed a protective effect, which was associated with a significant prolongation of both overall surviva and disease free survival with a statistical association (P<0.05)。

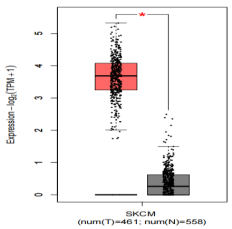

Figure1 Expression of EIF5AP4 in SKCM and normal tissues

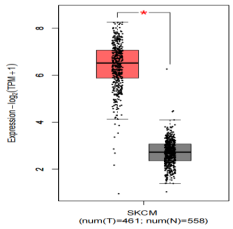

Figure2 Expression of ETV54 in SKCM and normal tissues

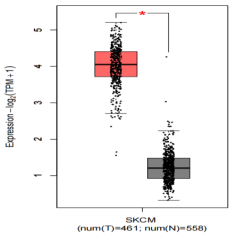

Figure3 Expression of HNRNPCP2 in SKCM and normal tissues

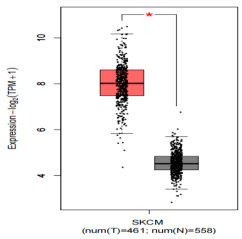

Figure4 Expression of PLOD3 in SKCM and normal tissues

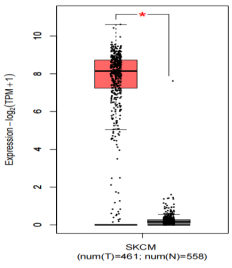

Figure5 Expression of PRAME in SKCM and normal tissues

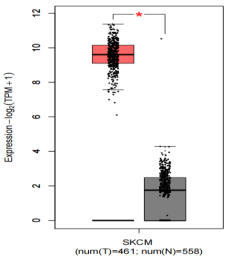

Figure6 Expression of RP11-40C6.2 in SKCM and normal tissues

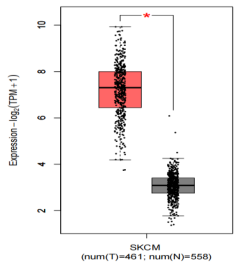

Figure7 Expression of SDC3 in SKCM and normal tissues

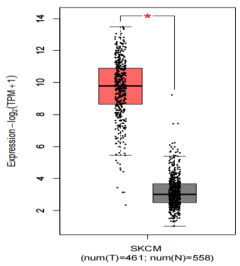

Figure8 Expression of SERPINE2in SKCM and normal tissues

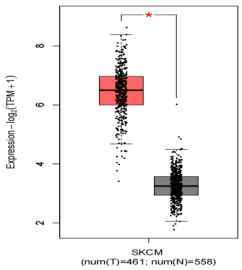

Figure9 Expression of UBE2SPINE2 in SKCM and normal tissues

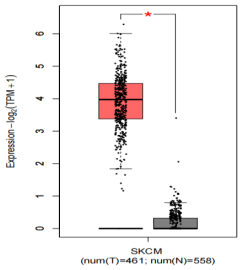

Figure10 Expression of UBE2SP2 in SKCM and normal tissues

Figure 1-10. Analysis of Differentially Expressed Genes in SKCM.

3 Discussion

In this study, we utilized the GEPIA database to elucidate the molecular characteristics of skin cutaneous melanoma (SKCM) and systematically identified 6,457 differentially expressed genes that were significantly upregulated in SKCM tissues. Among them, the top 10 genes with the most significant expression differences were, in order: *PRAME*, *RP11-40C6.2*, *SERPINE2*, *SDC3*, *UBE2SP2*, *ETV5*, *PLOD3*, *EIF5AP4*, *UBE2S*, and *HNRNPCP2*. The identification of these genes provides important clues for understanding the molecular mechanisms underlying SKCM pathogenesis. Functional enrichment analysis revealed that these differentially expressed genes were significantly involved in key biological processes such as cell cycle

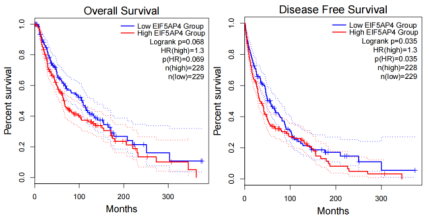

Figure11 Survival analysis of SKCM patients based on EIF5AP4 gene expression

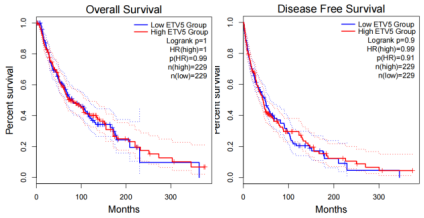

Figure12 Survival analysis of SKCM patients based on ETV5 gene expression

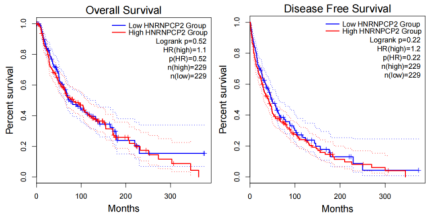

Figure13 Survival analysis of SKCM patients based on HNRNPCP2 gene expression

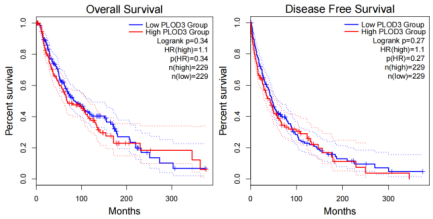

Figure14 Survival analysis of SKCM patients based on PLOD3 gene expression

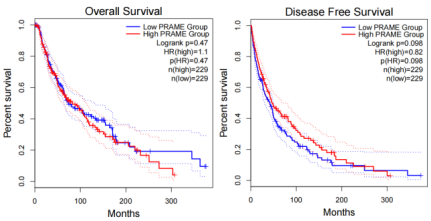

Figure15 Survival analysis of SKCM patients based on PRAME gene expression

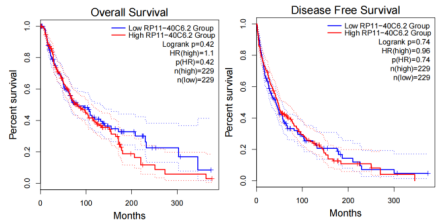

Figure16 Survival analysis of SKCM patients based on RP11-40C6.2 gene expression

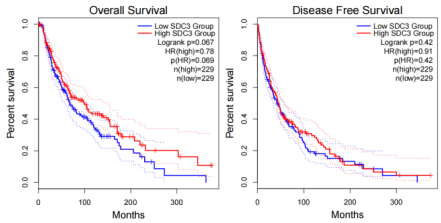

Figure17 Survival analysis of SKCM patients based on SDC3 gene expression

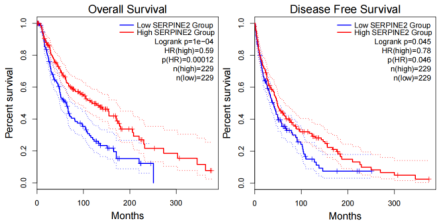

Figure18 Survival analysis of SKCM patients based on SERPINE2 gene expression

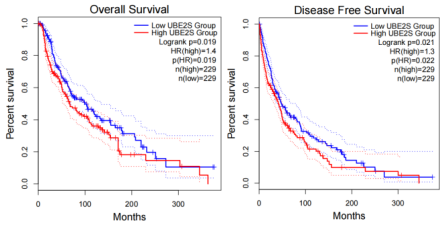

Figure19 Survival analysis of SKCM patients based on UBE2S gene expression

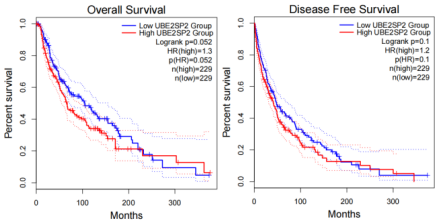

Figure20 Survival analysis of SKCM patients based on UBE2SP2 gene expression

Figure 11-20. Association of gene expression with survival prognosis.

regulation (e.g., *CDK1*, *CCNB1*), MAPK signaling pathways (e.g., *FGF2*, *EGFR*), and apoptosis-related pathways (e.g., *CASP3*, *BCL2*). These pathways are highly consistent with the core mechanisms of tumorigenesis and cancer progression reported in previous studies[1-3], further supporting the reliability and validity of our findings.

In terms of clinical prognosis, the genes *UBE2S* and *EIF5AP4* exhibited clear negative prognostic effects. Patients with high *UBE2S* expression showed shorter overall survival (OS) and significantly reduced disease-free survival (DFS), which aligns with previous findings that *UBE2S* promotes the proliferation of tumors such as hepatocellular carcinoma and breast cancer via the ubiquitin-proteasome system[4,5]. *EIF5AP4* was negatively associated with DFS; however, its dual role in regulating eukaryotic transla-

tion initiation may explain the lack of statistical significance in its effect on OS[6].Notably, *SERPINE2* demonstrated a protective effect in this study, with high expression associated with prolonged OS and improved DFS. This contrasts with earlier reports that *SERPINE2* promotes metastasis in gastric and lung cancers[7,8]. Such divergence may result from melanoma-specific microenvironmental regulatory mechanisms. For instance, TGF-β secreted by tumor-associated fibroblasts may inversely regulate *SERPINE2* function through the SMAD signaling pathway[9]. This hypothesis warrants further investigation using experimental approaches such as 3D co-culture models.

Although bioinformatics-based analyses of large datasets have highlighted the clinical relevance of key genes, several limitations must be acknowledged with caution. First, the retrospective nature of the GEPIA database may introduce selection bias, such as the exclusion of unpublished clinical subgroup data. Second, the current analyses have not addressed potential synergistic effects among genes; the construction of protein–protein interaction (PPI) networks and the calculation of combinatorial risk scores are required to enhance predictive power. Third, the biological functions of the identified differentially expressed genes urgently need to be validated at multiple levels using experimental approaches such as CRISPR-Cas9-mediated gene knockdown, organoid models, and patient-derived xenograft (PDX) mouse models. In particular, the specific role of *UBE2S* in melanoma metastasis warrants further in-depth mechanistic investigation.

It should be emphasized that the protective effect of SERPINE2 identified in the present study differs directionally from most previous findings, suggesting a potential gap between bioinformatic predictions and experimental validations. This discrepancy may be attributed to: (1) tumor heterogeneity resulting in tissue-specific gene functions; (2) regulation of protein activity through post-transcriptional modifications not accounted for in the analysis; and (3) confounding factors related to immune cell infiltration within the tumor microenvironment. Therefore, future studies should integrate single-cell sequencing technology with spatial transcriptomics to precisely resolve the expression patterns of this gene across distinct cellular subpopulations [10].

4 Conclusion

In conclusion, this study not only constructed melanoma-specific differential gene expression profiles but also demonstrated the clinical predictive value of UBE2S, EIF5AP4, and SERPINE2 through multidimensional prognostic analysis. These findings provide a theoretical foundation for the development of novel molecular diagnostic markers and targeted therapeutic strategies. Future research should focus on: (1) establishing a dynamic gene expression monitoring system to evaluate therapeutic responses; (2) developing biopsy techniques based on key genes; and (3) exploring the clinical translational potential of small-molecule inhibitors (e.g., UBE2S-specific inhibitors), thereby completing the innovation chain from basic research to clinical application.

Article History

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